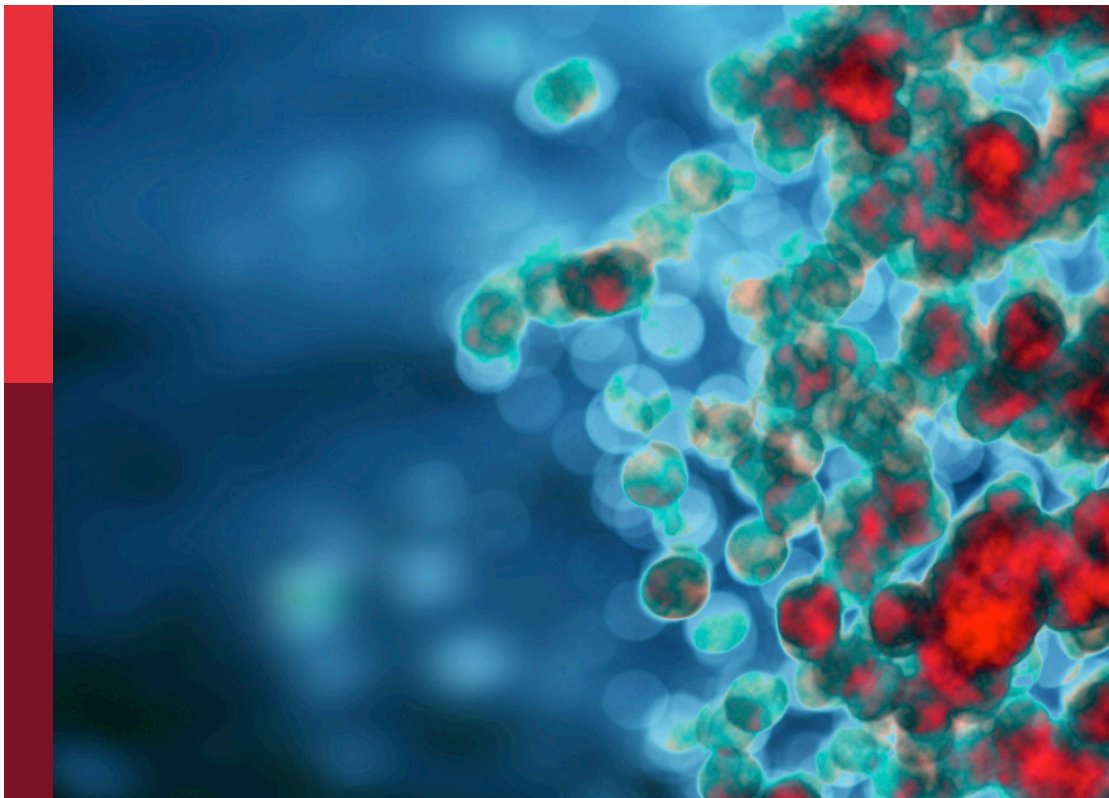
frontiers | Research Topics

Community series: systemic vasculitis: advances in pathogenesis and therapies, volume II

Edited by
Alexandre Wagner Silva De Souza, Joshua Daniel Ooi, Jun Deng, Poh-Yi Gan, Kelly L. Brown and Stefania Croci

Published in
Frontiers in Immunology



ISSN 1664-8714
ISBN 978-2-8325-7371-6
DOI 10.3389/978-2-8325-7371-6

Generative AI statement
Any alternative text (Alt text) provided alongside figures in the articles in this ebook has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Community series: systemic vasculitis: advances in pathogenesis and therapies, volume II

Topic editors

Alexandre Wagner Silva De Souza — Federal University of São Paulo, Brazil
Joshua Daniel Ooi — Monash University, Australia
Jun Deng — Shanghai Jiao Tong University, China
Poh-Yi Gan — Monash University, Australia
Kelly L. Brown — University of British Columbia, Canada
Stefania Croci — IRCCS Local Health Authority of Reggio Emilia, Italy

Citation

De Souza, A. W. S., Ooi, J. D., Deng, J., Gan, P.-Y., Brown, K. L., Croci, S., eds. (2026). *Community series: systemic vasculitis: advances in pathogenesis and therapies, volume II*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-7371-6

Table of contents

frontiers | Frontiers in Immunology

TYPE Editorial
PUBLISHED 06 January 2026
DOI 10.3389/fimmu.2025.1766442

OPEN ACCESS

EDITED AND REVIEWED BY
Betty Diamond,
Feinstein Institute for Medical Research,
United States

*CORRESPONDENCE
Alexandre Wagner Silva De Souza
alexandre_wagner@uol.com.br

RECEIVED 12 December 2025
ACCEPTED 15 December 2025
PUBLISHED 06 January 2026

CITATION
De Souza AWS, Ooi JD, Deng J, Croci S, Gan P-Y and Brown KL (2026) Editorial: Community series: systemic vasculitis: advances in pathogenesis and therapies, volume II. *Front. Immunol.* 16:1766442. doi: 10.3389/fimmu.2025.1766442

Editorial: Community series: systemic vasculitis: advances in pathogenesis and therapies, volume II

Alexandre Wagner Silva De Souza[1]*, Joshua Daniel Ooi[2], Jun Deng[3], Stefania Croci[4], Poh-Yi Gan[5] and Kelly L Brown[6]

[1]Rheumatology Division, Department of Medicine, Universidade Federal de São Paulo – Escola Paulista de Medicina, São Paulo, SP, Brazil, [2]Centre for Inflammatory Diseases, Department of Medicine, Monash Medical Centre, School of Clinical Sciences, Monash University, Clayton, VIC, Australia, [3]Henji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China, [4]Unit of Clinical Immunology, Allergy and Advanced Biotechnologies, Azienda Unità Sanitaria Locale-Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Reggio Emilia, Italy, [5]Centre for Inflammatory Diseases, Monash University, Clayton, VIC, Australia, [6]BC Children's Hospital Research Institute, Centre for Blood Research, and Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

KEYWORDS

adaptive immunity, innate immunity, pathophysiology, systemic vasculitis, vaccination

Editorial on the Research Topic
Community series: systemic vasculitis: advances in pathogenesis and therapies, volume II

Systemic vasculitis is a group of rare and multisystem diseases characterized by inflammation of blood vessels of different types and sizes (1). The etiology of systemic vasculitis is poorly understood. However, different immunological mechanisms have been recognized to play a role in its pathogenesis. These mechanisms include granuloma formation, neutrophilic or eosinophilic inflammation, immune complex deposition on vessel walls, and the presence of pathogenic autoantibodies, such as antineutrophil cytoplasmic antibodies (ANCA) and anti-glomerular basement membrane (anti-GBM) antibodies (2–8).

Vasculitis is classified according to the size of the blood vessels predominantly affected by the inflammatory process as large-, medium-, small-, and variable-vessel vasculitis. Vasculitis may affect a single organ or multiple organ systems simultaneously. It may also develop secondary to other systemic diseases such as systemic lupus erythematosus or rheumatoid arthritis. Infectious diseases, malignancies, and drug use, including illicit drug abuse, are also recognized as causes of vasculitis (9). People living with vasculitis experience protean manifestations due to the involvement of different organs and systems in various combinations (1).

In this Research Topic, Biegelmeyer et al. conducted a multicenter prospective cohort study to evaluate the response to primary and booster doses of the SARS-CoV-2 vaccination in patients with systemic vasculitis. They included 73 patients, 60 of whom completed the booster dose. Most of the patients had Behçet's disease (BD), Takayasu arteritis (TAK), and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). After the primary vaccination schedule of two doses, the ChAdOx1 nCoV-19

vaccine induced higher levels of IgG anti-RBD (SARS-CoV-2 spike receptor-binding domain) than the CoronaVac vaccine. However, no differences in immunogenicity were observed after the booster dose. Additionally, the immunogenicity of heterologous and homologous vaccination regimens or vasculitis forms was similar. Following vaccination, rates of new cases of COVID-19, hospitalization, and mortality were relatively low. There was no increase in the relapse rate, and adverse events were mostly mild. In TAK patients, Zarur et al. evaluated whether single-nucleotide polymorphisms (SNPs) of genes involved in homocysteine metabolism were responsible for the observed hyperhomocisteinemia (10). Using Sanger sequencing, they tested the following SNPs: C677T (rs1801133) and A1298C (rs1801131) in the *MTHFR* gene, A2756G (rs1805087) in the *MTR* gene, A66G (rs1801394) in the *MTRR* gene, and G80A (rs1051266) in the *SLC19A1* gene. They evaluated these SNPs in 73 TAK patients and 71 controls. Despite TAK patients having higher mean homocysteine levels than controls, the frequency of the SNPs carriage was similar in both groups. Takayasu arteritis itself was an independent risk factor for hyperhomocysteinemia, and thiazide diuretic use was an additional risk factor for increased homocysteine levels among TAK patients. Neither homocysteine levels nor SNP carriage was associated with ischemic events. The authors hypothesized that the inflammatory burden of TAK may be a risk factor for the hyperhomocysteinemia observed in this disease.

In AAV patients, Wu et al. conducted a case series of reduced-dose obinutuzumab in 16 adult patients with AAV who were refractory to cyclophosphamide or rituximab induction therapy or were treatment-naïve with multiorgan failure. The complete response rate at week 76 was 81.3%, and only one patient relapsed during follow-up. Despite the high frequency of treatment-emergent infections (43.8%), no severe infections occurred. Obinutuzumab is a promising type II anti-CD20 that is currently being tested in AAV patients, and these preliminary data highlight its potential effectiveness.

Furthermore, three review articles were published on this Research Topic, each approaching different aspects of the pathophysiology and management of vasculitis, particularly AAV (Zhang et al., Alberici et al., Tay et al.). Zhang et al. discuss the role of anti-endothelial cell antibodies (AECAs) in the pathogenesis of various forms of vasculitis. In their review, they describe the antigen targets of AECAs and the pro-inflammatory, pro-coagulant, and pro-apoptotic effects that AECAs trigger upon binding to endothelial cells. They also discuss how these effects contribute to the pathogenesis of systemic vasculitis. Alberici et al. reviewed the management of AAV patients, highlighting the burden of disease relapses and their risk factors, including clinical and exploratory biomarkers. They also reviewed AAV relapses and the treatment options for preventing and treating relapses in detail. Tay et al. reviewed the pathogenesis of myeloperoxidase (MPO)-AAV and the current therapeutic options for AAV. They also discussed emerging cell-based therapies, including the promising regulatory T (Treg) cell therapy, which involves the genetic engineering of Treg cells. These therapeutic modalities include TCR-Treg cells and CAR-Treg cells.

In addition to the original studies and review articles, three manuscripts detailing unusual case reports were published under this Research Topic. Rivet et al. presented a case-based literature review of three patients who developed severe digital necrosis while undergoing Immune Checkpoint Inhibitor (ICI) therapy with pembrolizumab, nivolumab, or a combination of nivolumab and ipilimumab for lung adenocarcinoma, renal cell carcinoma, or melanoma, respectively. The authors also identified 12 additional cases reported in the literature and described the primary characteristics of this severe ICI-related complication in all 15 cases. Zhang et al. reported rare and severe gastrointestinal manifestations of IgA vasculitis (IgAV) such as pancreatitis and esophageal necrosis in a 35-year-old male patient. The patient died due to severe gastrointestinal bleeding, hemorrhagic shock, and disseminated intravascular coagulation. Finally, Zhang et al. described a patient with long-standing Behçet's disease due to trisomy 8 and myelodysplastic syndrome. The patient developed an unusual combination of IgA nephropathy and acute tubular necrosis, which progressed to severe renal failure requiring renal replacement therapy. However, renal function recovered after receiving methylprednisolone therapy.

In conclusion, this Research Topic comprises original articles that investigate different topics related to systemic vasculitis, including the immunogenicity to SARS-CoV-2 vaccination in patients with vasculitis, the genetic basis for hyperhomocysteinemia in TAK, and the response to obinutuzumab therapy in AAV patients. Moreover, this Research Topic reviews important issues in systemic vasculitis, such as the pathogenesis by AECAs, the risk of relapse, and the management of AAV, as well as emerging cell-based therapies for AAV patients. We hope this Research Topic provides useful information for the clinical management of systemic vasculitis.

Author contributions

AS: Writing – original draft, Writing – review & editing. JO: Writing – review & editing. JD: Writing – review & editing. SC: Writing – review & editing. P-YG: Writing – review & editing. KB: Writing – original draft, Writing – review & editing.

Funding

The author(s) declared that financial support was received for this work and/or its publication. AWSS received grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (grant Nr. 309133/2023-8). KLB is supported by a BC Children's Hospital Salary Award and a Michael Smith Foundation for Health Research Scholar Award.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) AS and JO declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Briggs JA, McAdoo SP. Systemic vasculitides: an overview. *Medicine*. (2024) 52:746–53. doi: 10.1016/J.MPMED.2024.09.002

2. Guillevin L, Dörner T. Vasculitis: mechanisms involved and clinical manifestations. *Arthritis Res Ther*. (2007) 9 Suppl 2:S9. doi: 10.1186/AR2193

3. Emmi G, Vaglio A. The new look of classification criteria for systemic vasculitis. *Nat Rev Rheumatol*. (2023) 19:198–9. doi: 10.1038/S41584-023-00933-5

4. Pugh D, Karabayas M, Basu N, Cid MC, Goel R, Goodyear CS, et al. Large-vessel vasculitis. *Nat Rev Dis Primers*. (2022) 7:93. doi: 10.1038/s41572-021-00327-5

5. Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis. *Nat Rev Dis Primers*. (2020) 6:71. doi: 10.1038/s41572-020-0204-y

6. Perazzio SF, Andrade LEC, de Souza AWS. Understanding behçet's disease in the context of innate immunity activation. *Front Immunol*. (2020) 11:586558. doi: 10.3389/fimmu.2020.586558

7. Silva De Souza AW. Autoantibodies in systemic vasculitis. *Front Immunol*. (2015) 6:184. doi: 10.3389/fimmu.2015.00184

8. Savioli B, Torquato HFV, Paredes-Gamero EJ, Franco AFDV, Gigek CDO, Artigiani Neto R, et al. Effector CD4+ T-cell subsets in Takayasu arteritis-differences between the peripheral blood and the aorta. *Clin Exp Immunol*. (2024) 217:183–94. doi: 10.1093/CEI/UXAE046

9. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F F-SL, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. (2013) 65:1–11. doi: 10.1002/art.37715

10. De Souza AWS, Serrano De Lima C, Oliveira ACD, MaChado LSG, Pinheiro FAG, Hix S, et al. Homocysteine levels in Takayasu arteritis-A risk factor for arterial ischemic events. *J Rheumatol*. (2013) 40:303–8. doi: 10.3899/jrheum.121073

frontiers | Frontiers in Immunology

TYPE Brief Research Report
PUBLISHED 04 April 2025
DOI 10.3389/fimmu.2025.1574479

OPEN ACCESS

EDITED BY
Haner Direskeneli,
Marmara University, Türkiye

REVIEWED BY
Durga Prasanna Misra,
Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGI), India
Fatoş Önen,
Tınaztepe University, Türkiye

*CORRESPONDENCE
Alexandre Wagner Silva de Souza
alexandre_wagner@uol.com.br

RECEIVED 10 February 2025
ACCEPTED 13 March 2025
PUBLISHED 04 April 2025

CITATION
Zarur EB, Peron Filho F, de Oliveira AC, Keppeke GD, D'Almeida V and Silva de Souza AW (2025) Hyperhomocysteinemia in Takayasu arteritis—genetically defined or burden of the proinflammatory state? *Front. Immunol.* 16:1574479. doi: 10.3389/fimmu.2025.1574479

Hyperhomocysteinemia in Takayasu arteritis—genetically defined or burden of the proinflammatory state?

Eduarda Bonelli Zarur [1,2], Faustino Peron Filho [1], Allan Chiaratti de Oliveira [3], Gerson Dierley Keppeke [1,4], Vânia D'Almeida [5] and Alexandre Wagner Silva de Souza [1*]

[1]Rheumatology Division, Department of Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil, [2]Rheumatology Division, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, [3]Department of Pediatrics, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil, [4]Departamento de Ciencias Biomédicas, Facultad de Medicina, Universidad Católica del Norte, Coquimbo, Chile, [5]Department of Psychobiology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil

Takayasu arteritis (TAK) is associated with high plasma homocysteine (Hcy) and elevated Hcy predicts ischemic events. Thus, this study aims to compare the frequency of single-nucleotide polymorphisms (SNPs) of genes involved in Hcy metabolism between TAK and controls and analyze associations with Hcy levels, TAK features, and acute ischemic arterial events (AIAEs). A cross-sectional study was performed with 73 TAK patients and 71 controls. SNPs of genes involved in the Hcy metabolism, plasma Hcy, and risk factors were analyzed for hyperhomocysteinemia (HHcy), cardiovascular disease (CVD), and AIAEs. Patients presented a higher frequency of risk factors for CVD and HHcy. At least one AIAE was observed in 27 (37.0%) patients and one control. The frequency of the SNPs was similar between both groups, and there was no association between SNP carriage and AIAEs. TAK patients presented higher Hcy levels than controls (13.9 ± 5.6 μmol/L vs. 8.6 ± 4.0 μmol/L; $p < 0.001$), and patients carrying MTHFR677TT presented higher Hcy levels than those carrying MTHFR677CT (20.4 ± 7.8 μmol/L vs. 13.7 ± 5.2 μmol/L; $p = 0.02$) or MTHFR677CC (20.4 ± 7.8 μmol/L vs. 13.1 ± 4.7 μmol/L; $p = 0.009$). TAK was an independent risk factor for HHcy [odds ratio (OR) = 10.20; 95% confidence interval (95% CI): 4.16–25.00; $p < 0.001$], and in TAK, thiazide diuretic use was a risk factor for HHcy (OR = 11.61; 95% CI: 1.63–82.63; $p < 0.01$). In conclusion, TAK was a risk factor for HHcy but not related to SNPs in genes encoding Hcy metabolism enzymes. The burden of chronic inflammation and thiazide diuretics contribute to HHcy in TAK.

KEYWORDS

Takayasu Arteritis, hyperhomocysteinemia, cardiovascular disease, arterial inflammation, single nucleotide polymorphism, homocysteine, ischemic arterial events

Highlights

- Higher Hcy levels in TAK are not associated with SNPs in genes of Hcy metabolism.
- TAK and thiazide diuretics *are* independent risk factors for HHcy.
- MTHFR677TT carriage is associated with higher Hcy levels in TAK.
- Hcy and SNPs in Hcy metabolism are not associated with ischemic events in TAK.

Introduction

Takayasu arteritis (TAK) is a systemic large-vessel vasculitis affecting the aorta, its primary branches, and pulmonary arteries. TAK is a chronic disease affecting young individuals with a peak incidence around the third and fourth decades (1–3), and it is associated with high morbidity, which is especially due to cerebrovascular disease, cardiac ischemic events, and heart failure (4–6). Moreover, cardiomyopathy and ischemic stroke are the most frequent causes of death in TAK patients (7, 8) and a French study with 318 patients demonstrated that one-half of the patients will experience at least a vascular complication within 10 years after the diagnosis (9).

Homocysteine (Hcy) is an intermediate amino acid formed during the metabolism of the essential amino acid methionine. Genetic variants in enzymes involved in Hcy metabolism, nutritional deficiencies, medications such as proton pump inhibitor (PPI) and methotrexate (MTX), and comorbidities are some of the many causes of increased Hcy levels (10). Hyperhomocysteinemia (HHcy) is defined as Hcy levels higher than 10–15 µmol/L (11–13), but levels above 10 µmol/L are already associated with adverse outcomes (14, 15). The association between HHcy and cardiovascular events (CVEs) has long been demonstrated. However, its causal relation is yet to be confirmed (12, 15–18). A previous study from our group was the first to describe higher plasma Hcy levels in TAK patients compared to controls and its association with ischemic events in TAK (3). Afterward, Chen et al. confirmed the finding of higher Hcy levels in TAK patients, whereas, in contrast to our previous study, patients presenting active disease had higher Hcy levels than those in remission. In addition, higher Hcy levels were an independent risk factor for coronary artery stenosis ≥50% in TAK (19).

Although both studies have demonstrated higher Hcy levels in TAK, to date, no study has investigated factors leading to HHcy in this form of large-vessel vasculitis. Therefore, we aimed to compare the frequency of single-nucleotide polymorphisms (SNPs) of genes encoding proteins involved in the Hcy [i.e., methylenetetrahydrofolate reductase (MTHFR), methyltransferase (MTR), and methyltransferase reductase (MTRR)] and folate [i.e., reduced folate carrier (RCF-1)] metabolism pathways between patients with TAK and controls, as well as to analyze associations between Hcy levels with these SNPs, TAK features, and acute ischemic arterial events (AIAEs).

Materials and methods

Study design and participants

A cross-sectional study with a control group was performed. TAK patients under regular follow-up at the Universidade Federal de São Paulo Vasculitis Unit were recruited for the study. The enrollment started in July 2019, and the last patient was included in July 2023. TAK patients had to fulfill either the American College of Rheumatology 1990 criteria (20) or Ishikawa diagnostic criteria modified by Sharma (21). All participants had to be at least 18 years old and were excluded if they presented end-stage renal disease. Participants from the control group were recruited from non-relative companions of patients followed by the Vasculitis Outpatient Clinic. Controls were excluded if they had any systemic inflammatory or autoimmune disease.

Study assessments

The following data were recorded from both groups: demographic and anthropometric data; a previous history of AIAE; risk factors for cardiovascular disease (CVD) such as arterial hypertension (HTN), smoking status, diabetes mellitus, and sedentary lifestyle; known vitamin deficiencies or diseases related to vitamin deficiencies including atrophic gastritis, hypothyroidism, and alcoholism; history of chronic kidney disease and concomitant use of medications that may interfere with Hcy levels, e.g., MTX, PPI, nicotinic acid, and fibrates. The AIAEs analyzed were stroke and transient ischemic attack (TIA), myocardial infarction, angina pectoris, mesenteric angina, and peripheral ischemia according to established definitions (22–26). Study participants with less than 3 hours of aerobic exercise weekly for at least 2 months were considered to have a sedentary lifestyle (27). In the TAK group, we analyzed age at diagnosis, disease duration, and current therapy, while disease activity was evaluated by Kerr's criteria (28). Finally, laboratory data performed routinely by the patients (e.g., lipid and glycemic profiles, erythrocyte sedimentation rate, creatinine, B12 vitamin, and folic acid) were retrieved from medical records.

Laboratory tests

Briefly, blood sampling was performed by collecting 6 mL of peripheral blood in ethylenediaminetetraacetic acid (EDTA) tubes for DNA extraction and Hcy measurement. As previously reported, plasma Hcy was measured by high-performance liquid chromatography (29). The DNA was extracted using the *FlexiGene® DNA* (ref 51206, Qiagen®, Hilden, Germany) extraction kit, following the manufacturer's instructions. Gene fragments of interest were amplified by polymerase chain reaction (PCR) using the primers presented in Supplementary Table S1, with the *Phusion Flash High-fidelity PCR Master Mix®* (ref F-548

Thermo Fisher®, Waltham, MA, USA). Fragment sizes were confirmed by agarose gel. All reference sequences were extracted from the National Center for Biotechnology Information (NCBI) gene database (Supplementary Table S1). Finally, SNP sequencing was performed using the Sanger technique (30) with either the forward or reverse primer. The following SNPs and their respective genes of proteins involved in the Hcy and folate metabolism were evaluated in the study: C677T (rs1801133) and A1298C (rs1801131) in the *MTHFR* gene, A2756G (rs1805087) in the *MTR* gene, A66G (rs1801394) in the *MTRR* gene, and G80A (rs1051266) of the *SLC19A1* gene.

Statistical analysis

The sample size was estimated as 70 individuals in each group, and it was based on a possible difference of 25% in the MTHFRC677T SNP between TAK patients and controls. The alpha error was 5% with a power of 90%.

Categorical variables are presented by percentage and absolute number, while continuous variables are presented by mean ± (SD) or median [interquartile range (IQR)], according to the distribution. Categorical data were compared between groups by Fisher's exact test or chi-square test. Continuous data were compared by Student's t-test or Mann–Whitney U test, and the Kruskal–Wallis test or one-way ANOVA, according to the number of groups and variable distribution. The Mann–Whitney U test and Scheffe's test were performed for the *post-hoc* analysis of the Kruskal–Wallis and one-way ANOVA, respectively. Hcy was evaluated as a continuous variable as well as a categorical variable, with a cut-off of 10 µmol/L, according to previous studies (14, 17, 18). Two models of multivariate binary logistic regression were built to assess predictors of HHcy in all participants including the SNPs of genes involved in the Hcy and folate metabolism, TAK, and some risk factors for CVD and HHcy as independent variables. A third logistic regression model included only TAK patients, and its independent variables were HTN, anti-hypertensive drugs, and other drugs related to HHcy. Results are presented as an odds ratio (OR) with a 95% confidence interval (95% CI).

The Hardy–Weinberg equilibrium in analyzed genes was tested by the chi-square test with one degree of freedom with the R software version 4.3.2. Statistical analysis was performed using the IBM SPSS software for Windows v. 21.0 (Armonk, NY, USA), and graphs were built using the GraphPad Prism for Windows v. 9.0 (San Diego, CA, USA). A p-value of <0.05 was considered significant. For multiple *post-hoc* comparisons, the adjusted p-value was 0.01 according to Bonferroni's correction.

Results

Patients with TAK and controls

We included 144 participants in the study: 73 in the TAK group and 71 in the control group. Most of the participants were female in both groups (95.9% vs. 94.3%; $p = 0.67$), and the median age was also similar between TAK and controls [43.0 years (32.0–50.5) vs. 41.0 years (33.5–53.5); $p = 0.53$]. However, the groups differed in self-reported race, with a higher frequency of White persons in controls and Mestizos predominant among TAK patients ($p < 0.001$ and $p = 0.003$, respectively). The median time since TAK diagnosis was 120.0 months (48.0–204.0).

Patients with TAK showed a higher frequency of risk factors for CVD such as obesity (36.8% vs. 19.1%; $p = 0.02$), sedentary lifestyle (78.6% vs. 50.7%; $p = 0.001$), and HTN (82.2% vs. 11.6%; $p < 0.001$) than controls, whereas the frequencies of diabetes (12.3% vs. 10.1%; $p = 0.68$) and current smoking (5.5% vs. 1.4%; $p = 0.38$) were similar between both groups. Regarding the risk factors for HHcy, only TAK patients used MTX (24.7%), and more TAK patients used PPI than controls (38.4% vs. 4.3%; $p < 0.001$). However, no differences were found in the frequency of hypothyroidism (6.8% vs. 14.5%; $p = 0.14$) or metformin use (15.1% vs. 10.1%; $p = 0.14$).

Among protective factors for HHcy, only TAK patients were under acetylsalicylic acid (ASA) therapy (83.6%), while statin was more frequently used by TAK patients than controls (63.0% vs. 10.2%; $p = 0.001$). Folic acid was taken by 28.8% of TAK patients and 5.8% of the controls ($p < 0.001$). However, most of the TAK patients taking folic acid were also under MTX therapy. The use of B-complex vitamins was similar between the TAK patients and controls (2.7% vs. 4.3%; $p = 0.60$).

Twenty-seven (37.0%) patients experienced at least one AIAE, and most of them had angina pectoris (48.1%), stroke (25.9%), or myocardial infarction (22.2%). Abdominal angina was observed in only 14.8% of the patients, and one patient had a previous TIA. No cases of peripheral ischemia were observed. Only one AIAE (i.e., stroke) was found in the control group.

Homocysteine levels and TAK characteristics

Mean Hcy levels were significantly higher in TAK patients than in controls (13.9 ± 5.6 µmol/L vs. 8.6 ± 4.0 µmol/L; $p < 0.001$) (Figure 1A). Hyperhomocysteinemia (i.e., plasma Hcy >10 µmol/L) was observed in 82.5% of hypertensive patients with TAK, while only 53.8% of those without HTN presented HHcy ($p = 0.03$). Such a difference was not found in the control group. Furthermore, HHcy was more frequently presented in patients using hydrochlorothiazide than those without it (42.6% vs. 12.5%; $p = 0.003$), while no differences in Hcy levels were found regarding the use of other anti-hypertensive drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, hydralazine, and spironolactone, as well as statins or furosemide (Supplementary Table S3).

Patients with previous AIAEs had lower Hcy levels than those without [12.0 ± 4.6 µmol/L vs. 14.8 ± 5.9 µmol/L; $p = 0.04$), whereas there was no difference in the frequency of AIAEs between patients with and without HHcy (29.6% vs. 50.0%; $p = 0.13$). Finally, patients in remission tended to present lower Hcy levels than those with active disease [11.5 ± 5.3 µmol/L vs. 14.6 ± 5.6 µmol/L; $p = 0.05$].

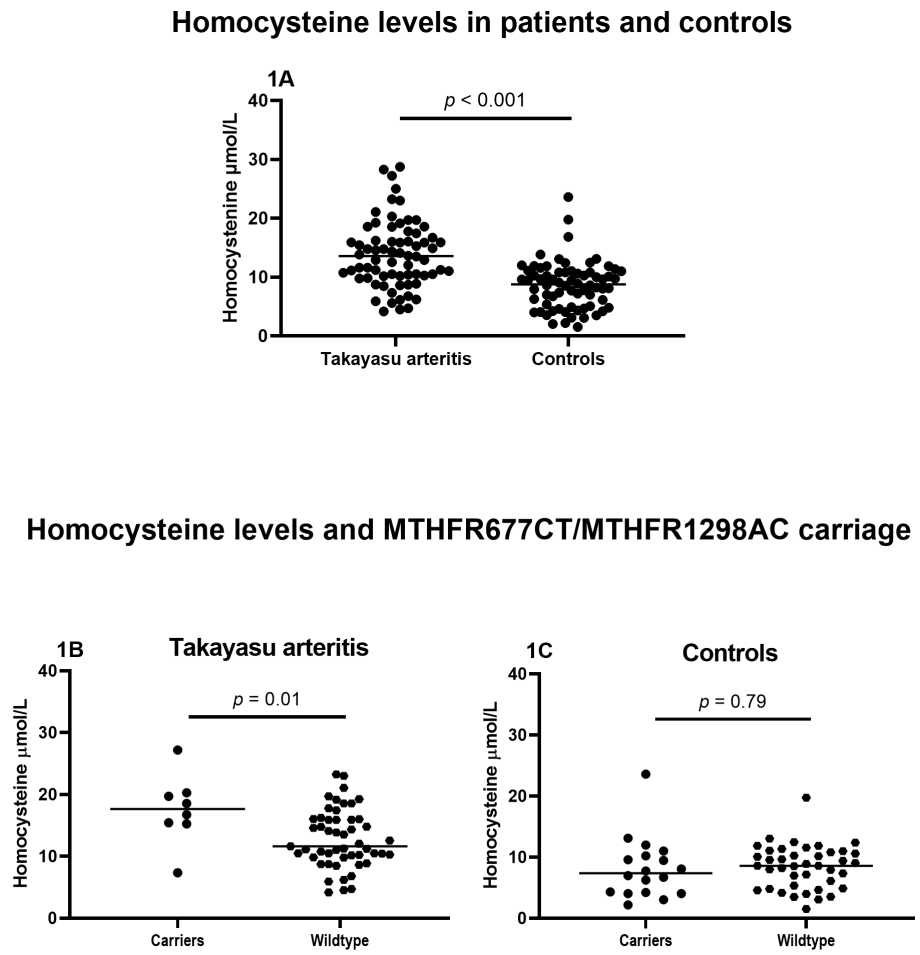


FIGURE 1
Plasma homocysteine levels among TAK patients and controls and according to different *MTHFR* genotypes. Legend: TAK, Takayasu arteritis. The transverse bar represents the mean concentration of homocysteine. **(A)** Homocysteine levels among patients and controls. **(B)** Homocysteine levels among patients carrying MTHFR677CT and MTHFR1298AC vs. wild type. **(C)** Homocysteine levels among controls carrying MTHFR677CT and MTHFR1298AC vs. wild types.

Genetic polymorphism frequencies and Hcy levels

In both groups, all genes encoding enzymes involved in Hcy metabolism were in Hardy–Weinberg equilibrium, while only in TAK patients was the *SLC19A1* gene encoding the protein reduced folate carrier-1 (RFC-1) not in Hardy–Weinberg equilibrium (x^2 = 6.829; p = 0.03). The frequencies of the SNPs of genes encoding enzymes involved in the Hcy (i.e., MTHFR, MTR, and MTRR) and folate (i.e., RCF-1) metabolic pathways were similar between TAK patients and controls (Table 1) and between TAK patients with and without previous AIAEs (Supplementary Table S4). Plasma Hcy levels were higher in patients carrying the MTHFR677TT genotype compared to the CT genotype (p = 0.02) and CC (p = 0.01) and among those carrying both *MTHFR* SNPs (i.e., *MTHFR* C677T and *MTHFR* A1298C) in heterozygosis compared to both *MTHFR* wild types (Figures 1B, C). Conversely, no difference was found in Hcy levels between all individual SNPs in controls (Table 2).

Analyses of predictors of HHcy

We built multivariate binary logistic regression analysis to assess predictors for HHcy, defined as Hcy levels higher than 10 µmol/L. The first model included the SNPs of genes involved in the Hcy and folate metabolism pathways and TAK. TAK increased 10 times the risk of presenting HHcy, regardless of the carriage of any of the individual SNPs. We performed another logistic regression model, including the genotype MTHFR677TT, some CVD and HHcy risk factors, and TAK. TAK persisted as an independent risk factor for HHcy in this model (Table 3). Since TAK was found to be an independent risk factor for HHcy, we performed a third multivariate binary logistic regression model including only TAK patients to analyze predictors for HHcy. In this model, HTN, anti-hypertensive drugs, and other drugs typically used for the treatment of TAK, which are known to interfere with plasma Hcy levels, were the independent variables. We found that thiazide diuretic use was the only predictor for HHcy in TAK patients, with an 11-fold increase in the risk of HHcy (Table 3).

10.3389/fimmu.2025.1574479

TABLE 1 The frequency of specific genotypes between TAK patients and controls.

Variables	TAK (n = 73)	Controls (n = 71)	*p*
MTHFR677TT	6 (8.3)	7 (10.1)	0.52
MTHFR677CT	32 (44.4)	36 (52.2)	
MTHFR677CC	34 (47.2)	26 (37.7)	
MTHFR1298CC	6 (8.5)	2 (4.0)	0.29
MTHFR1298AC	27 (38.0)	32 (45.7)	
MTHFR1298AA	38 (53.5)	36 (51.4)	
MTR2756GG	2 (2.8)	6 (8.8)	0.27
MTR2756AG	24 (33.3)	24 (35.3)	
MTR2756AA	46 (63.9)	38 (55.9)	
MTRR66GG	13 (20.3)	15 (21.1)	0.88
MTRR66AG	36 (56.3)	37 (52.1)	
MTRR66AA	19 (26.8)	15 (23.4)	
SLC19A1 80AA	9 (13.0)	13 (21.0)	0.39
SLC19A1 80AG	45 (65.2)	34 (54.8)	
SLC19A1 80GG	15 (21.7)	15 (24.2)	

There are a few missing values in different SNPs. Data presented as n (%).
TAK, Takayasu arteritis; MTHFR, methylenetetrahydrofolate reductase; MTR, methyltransferase; MTRR, methyltransferase reductase; SNPs, single-nucleotide polymorphisms; SLC19A1, solute carrier family 19 member 1; n, total number of participants in each group.

Discussion

This is the first study to address possible mechanisms involved in the HHcy described in TAK. Indeed, we confirm that HHcy is more frequently observed in TAK compared to those without TAK, and we identified TAK *per se* as an independent risk factor for HHcy, increasing its risk by 10-fold. Furthermore, among TAK patients, thiazide diuretic use was associated with an 11-fold increase in the risk of presenting HHcy. Nevertheless, we did not find differences regarding the frequency of Hcy and folate metabolism-related SNPs between TAK patients and controls, reinforcing that TAK-associated HHcy may be due to the pro-inflammatory state observed in TAK or therapy, but not genetically inherited.

In this study, traditional cardiovascular risk factors (e.g., obesity, smoking, sedentary lifestyle, and HTN) were more frequent among TAK patients. In line with our findings, previous studies detected a higher prevalence of HTN (27, 31–33), metabolic syndrome (27), and dyslipidemia (27) in TAK. A previous study from our group also found a higher prevalence of HTN and hypertriglyceridemia in TAK patients compared to controls. Still, the frequency of obesity and smoking was not higher in TAK. Indeed, other studies could not find an increased frequency of smoking or obesity in TAK (31, 32).

TAK patients present a higher frequency of CVE than the general population, and they represent the main cause of mortality in TAK (7, 34, 35). Nevertheless, the burden of risk factors for cardiovascular disease does not thoroughly explain the higher

TABLE 2 Homocysteine serum levels among different genotypes.

Hcy, µmol/L	Wild type	Heterozygous	Homozygous for the MAF	*p*
TAK				
MTHFR677	13.0 ± 4.7	13.7 ± 5.2	20.4 ± 7.8	0.01*
MTHFR1298	11.6 (9.8–15.9)	15.4 (10.8–18.6)	14.9 (9.3–22.3)	0.32
MTR2756	14.1 ± 5.7	13.8 ± 5.5	NA	NA
MTRR66	14.8 ± 5.1	13.4 ± 5.8	14.8 ± 5.4	0.58
SLC19A1	15.8 ± 5.7	13.5 ± 5.7	14.8 ± 4.0	0.37
Controls				
MTHFR677	8.5 ± 3.6	8.4 ± 4.3	8.7 ± 3.5	0.99
MTHFR1298	8.5 ± 3.5	8.7 ± 4.6	NA	NA
MTR2756	8.1 ± 4.0	8.8 ± 4.5	9.8 ± 3.1	0.61
MTRR66	7.5 ± 3.6	7.9 ± 2.9	10.0 ± 5.5	0.17
SLC19A1	8.8 ± 5.7	8.3 ± 3.8	8.0 ± 2.8	0.88

Results are presented as mean and standard deviation or as median and interquartile range.
Hcy, homocysteine; TAK, Takayasu arteritis; NA, not applicable; MAF, minor allele frequency; MTHFR, methylenetetrahydrofolate reductase; MTR, methyltransferase; MTRR, methyltransferase reductase; SLC19A1, solute carrier family 19 member 1.
*Flags significant results.

10.3389/fimmu.2025.1574479

TABLE 3 Binary logistic regression models for HHcy predictors.

Variables	OR	95% CI	*p*
Model 1			
TAK	10.20	4.16–25.00	<0.001*
MTHFR677TT	1.89	0.42–8.55	0.41
MTHFR1298CC	3.81	0.34–42.20	0.28
MTR2756GG	4.19	0.63–27.92	0.14
MTRR66GG	3.09	0.99–9.63	0.05
SLC19A1AA	1.46	0.48–4.46	0.50
Model 2			
TAK	4.28	1.40–13.03	0.01*
MTHFR677TT	2.08	0.50–8.61	0.31
HTN	2.03	0.60–6.84	0.25
Diabetes	0.81	0.23–2.87	0.74
Obesity	0.71	0.27–1.86	0.49
Hypothyroidism	0.50	0.13–1.89	0.31
Model 3			
Thiazide diuretics	11.61	1.63–82.63	0.01*
HTN	2.09	0.41–10.79	0.38
ACEi	4.67	0.68–32.12	0.12
Beta-blockers	0.37	0.08–1.60	0.18
ASA	0.11	0.01–1.10	0.06
PPI	1.99	0.51–7.71	0.32
MTX	1.56	0.36–6.78	0.56

ACEi, angiotensin-converting enzyme inhibitors; ASA, acetylsalicylic acid; HTN, hypertension; MTHFR, methylenetetrahydrofolate reductase; MTR, methyltransferase; MTRR, methyltransferase reductase; MTX, methotrexate; OR, odds ratio; PPI, proton pump inhibitor; SLC19A1, solute carrier family 19 member 1; SNP, single-nucleotide polymorphism; TAK, Takayasu arteritis; HHCy, hyperhomocysteinemia (i.e., Hcy > 10 µmol/L).
*Flags significant results.

frequency of CVE in TAK, and available risk estimation tools do not seem to estimate accurately cardiovascular risk in TAK as they estimate in the general population (31, 34, 35). Disease-related factors such as accelerated atherosclerosis, regardless of cardiovascular risk factors, arterial damage from previous inflammation, and Hata and Numano angiographic type V, seem to contribute to the CVE burden in TAK (31, 32, 34, 35).

Hyperhomocysteinemia has long been associated with cardiovascular events. However, its causal relationship is yet to be confirmed (12, 15–18). In this study, we confirm previous findings of higher Hcy levels in TAK patients (3, 19). In contrast to our results, previous studies had found an association between HHcy and acute ischemic events (3) and coronary artery involvement in TAK (19), while in the present study, patients with previous AIAEs had surprisingly lower Hcy levels than patients without AIAEs. The smaller sample size of the first study (N = 29) (3) compared to this one (N = 73) may have contributed to that different finding regarding ischemic events, and we speculate if the treatment required after a first CVE could contribute to lower Hcy levels. As for coronary involvement, we did not perform routinely coronary angiography or CTA to assess possible asymptomatic coronary involvement, and asymptomatic patients with coronary artery involvement may have been missed in our study (19). Nevertheless, Hcy levels higher than 10 µmol/L were not associated with an increased frequency of AIAEs in TAK patients, and only 16 patients presented Hcy levels equal to or lower than 10 µmol/L, which is the cut-off point already associated with higher adverse outcomes of HHcy (14, 15).

We observed that most hypertensive TAK patients presented HHcy. Similarly, previous studies have demonstrated that HHcy increases the risk of presenting HTN (17, 36) and that patients with HTN carrying the MTHFR677T allele had higher Hcy levels than those without HTN (17). Furthermore, a 5 µmol/L increase in plasmatic Hcy was associated with a 50% increase in HTN risk among women (37), and those patients who present HTN associated with Hcy levels >10 µmol/L are regarded as "H-HTN" (14, 38). However, other studies have failed to find associations between HHcy and increased risk of HTN (39, 40). Patients with H-HTN seem to have an increased risk of stroke (14, 36), and a mega trial including 20,000 Chinese hypertensive patients demonstrated that therapy with anti-hypertensive drugs associated with folic acid supplementation prevented primary neurovascular events (41).

In this study, we found a higher frequency of HHcy among patients treated with hydrochlorothiazide and that thiazide diuretic use was an independent risk factor for HHcy in TAK patients, increasing the risk by 11-fold. Indeed, it has been previously described that diuretics in general (42) and specifically hydrochlorothiazide (43, 44) use may increase Hcy plasma levels, while beta-blockers and angiotensin-converting enzyme (ACE) inhibitors have been associated with a reduction in Hcy levels (43, 44). In line with this, we observed that thiazide diuretics were the only antihypertensive agents interfering with plasma Hcy. One may argue that hydrochlorothiazide is usually the first-line agent prescribed as an antihypertensive treatment and that this could contribute as a confounding factor to the association of HHcy and thiazide diuretics, as well as between HHcy and HTN. Conversely, only 27 out of the 60 hypertensive patients analyzed in this study were treated with a thiazide diuretic. Moreover, in the multivariate analysis including HTN and thiazide diuretic use, the latter remained as the only predictor of HHcy. Thus, our study suggests that there may be an association between HHcy and thiazide diuretic use in TAK, and further studies are required to unravel if there is a causal relationship and if it is of clinical relevance.

The frequency of the genotypes was similar between TAK patients and controls, suggesting that TAK-associated HHcy is not due to genetic factors. Only in the TAK group were Hcy levels higher in patients presenting the MTHFR677 minor allele in homozygosis (i.e., MTHFR677TT) compared to other MTHFR677 genotypes, as well as in those carrying both *MTHFR* SNPs (i.e., *MTHFR* C677T and *MTHFR* C1298A) in heterozygosis compared to both wild types. One possible explanation for this finding is the folic acid fortification policy in Brazil, which possibly attenuates the HHcy observed by the

carriage of these SNPs (45). We speculate that TAK-associated HHcy mechanisms may overpower the effect of folic acid fortification, leading to higher Hcy levels upon MTHFR677 minor allele carriage in homozygosis. In line with that, we demonstrated that TAK *per se* independently increased 10 times the risk for HHcy. HHcy has long been associated with inflammatory states, but the mechanism through which it occurs remains poorly elucidated. One hypothesis is that the chronic inflammatory states would lead to a reduction in pyridoxal phosphate (PLP) bioavailability (i.e., the active form of vitamin B6) due to its recruitment to inflammatory sites. PLP has a role in reactions involving immunotolerance and modulation, suppression of inflammation, and proliferation of immune cells (46). The lower availability of PLP, which is a cofactor of cystathionine B-synthase (CBS), could lead to reduced activity of CBS, culminating in higher Hcy levels (47). It has been demonstrated in observational studies that IL-6 and IL-1ra levels were strongly and independently correlated with HHcy (48) and that IL-6 and PLP levels were negatively correlated (49). In addition, an intervention study with rheumatoid arthritis demonstrated that vitamin B6 supplementation was able to suppress IL-6 and TNF-alpha production (50).

Finally, it is of utmost importance to further explore the relationship between TAK, HHcy, HTN, thiazide diuretic use, and CVE, especially cerebrovascular events, in prospective studies due to the following reasons: CVEs are the main cause of mortality among TAK patients (7, 8), HHcy may be associated with CVE (12, 15–18), H-HTN increases the risk of stroke (14, 36), HTN is highly prevalent among TAK patients (27, 31–33), TAK is an independent risk factor for HHcy, and thiazide diuretic use is an independent risk factor for HHcy in TAK patients. Hence, HHcy may be a biomarker or act synergically with HTN to increase the cardiovascular risk in TAK. Stricter HTN treatment and HHcy-lowering interventions may be of benefit in preventing cerebrovascular events. It must be further investigated whether the thiazide diuretic's increment on Hcy levels is indeed clinically relevant to tailoring its use by plasma Hcy levels in TAK patients.

Our study has some limitations; first, its cross-sectional design impairs the inference of causality between HHcy and SNP carriage, thiazide diuretic use, or TAK status and features. Furthermore, some data were retrospectively collected through chart review and patient interviews, which may have been subject to recall bias. Moreover, the TAK criteria used to select patients were not uniform, and there was a significant difference in self-reported race between TAK patients and the control group, both of which could have influenced the results. Another limitation that should be acknowledged in this study is its relatively small sample size, which is commonly seen among TAK studies since it is a rare disease. However, the sample size estimated for the most common SNP (i.e., MTHFR677) was achieved. Finally, one of the studied genes was not in Hardy–Weinberg equilibrium among patients, which may also have influenced the results.

Our study confirms the higher Hcy levels presented by TAK patients. However, it refutes the association between HHcy and the carriage of SNPs of genes involved in Hcy and folate metabolism, and we speculate that it may possibly be due to the pro-inflammatory state of TAK patients. The TAK status increases the risk of HHcy, and among TAK patients, thiazide diuretic use and the carriage of the MTHFR677 minor allele are associated with a higher frequency of HHcy. Further studies are necessary to unravel these associations and to investigate the effect of folic acid supplementation on plasma Hcy levels in TAK patients, particularly those at higher risk for HHcy, such as those using thiazide diuretics.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitê de Ética em Pesquisa/UNIFESP. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

EZ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. FP: Data curation, Investigation, Methodology, Writing – review & editing. Ad: Methodology, Writing – review & editing. GK: Conceptualization, Data curation, Investigation, Methodology, Software, Supervision, Writing – review & editing. VD: Conceptualization, Formal Analysis, Methodology, Supervision, Validation, Writing – review & editing. AS: Conceptualization, Formal Analysis, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study was supported by Conselho Nacional de Desenvolvimento Científico (CNPq) grant number 425567/2018-4. Dr Alexandre Wagner Silva de Souza received support from CNPq (grant number 309133/2023-8).

Acknowledgments

The authors thank Prof. Dr. Caio Robledo Dángioli Costa Quaio, Profa. Dra. Christiane Pereira Gouveia, Profa. Dra Gleice Clemente Souza Russo, and Prof. Dr. Mauro Goldfarb for their suggestions, which helped improve the final manuscript. Finally, the authors thank Prof. João Pesquero, Beatriz Ribeiro Nogueira, and Joyce Pinto Yamamoto for their important contributions to the development of this work.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2025.1574479/full#supplementary-material

References

1. Vieira M, Ochtrop MLG, Sztajnbok F, Souto Oliveira Elias C, Verztman JF, Bica BERG, et al. The epidemiology of Takayasu arteritis in Rio de Janeiro, Brazil: A large population-based study. *J Clin Rheumatol.* (2023) 29:E100–3. doi: 10.1097/RHU.0000000000001964

2. Esatoglu SN, Hatemi G. Takayasu arteritis. *Curr Opin Rheumatol.* (2022) 34:18–24. doi: 10.1097/BOR.0000000000000852

3. De Souza AWS, Serrano De Lima C, Oliveira ACD, MaChado LSG, Pinheiro FAG, Hix S, et al. Homocysteine levels in takayasu arteritis-A risk factor for arterial ischemic events. *J Rheumatol.* (2013) 40:303–8. doi: 10.3899/jrheum.121073

4. Ucar AK, Ozdede A, Kayadibi Y, Adaletli I, Melikoglu M, Fresko I, et al. Increased arterial stiffness and accelerated atherosclerosis in Takayasu arteritis. *Semin Arthritis Rheum.* (2023) 60:1–9. doi: 10.1016/j.semarthrit.2023.152199

5. Duarte MM, Geraldes R, Sousa R, Alarcão J, Costa J. Stroke and transient ischemic attack in Takayasu's arteritis: A systematic review and meta-analysis. *J Stroke Cerebrovasc Dis.* (2016) 25:781–91. doi: 10.1016/j.jstrokecerebrovasdis.2015.12.005

6. De Souza AWS, de Carvalho JF. Diagnostic and classification criteria of Takayasu arteritis. *J Autoimmun.* (2014) 48–49:79–83. doi: 10.1016/j.jaut.2014.01.012

7. Laurent C, Prieto-González S, Belnou P, Carrat F, Fain O, Dellal A, et al. Prevalence of cardiovascular risk factors, the use of statins and of aspirin in Takayasu Arteritis. *Sci Rep.* (2021) 11:1–6. doi: 10.1038/s41598-021-93416-0

8. Jagtap S, Mishra P, Rathore U, Thakare DR, Singh K, Dixit J, et al. Increased mortality rate in Takayasu arteritis is largely driven by cardiovascular disease—a cohort study. *Rheumatology.* (2023) 63:3337–45. doi: 10.1093/rheumatology/kead584

9. Comarmond C, Biard L, Lambert M, Mekinian A, Ferfar Y, Kahn JE, et al. Long-term outcomes and prognostic factors of complications in Takayasu arteritis: a multicenter study of 318 patients. *Circulation.* (2017) 136:1114–22. doi: 10.1161/CIRCULATIONAHA.116.027094

10. González-Lamuño D, Arrieta-Blanco FJ, Fuentes ED, Forga-Visa MT, Morales-Conejo M, Peña-Quintana L, et al. Hyperhomocysteinemia in adult patients: A treatable metabolic condition. *Nutrients.* (2023) 16:135. doi: 10.3390/nu16010135

11. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: A statement for healthcare professionals from the American Heart Association/American Stroke Association council on stroke - Co-sponsored by the council on cardiovascular radiology and intervention. The American Academy of Neurology affirms the value of this guideline. *Stroke.* (2006) 37:577–617. doi: 10.1161/01.STR.0000199147.30016.74

12. Rehman T, Shabbir MA, Inam-Ur-Raheem M, Manzoor MF, Ahmad N, Liu ZW, et al. Cysteine and homocysteine as biomarker of various diseases. *Food Sci Nutr.* (2020) 8:4696–707. doi: 10.1002/fsn3.1818

13. Kumar A, Palfrey HA, Pathak R, Kadowitz PJ, Gettys TW, Murthy SN. The metabolism and significance of homocysteine in nutrition and health. *Nutr Metab (Lond).* (2017) 14:1–12. doi: 10.1186/s12986-017-0233-z

14. Li J, Jiang S, Zhang Y, Tang G, Wang Y, Mao G, et al. H-type hypertension and risk of stroke in chinese adults: A prospective, nested case–control study. *J Transl Int Med.* (2015) 3:171–8. doi: 10.1515/jtim-2015-0027

15. Smith AD, Refsum H. Homocysteine – from disease biomarker to disease prevention. *J Internal Med.* (2021) 290:826–54. doi: 10.1111/joim.v290.4

16. Martí-Carvajal AJ, Solà I, Lathyris D, Dayer M. Homocysteine-lowering interventions for preventing cardiovascular events. *Cochrane Database Syst Rev.* (2017) 2017:1–65. doi: 10.1002/14651858.CD006612.pub5

17. Al Hageh C, Alefishat E, Ghassibe-Sabbagh M, Platt DE, Hamdan H, Tcheroyan R, et al. Homocysteine levels, H-Hypertension, and the MTHFR C677T genotypes: A complex interaction. *Heliyon.* (2023) 9:1–9. doi: 10.1016/j.heliyon.2023.e16444

18. Miao L, Deng GX, Yin RX, Nie RJ, Yang S, Wang Y, et al. No causal effects of plasma homocysteine levels on the risk of coronary heart disease or acute myocardial infarction: A Mendelian randomization study. *Eur J Prev Cardiol.* (2021) 28:227–34. doi: 10.1177/2047487319894679

19. Chen S, Luan H, He J, Wang Y, Zeng X, Li Y, et al. The relationships of serum homocysteine levels and traditional lipid indicators with disease activity and coronary artery involvement in Takayasu arteritis. *Immunol Res.* (2020) 68:405–13. doi: 10.1007/s12026-020-09157-1

20. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American college of rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheumatol.* (1990) 33:1129–34. doi: 10.1002/art.1780330811

21. Sharma BK, Jain S, Suri S, Numano F. Diagnostic criteria for Takayasu arteritis. *Int J Cardiol.* (1996) 54:S141–7. doi: 10.1016/S0167-5273(96)88783-3

22. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Circulation.* (2012) 126:2020–35. doi: 10.1161/CIR.0b013e31826e1058

23. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: A statement from the AHA council on epidemiology and prevention. *Circulation.* (2003) 108:2543–9. doi: 10.1161/01.CIR.0000100560.46946.EA

24. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American heart association/American stroke association. *Stroke.* (2013) 44:2064–89. doi: 10.1161/STR.0b013e318296aeca

25. American Gastroenterological association. American Gastroenterological Association Medical Position Statement: Guidelines on Intestinal Ischemia. *Gastroenterology* (2000) 118:951–3. doi: 10.1016/s0016-5085(00)70182-x

26. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg.* (2007) 45(1 SUPPL):5–67. doi: 10.1016/j.jvs.2006.12.037

27. Da Silva TF, Maurício LN, Bonfá E, Pereira RMR. High prevalence of metabolic syndrome in takayasu arteritis: Increased cardiovascular risk and lower adiponectin serum levels. *J Rheumatol.* (2013) 40:1897–904. doi: 10.3899/jrheum.130162

28. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. *Ann Intern Med.* (1994) 120:919–29. doi: 10.7326/0003-4819-120-11-199406010-00004

29. Pfeiffer CM, Huff DL, Gunter EW. Rapid and accurate HPLC assay for plasma total homocysteine and cysteine in a clinical laboratory setting. *Clin Chem.* (1999) 45:290–2. doi: 10.1093/clinchem/45.2.290

30. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. *Proc Natl Acad Sci.* (1977) 74:5463–7. doi: 10.1073/pnas.74.12.5463

31. Alibaz-Oner F, Koster MJ, Unal AU, Yildirim HG, Çikikçi C, Schmidt J, et al. Assessment of the frequency of cardiovascular risk factors in patients with Takayasu's arteritis. *Rheumatol (United Kingdom).* (2017) 56:1939–44. doi: 10.1093/rheumatology/kex300

32. de Souza AWS, Ataíde Mariz H, Torres Reis Neto E, Diniz Arraes AE, Silva NP, Sato EI. Risk factors for cardiovascular disease and endothelin-1 levels in Takayasu arteritis patients. *Clin Rheumatol*. (2009) 28:379–83. doi: 10.1007/s10067-008-1056-0

33. dos Santos AM, Misse RG, Borges IBP, Gualano B, de Souza AWS, Takayama L, et al. Increased modifiable cardiovascular risk factors in patients with Takayasu arteritis: a multicenter cross-sectional study. *Adv Rheumatol*. (2021) 61:1–9. doi: 10.1186/s42358-020-00157-1

34. Kwon OC, Park JH, Park YB, Park MC. Disease-specific factors associated with cardiovascular events in patients with Takayasu arteritis. *Arthritis Res Ther*. (2020) 22:1–7. doi: 10.1186/s13075-020-02275-z

35. Clifford AH. Cardiovascular disease in large vessel vasculitis: risks, controversies, and management strategies. *Rheum Dis Clinics North America*. (2023) 49:81–96. doi: 10.1016/j.rdc.2022.08.004

36. Towfighi A, Markovic D, Ovbiagele B. Pronounced association of elevated serum homocysteine with stroke in subgroups of individuals: A nationwide study. *J Neurol Sci*. (2010) 298:153–7. doi: 10.1016/j.jns.2010.07.013

37. Lim U, Cassano PA. Homocysteine and blood pressure in the Third National Health and Nutrition Examination Survey, 1988-1994. *Am J Epidemiol*. (2002) 156:1105–13. doi: 10.1093/aje/kwf157

38. Qian XL, Cao H, Zhang J, Gu ZH, Tang WQ, Shen L, et al. The prevalence, relative risk factors and MTHFR C677T genotype of H type hypertension of the elderly hypertensives in Shanghai, China: a cross-section study: Prevalence of H type hypertension. *BMC Cardiovasc Disord*. (2021) 21:1–10. doi: 10.1186/s12872-021-02151-x

39. Wang Y, Chen S, Yao T, Li DQ, Wang YX, Li YQ, et al. Homocysteine as a risk factor for hypertension: A 2-year follow-up study. *PloS One*. (2014) 9:1–8. doi: 10.1371/journal.pone.0108223

40. Bowman TS, Gaziano JM, Stampfer MJ, Sesso HD. Homocysteine and risk of developing hypertension in men. *J Hum Hypertens*. (2006) 20:631–4. doi: 10.1038/sj.jhh.1002052

41. Xu X, Qin X, Li Y, Sun D, Wang J, Liang M, et al. Efficacy of folic acid therapy on the progression of chronic kidney disease: The renal substudy of the China stroke primary prevention trial. *JAMA Intern Med*. (2016) 176:1443–50. doi: 10.1001/jamainternmed.2016.4687

42. Morrow LE, Grimsley EW. Long-term diuretic therapy in hypertensive patients: effects on serum homocysteine, vitamin B6, vitamin B12, and red blood cell folate concentrations. *South Med J*. (1999) 92:866–70. doi: 10.1097/00007611-199909000-00003

43. Poduri A, Kaur J, Thakur JS, Kumari S, Jain S, Khullar M. Effect of ACE inhibitors and β-blockers on homocysteine levels in essential hypertension. *J Hum Hypertens*. (2008) 22:289–94. doi: 10.1038/sj.jhh.1002325

44. Westphal S, Rading A, Luley C, Dierkes J. Antihypertensive treatment and homocysteine concentrations. *Metabolism*. (2003) 52:261–3. doi: 10.1053/meta.2003.50060

45. Holmes MV, Newcombe P, Hubacek JA, Sofat R, Ricketts SL, Cooper J, et al. Effect modification by population dietary folate on the association between MTHFR genotype, homocysteine, and stroke risk: a meta-analysis of genetic studies and randomised trials. *Lancet*. (2011) 378:584–94. doi: 10.1016/S0140-6736(11)60872-6

46. Paul L, Ueland PM, Selhub J. Mechanistic perspective on the relationship between pyridoxal 5'-phosphate and inflammation. *Nutr Rev*. (2013) 71:239–44. doi: 10.1111/nure.2013.71.issue-4

47. McCarty MF. Increased homocyst(e)ine associated with smoking, chronic inflammation, and aging may reflect acute-phase induction of pyridoxal phosphatase activity. *Med Hypotheses*. (2000) 55:289–93. doi: 10.1054/mehy.1999.1032

48. Gori AM, Corsi AM, Fedi S, Gazzini A, Sofi F, Bartali B, et al. A proinflammatory state is associated with hyperhomocysteinemia in the elderly. *The American J Clin Nutr*. (2005) 82:1–3. doi: 10.1093/ajcn/82.2.335

49. Kiblawi R, Holowatyj AN, Gigic B, Brezina S, Geijsen AJMR, Ose J, et al. One-carbon metabolites, B vitamins and associations with systemic inflammation and angiogenesis biomarkers among colorectal cancer patients: Results from the ColoCare Study. *Br J Nutr*. (2020) 123:1187–200. doi: 10.1017/S0007114520000422

50. Huang SC, Wei JCC, Wu DJ, Huang YC. Vitamin B6 supplementation improves pro-inflammatory responses in patients with rheumatoid arthritis. *Eur J Clin Nutr*. (2010) 64:1007–13. doi: 10.1038/ejcn.2010.107

frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 30 April 2025
DOI 10.3389/fimmu.2025.1567293

OPEN ACCESS

EDITED BY
Alexandre Wagner Silva De Souza,
Federal University of São Paulo, Brazil

REVIEWED BY
Paweł Cieślik,
Medical University of Silesia, Poland
Renate Kain,
Medical University of Vienna, Austria

*CORRESPONDENCE
Ju Liu
ju.liu@sdu.edu.cn

RECEIVED 27 January 2025
ACCEPTED 09 April 2025
PUBLISHED 30 April 2025

CITATION
Zhang T, Li L, Huang S, Starodubtseva MN and Liu J (2025) Anti-endothelial cell antibodies in pathogenesis of vasculitis. *Front. Immunol.* 16:1567293. doi: 10.3389/fimmu.2025.1567293

Anti-endothelial cell antibodies in pathogenesis of vasculitis

Tian Zhang[1,2,3], Liqun Li[4], Shengshi Huang[1,2,3], Maria N. Starodubtseva[5,6] and Ju Liu[1,2,3]*

[1]Laboratory of Translational Medicine in Microvascular Regulation, Medical Research Center, The First Affiliated Hospital of Shandong First Medical University and Shandong Provincial Qianfoshan Hospital, Jinan, Shandong, China, [2]Shandong Provincial Key Medical and Health Laboratory of Translational Medicine in Microvascular Aging, The First Affiliated Hospital of Shandong First Medical University and Shandong Provincial Qianfoshan Hospital, Jinan, Shandong, China, [3]Laboraotry for Future Industry in Gene Editing in Vascular Endothelial Cells of Universities of Shandong Province, The First Affiliated Hospital of Shandong First Medical University and Shandong Provincial Qianfoshan Hospital, Jinan, Shandong, China, [4]Department of Clinical Laboratory, Qingdao Municipal Hospital, University of Health and Rehabilitation Sciences, Qingdao, Shandong, China, [5]Gomel State Medical University, Gomel, Belarus, [6]Institute of Radiobiology of NAS of Belarus, Gomel, Belarus

Vasculitis is a group of syndromes characterized by inflammation, presence of autoantibodies and endothelial cells (ECs) damage, which lead to stenosis or occlusion of the vascular lumen. Anti-endothelial cell antibodies (AECAs) are a heterogeneous group of autoantibodies in vasculitis. AECAs bind to antigens and membrane-bound proteins of ECs, inducing inflammation, coagulation, and apoptosis. In this review, we discuss the pathological role of AECAs in different types of vasculitis. In addition, AECAs potentially induce alterations of ECs mechanical properties, and subsequently promotes angiogenic phenotypes in the occurrence of vasculitis.

KEYWORDS

vasculitis, endothelial cells, anti-endothelial cell antibodies (AECAs), angiogenesis, mechanical properties, stiffness

Introduction

Vasculitis encompasses a spectrum of immune-mediated diseases marked by the immune system's aberrant attack on blood vessels in various body organs, such as the skin, lungs, and kidneys. This disorder is categorized based on the size of the affected blood vessel (1). In 2012, the Chapel Hill International Consensus Conferences established and standardized vasculitis nomenclature. The classification of vasculitis includes seven primary categories: large vessel vasculitis, medium vessel vasculitis, small vessel vasculitis, variable vessel vasculitis, single-organ vasculitis, vasculitis associated with systemic diseases, and vasculitis linked to probable etiology (2) (Table 1).

The occurrence of vasculitis typically precipitates vascular stenosis or occlusion, which in turn induces organ ischemia or contributes to the attenuation of blood vessel walls, thereby

TABLE 1 The classification of vasculitis.

Classification		Diseases
LVV		TAK, GCA
MVV		PAN, KD
SVV	AAV	MPA, GPA, EGPA
	Immune complex SVV	IgAV, anti-glomerular basement membrane disease, cryoglobulin vasculitis
VVV		BD, Cogan's syndrome
SOV	Diffuse SOV	Cutaneous polyarteritis nodosa, Cutaneous leukocytoclastic angiitis, Primary angiitis of the central-nervous system, Lower-limb-restricted polyarteritis nodosa
	Focal SOV	Localized vasculitis of the aorta, Vasculitis of the gastrointestinal tract, urogenital tract, breast, Retinal vasculitis, Muscular vasculitis
VASD		SLE, Sarcoidosis
VAPE		HCV-associated cryoglobulinemic vasculitis, HBV-associated vasculitis, Syphilis-associated aortitis, Drug-associated immune complex vasculitis, Drug-associated ANCA-associated vasculitis

This table summarizes the classification of vasculitis based on CHCC in 2012. LVV, large vessel vasculitis; GCA, giant cell arteritis; TAK, Takayasu's arteritis; MVV, medium vessel vasculitis; KD, kawasaki disease; SVV, small vessel vasculitis; AAV, anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiiti; IgAV, IgA vasculitis (Henoch-Schönlein); VASD, vasculitis associated with systemic disease; VAPE, vasculitis associated with probable etiology; VVV, variable vessel vasculitis; BD, Behçcet's disease; SLE, systemic lupus erythematosus; HCV, hepatitis C virus; SOV, single-organ vasculitis.

facilitating the formation of aneurysms or provoking hemorrhage. Central to this pathophysiological process is ECs injury, accompanied by the infiltration of leukocytes, which collectively underpin the common pathological mechanism inherent in such conditions (3). Contemporary research emphasizes the critical role of autoantibodies in the etiology of vasculitis. These autoantibodies in vasculitis predominantly target elements of the immune system or act directly against ECs (4–6). Anti-Endothelial Cell Antibodies (AECAs) are identified as one of the key autoantibodies in the context of vasculitis. These AECAs are often detected in patients diagnosed with vasculitis syndrome and are considered to be reliable indicators of both the activity and severity of the condition, as evidenced by various studies (7–10). AECAs have been identified in a spectrum of vasculitis disorders, encompassing Takayasu arteritis (TAK) (11), giant cell arteritis (GCA) (12), Kawasaki disease (KD) (13), granulomatosis with polyangiitis (GPA) (14), microscopic polyangiitis (MPA) (15), IgA vasculitis (IgAV) (16), Behçet's disease (BD) (17), systemic lupus erythematosus (SLE) (18), and sarcoidosis (19). The presence of AECAs in vasculitis highlights their potential role in the pathogenesis and clinical progression of vasculitis. The pathological mechanisms include activation of ECs, induction of coagulation and apoptosis. The above conditions in turn lead to angiogenesis and changes in the mechanical properties of ECs. In this review, we summarized our current understanding of the diverse mechanisms of AECAs in ECs dysfunction, highlighting the angiogenesis and cellular mechanics properties of AECAs in vasculitis.

AECAs characteristics

Antigen types

AECAs are circulating antibodies that recognize various antigenic determinants on ECs (20). Most scholars believe that AECAs' antigens are classified into three categories: "planted" antigens, constitutively expressed antigens, and cryptic antigens (21, 22).

"Planted" antigens adhere to the endothelium either directly, such as myeloperoxidase (MPO) and β2-glycoprotein I (β2-GPI), or indirectly adhere through DNA or DNA-histone complexes. Because of the presence of "planted" antigens, AECAs are capable cross-link with many autoantibodies (23). Constitutively expressed antigens include human leukocyte antigen (HLA) I antigens, cardiolipin, and other phospholipid components, as well as extracellular matrix components (24). HLA I antigens present on ECs represent some of the antigenic epitopes for AECAs. Cardiolipin and other phospholipid structures are some of the antigenic determinants for a subset of AECAs in vasculitis. In addition, different extracellular matrix components such as collagen type II, IV, VII, vimentin, tropomyosin, and laminin are also target antigens for AECAs (25). Cryptic antigens include HLA II antigen and proteinase 3 (PR3). HLA II and PR3 determinants are present only on activated ECs and represent target antigens for AECAs (26). Cytokine activation human umbilical vein endothelial cells (HUVECs) lead to PR3 translocation from the cytoplasm to the cell membrane. This is followed by the development of vasculitis in conjunction with AECAs.

Other antigens include α-enolase, heat shock protein (HSP) 60, HSP70, ribosomal P protein P0, calreticulin, and tubulin (27–29). Besides, adhesion molecules such as intercellular cell adhesion molecule-1 (ICAM-1) also serve as specific target antigens for AECAs (29) (Table 2). Numerous target antigens for AECAs in vasculitis have been studied, including HLA in Takayasu's arteritis and KD (30, 31), β2-GPI in GCA (32) and IgAV (33), DNA, PR3, MPO and phospholipid in anti-neutrophil cytoplasmic antibodies-associated vasculitis (34), HSP60, HSP70 in GCA and KD (35). However, the specific pathogenesis has not been elucidated (Table 2).

However, it is crucial to emphasize that AECAs exhibit cross-reactivity with multiple cell types, as their epitopes are expressed not only on ECs but also on fibroblasts, leukocytes, and monocytes (36). Although ECs models are commonly used in AECA studies, their biological properties differ from pathological targets. For example, HUVECs derive from embryonic umbilical veins. These cells exhibit distinct phenotypic features, including short-chain von Willebrand factor (vWF) multimers, compared to adult arterial or capillary ECs. This model-target mismatch causes discrepancies between experimental and clinical findings. Vascular bed heterogeneity influences AECAs targeting specificity. In sarcoidosis, AECAs react more strongly with bone marrow ECs than HUVECs. In BD, they show higher reactivity with omental microvascular ECs versus HUVECs. Conversely, in TAK, AECAs activate HUVECs but not microvascular ECs (23, 37). Additionally,

TABLE 2 The classification of AECAs target antigens.

Classification	Antigens	
"Planted"antigens	MPO	
	B2-GPI	
	DNA or DNA histone complexes	
Constitutively expressed antigens	HLA I antigens	
	Cardiolipin and other phospholipids components	
	Extracellular matrix components	collagen type II, IV, VI
		vimentin
		tropomyosin
		laminin
Cryptic antigens	HLA II antigen	
	PR3	
Other antigens	α-enolase	
	HSP60, HSP70	
	ribosomal P protein P0	
	CRT	
	tubulin	

This table summarizes the classification of AECAs target antigens. MPO, myeloperoxidase; β2-GPI, β2-glycoprotein I; HLA, human leukocyte; PR3, protease 3; HSP, heat shock protein; CRT, calreticulin.

epigenetic modifications (e.g., DNA methylation) in ECs show significant heterogeneity, potentially influencing antigen accessibility and immunogenicity. Furthermore, AECAs detection has limited diagnostic value in clinical practice. These antibodies lack a specific target antigen to guarantee immune specificity. Current detection methods show suboptimal accuracy and face technical challenges in standardization (38).

Pro-inflammatory effects

Under normal conditions, leukocytes race in laminar blood and do not adhere to ECs (39). As inflammation progresses, ECs produce tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, enhance the expression of ICAM-1, vascular cell adhesion molecule 1 (VCAM-1), and synthesize E-selectin, causing leukocytes to roll on ECs (40–43). E-selectin binds to leukocytes through their ligands and promotes leukocyte adhesion (44). There is evidence that AECAs bind to β2-GPI on the surface of ECs, up-regulating IL-1, TNF-α, ICAM-1, VCAM-1 and E-selectin, and increasing leukocyte adhesion to ECs (45–47). Leukocyte adhesion leads to endothelial dysfunction, decreased endothelium-dependent vasodilation, excessive capillary filtration, and increased protein leakage in venules (48) (Figure 1). The increased expression of AECAs mediates ECs injury and activates the nuclear factor-κB (NF-κB) signaling pathway (49). NF-κB activation occurs through the degradation of the inhibitor of NF-κB (IκB). The degradation of IκB requires the activation of IκB kinase (IKK) to phosphorylate IκB. IKK increases IκB degradation, leading to nuclear translocation of NF-κB subunit and NF-κB mediated expression of pro-inflammatory cytokines (50). Leukocyte adhesion is further promoted by up-regulating the expression of IL-1, TNF-α, ICAM-1, VCAM-1, and E-selectin (51–53) (Figures 1, 2).

Pro-coagulant effects

ECs have the function of maintaining blood flow and regulating blood coagulation (54). When ECs are damaged, coagulation becomes dysfunctional, leading to occlusive thrombosis, local tissue and organ necrosis (55). vWF and tissue factor (TF) are essential indicators of thrombosis caused by ECs injury (56–58). Evidence suggests that AECAs stimulate ECs to secrete vWF and its ultra-large polymers (ULvWF) (13, 56). ULvWF located on the surface of damaged ECs interacts with platelets (59). Platelets are activated by vWF and form thrombus with vWF and fibrin in damaged ECs. Activated platelets release P-selectin and promote the release of neutrophil extracellular trap (NET), comprising condensed chromatin and histone. Histone induce platelet aggregation and platelet accumulation (60, 61). In addition, the interaction between AECAs and ECs surface antigen leads to the production of tissue factor (TF), and TF activity is dose-dependent on the AECAs titer, contributing to thrombosis (13, 56, 62). In summary, AECAs binding to ECs promotes the release of vWF, ULvWF, and TF, causing inflammation and thrombosis (Figure 3).

Pro-apoptotic effects

At present, there are two ways to induce apoptosis: the mitochondrial pathway, also known as the endogenous pathway, activates caspase by regulating mitochondrial membrane permeability and releasing apoptosis-activating factors (63). The death receptor-mediated pathway activates caspase by combining extracellular death receptors and corresponding ligands (64, 65). Both pathways are characterized by caspase activation. The following evidence provides that how AECAs induce ECs apoptosis through two pathways (66) (Figure 2).

Mitochondrial pathway

Mitochondrial proteins such as heat shock protein 60 (HSP60) and nitric oxide (NO) mediate ECs apoptosis. HSP60 exists in mitochondria. 15% to 20% of HSP60 exists in the cytoplasm and forms a complex with Bax in the cytoplasm (67). When ECs are stressed or damaged, HSP60 is located on the plasma membrane and separated from Bax. With the decrease of HSP60, Bax moves from the cytoplasm to mitochondria and is accompanied by the release of cytochrome c, and apoptosis is triggered. As a result, apoptosis is initiated, HSP60 is released, and this, in turn, accelerates the activation of procaspase-3 (67). The abnormal

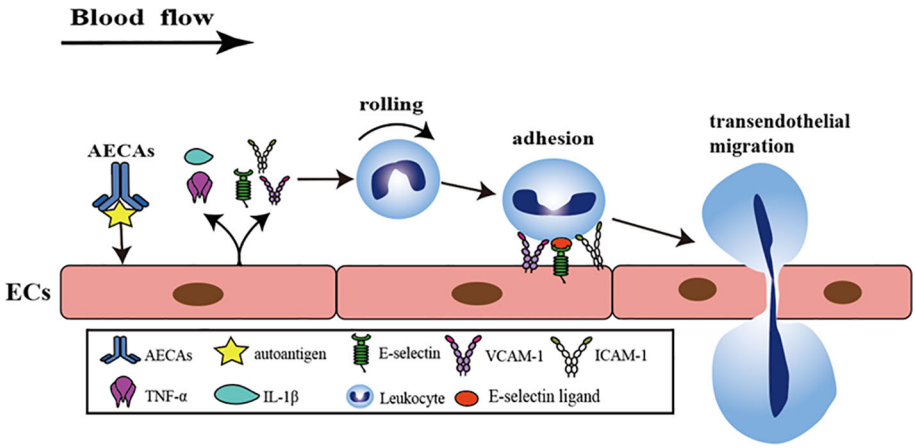


FIGURE 1
AECAs pro-inflammatory effects in ECs. AECAs bind to antigens on the surface of ECs and release IL-1β, TNF-α, E-selectin, ICAM-1, and VCAM-1 to promote leukocyte rolling. ICAM-1, VCAM-1, and E-selectin bind to leukocytes via ligands to promote adhesion and eventual leukocyte crossing of the endothelial gap (AECAs, anti-endothelial cell antibodies; ICAM-1, intercellular cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; IL-1β, Interleukin-1β; TNF-α, tumor necrosis factor-α).

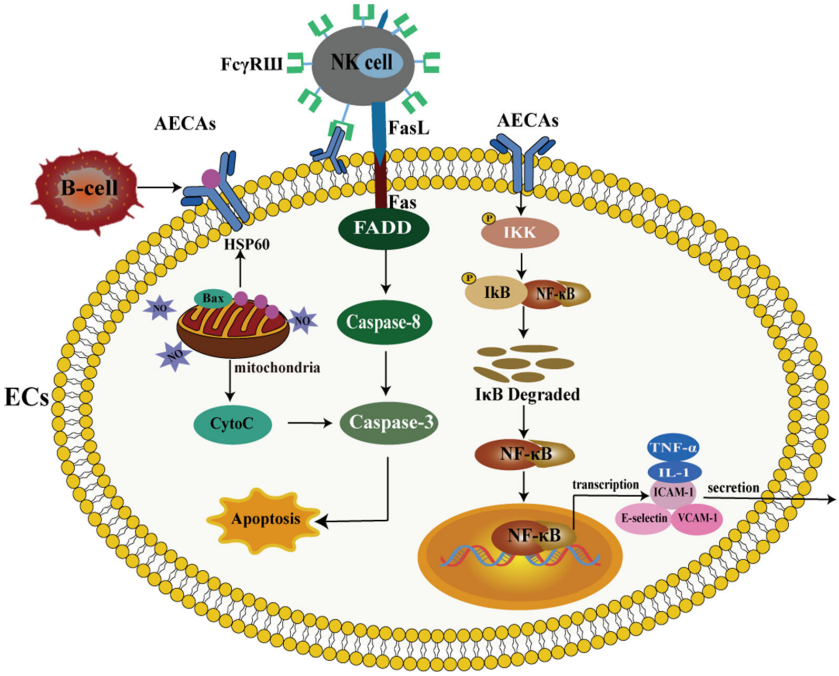


FIGURE 2
AECAs pro-apoptotic and pro-inflammatory effects in ECs. On the left, AECAs regulate mitochondrial pathway-mediated apoptosis through NO and HSP60 production. When ECs are injured, HSP60 is located on the plasma membrane and separated from Bax. With the decrease of HSP60, Bax moves from the cytoplasm to the mitochondria and is accompanied by the release of Cytoc, which activates caspase-3 and induces apoptosis in ECs. FcγRIII mediates NK cells, binds to AECAs and directly kills antibody-linked target cells. AECAs causes ECs apoptosis through Fas/FasL interaction. Upon binding of Fas to its cognate ligand FasL, Fas is recruited in the cytoplasm via the death domain of the intracellular FADD and caspase-8-associated Fas, forming a death-inducing signaling complex consisting of Fas, FADD and caspase-8, which activates caspase-3 and ultimately leads to apoptosis. On the right, AECAs interact with ECs antigens and activate IKK. Activated IKK phosphorylates IκB protein and induces ubiquitination and degradation of IκB, which subsequently leads to NF-κB activation. After NF-κB translocation into the nucleus, the expression of IL-1, TNF-α, ICAM-1 and VCAM-1 is upregulated (AECAs, anti-endothelial cell antibodies; ECs, endothelial cells; NO, nitric oxide; HSP60, heat shock protein 60; NK, Natural Killer; IκB, inhibitor of NF-κB; IKK, IκB Kinase; Fas, factor associated suicide; FasL, Fas ligand; FADD, Fas-associating protein with a novel death domain; IL-1, Interleukin-1; TNF-α, tumor necrosis factor-α; ICAM-1, intercellular cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1).

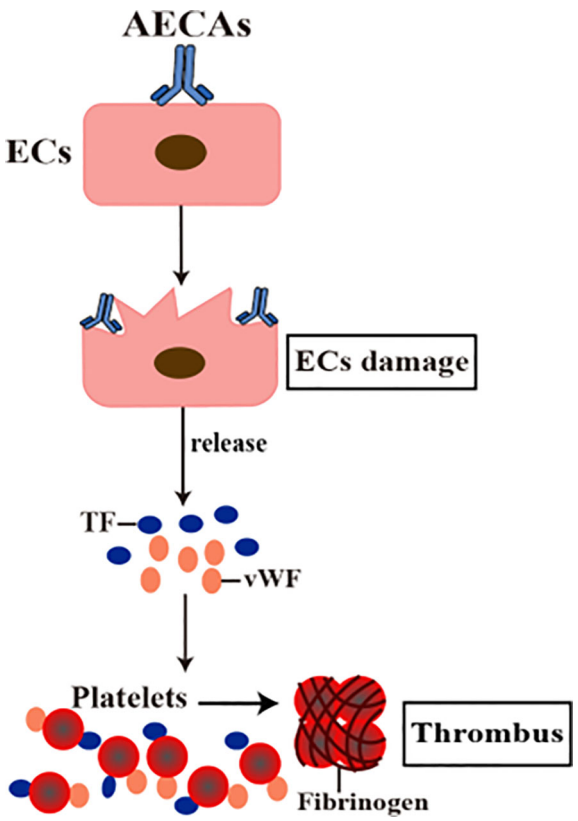


FIGURE 3
AECAs pro-coagulant effects in ECs. AECAs act on ECs, resulting in damage to ECs and release of coagulation factors such as vWF and TF. Platelets are activated by vWF and TF. Thrombus formation with vWF, TF and fibrinogen in damaged ECs (AECAs, anti-endothelial cell antibodies; ECs, endothelial cells; vWF, Von Willebrand factor; TF, tissue factor).

expression of HSP60 on the cytoplasmic membrane makes ECs susceptible to apoptosis (68). As a result, HSP60 dissociates from the plasma membrane and interacts with AECAs. Bax moves to mitochondria, leading to the release of cytochrome c and further activation of caspases-3, triggering apoptosis (69). Furthermore, ECs undergo apoptosis via the mitochondria-dependent pathway regulated by NO production (70). There is evidence that AECAs induce ECs apoptosis through a NO-mediated mechanism in dengue virus infection (66). NO-regulated ECs injury thus plays a role in disrupting ECs integrity and contributing to the pathogenesis of vasculopathy induced by AECAs. In conclusion, AECAs exert apoptosis by acting on ECs through the mitochondrial pathway via mitochondrial-associated proteins such as HSP60 and NO.

Fas/FasL pathway

AECAs contribute to the apoptosis of ECs through antibody-dependent cell-mediated cytotoxicity (ADCC), underscoring their role in the pathophysiological mechanisms affecting vascular integrity and function (71). Natural Killer (NK) cells are the mediators of ADCC. FcγRIII mediates on NK cells, binding to AECAs (72), and directly kills the target cells attached to the antibody. NK cells have two different cytotoxic mechanisms. The first is granule-mediated apoptosis, which depends on the synergistic effect of the perforin and serine protease granzymes (73). The other is factor-associated suicide (Fas)/Fas ligand (FasL) interaction mediated apoptosis (74). Existing research indicates that the granzyme A gene is expressed in systemic sclerosis, suggesting that granzyme mediates ECs injury (71), but whether AECAs are induced by granzyme A expression has not been functionally confirmed. A study has confirmed that AECAs induce apoptosis of human dermal microvascular ECs through Fas, while blocking anti-FasL antibodies inhibited ECs apoptosis (75). Therefore, AECAs may cause apoptosis of ECs through the Fas/FasL interaction. After Fas binds to its homologous ligand FasL, Fas recruits Fas-associated death domain (FADD) and caspase-8/10 in the cytoplasm through the death domain of the intracellular segment, forming a death-inducing signal complex composed of Fas, FADD and caspase-8/10, which activates caspases-3 and eventually leads to apoptosis (76, 77).

Pathological role of AECAs in vasculitis

In examining the pathological role of AECAs in vasculitis, it is imperative to acknowledge their pervasive presence across a multitude of vasculitic disorders. The function of AECAs extends beyond serving merely as biomarkers of disease; they play a pivotal role in the pathophysiology of disease development and progression (12, 78). We will delve into the specific roles of AECAs in various forms of vasculitis, as well as their impact on clinical manifestations of these diseases (as shown in Table 3).

Large vessel vasculitis

TAK is a chronic idiopathic granulomatous large-vessel vasculitis that affects the aorta, its main branches, and pulmonary arteries (79). Evidence has shown that AECAs are related to the pathogenesis of TAK (78). The positive rates of IgG and IgM AECAs in TAK patients were over 68%, and the titer of IgM AECA was higher (80). Study shows that most patients with TAK have circulating AECAs, which are directed predominantly to a triplet of aortic ECs antigens ranging in size from 60kD to 65kD. These AECAs induce the expression of VCAM-1 and E-selectin, as well as the production of inflammatory cytokines such as IL-4, IL-6, and IL-8 by aortic ECs, leading to the apoptosis of aortic ECs (81). Another study found that AECAs derived from a single patient with TAK were found to activate HUVEC, as shown by increased secretion of IL-6, vWF and increased expression of VCAM-1, ICAM-1, E-selectin, associated with NF-κB activation and increased adhesion of monocytes to these cells (82).

GCA, also known as temporal arteritis, is a primary systemic vasculitis involving large and medium vessels. However, with the

TABLE 3 The pathological role of AECAs in vasculitis.

Diseases	Pathological role
TAK	VCAM-1, ICAM-1, E-selectin, IL-4, IL-6, IL-8↑; NF-κB activation
GCA	–
KD	E-selectin, VCAM-1, ICAM-1, TNF-α, IL-6↑; NF-κB activation
GPA	MICA, VAP-1↑; SAPK/JNK, NF-κB activation
MPA	–
IgAV	ERK-1 phosphorylation, IL-8↑
BD	ICAM-1, ERK1, ERK2↑
Sarcoidosis	Fas/FasL signaling pathway
SLE	sE-selectin, sVCAM-1, endothelin-1↑

This table summarizes the vasculitis associated with AECAs as well as the pathological roles. TAK, Takayasu's arteritis; GCA, giant cell arteritis; KD, kawasaki disease; GPA, granulomatosis with polyangiiti; MPA, microscopic polyangiitis; IgAV, IgA vasculitis; BD, Behçcet's disease; SLE, systemic lupus erythematosus; ICAM-1, intercellular cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; IL-4, Interleukin-4; IL-6, Interleukin-6; IL-8, Interleukin-8; TNF-α, tumor necrosis factor-α; MICA, MHC class I-related antigen A; VAP-1, vascular adhesion protein-1; SAPK/JNK, stress-activated protein kinase/c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinases; Fas, factor associated suicide; FasL, Fas ligand.

advancement of vascular imaging technology, GCA is now considered to be a systemic disease beyond the superficial temporal artery, which causes large artery stenosis or aortic involvement (aortitis, aneurysm formation, or dissection) (83–86). A study has confirmed that IgG, IgM, and IgA AECA are positive in GCA patients, with IgA AECA is highly expressed, and IgG AECA plays a vital role in maintaining homeostasis (12).

Medium vessel vasculitis

KD is the most representative disease of medium vessel vasculitis. The research indicates that AECAs are related to KD pathogenesis and clinical diagnosis. E. Grunebaum (87) et al. confirmed that AECAs activated ECs, thereby increasing the secretion of IL-6, the expression of adhesion molecules such as E-selectin, VCAM-1, ICAM-1, and the adhesion of U937 cells to HUVECs. A study has found that the high expression of E-selectin in acute KD is related to the activation of NF-κB in vascular ECs and then increase the release of TNF-α (88). In conclusion, AECAs activate ECs through the NF-κB signaling pathway and increase the expression of cytokines such as IL-6, TNF-α and adhesion factors such as VCAM-1, ICAM-1, E-selectin, leading to impaired function of ECs, and participating in the pathogenesis of KD.

Small vessel vasculitis

GPA was formerly known as Wegener's granuloma, and is characterized by necrotizing vasculitis of small vessels and granulomatous inflammation (89). Current research has confirmed that AECAs are a critical factor in the pathogenesis of GPA. Many patients with GPA have AECAs that react with human kidney microvascular ECs. Stimulation of human kidney microvascular ECs with IgG AECA upregulated MHC class I -related antigen A (MICA) and vascular adhesion protein-1 (VAP-1) expression, triggered rapid Ca^{2+} flux, induced stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK), specific phosphorylation of transcription factor c-Jun and activating transcription factor-2, and activated NF-κB. However, specific SAPK/JNK inhibitors significantly reduced AECAs-induced chemokine production and phosphorylation of c-Jun and activating transcription factor-2 and eliminated MICA protein expression (14). Taken together, the elevated expression of AECAs mediates the pathogenesis of GPA and is associated with the SAPK/JNK pathway and the endothelial inflammatory protein VAP-1.

MPA is a systemic autoimmune necrotizing vasculitis. A reported study showed the presence of AECAs in patients with MPA and suggested a correlation between AECAs titer and disease activity (15). Régent et al. confirmed that purified serum IgG from patients with MPA induced extracellular regulated kinase (ERK) phosphorylation in ECs than IgG from healthy controls *in vitro*, which supports a possible pathogenic role of AECAs in MPA (90).

IgAV, also known as Henoch-Schönlein. IgAV is a type of vasculitis with IgA1-dominated immune deposits affecting small vessels (capillaries, veins or arterioles) (91). Studies found that AECAs are involved in the pathogenesis of IgAV. Yang YH (92) and Cynthia C (16)et al showed that AECAs were significantly elevated in patients with acute Henoch-Schönlein (16, 92). The mechanism of occurrence is related to the binding of AECAs to EC antigen, leading to ERK-1 phosphorylation, which activates protein-1 phosphorylation and promotes IL-8 expression (93).

Variable vessel vasculitis

BD is a variable-vessel vasculitis with a predominance of recurrent thrombophlebitis, thrombosis and cutaneous vasculitis (94). Direskeneli H (95) found a high rate of positive AECAs in patients with BD. AECAs are associated with disease activity in BD. Studies have found that AECAs positive sera from BD patients lead to changes in the expression of adhesion molecules on the cell surface of human dermal microvascular ECs (HDMECs) and promote the adherence of T lymphocytes to HDMECs and, thereby initiating or amplifying inflammatory vascular injury (96). IgM AECAs play a pathogenetic role in BD by activating ECs directly. In addition, extracellular signal-regulated kinases (ERK) 1 and 2 were involved in the expression of ICAM-1 on HDMECs stimulated by AECAs (97, 98). Although the exact pathogenesis of BD is still unknown, it seems that it involves at least three steps: activation of ECs, adhesion molecule expression, and lymphocyte adhesion. Activation of ECs facilitates leukocyte traffic and thus initiate an inflammatory injury.

Vasculitis associated with systemic disease

Sarcoidosis is an inflammatory disease characterized by granuloma (abnormal inflammatory cell mass) in almost all organs that usually affects the lungs, lymph nodes, skin, and eyes (99). Naoki Inui et al. showed that AECAs positive rate and AECAs level in sarcoidosis patients' serum and bronchoalveolar lavage fluid were significantly increased (20). Initial AECAs levels were further elevated in patients with multiple organ involvement or requiring glucocorticoid therapy. AECAs leading to ECs apoptosis were found to be mediating the pathogenesis of sarcoidosis (100). The mechanism induced by ADCC via Fas/FasL interactions (75). Taken together, AECAs induces ECs apoptosis through the Fas/FasL pathway, which is one of the pathological mechanisms in the development of sarcoid vasculitis.

SLE is a chronic autoimmune disease characterized by a multisystem disorder caused by immune dysregulation (101). Study confirms that AECAs are useful diagnostic and prognostic tools for SLE patients (102, 103). The expression of AECAs is increased at the initial stage of vascular injury in SLE. In SLE, AECAs demonstrate significant correlations with elevated serum concentrations of sE-selectin and sVCAM-1, mechanistically contributing to ECs activation through enhanced leukocyte adhesion and pro-inflammatory signaling (46, 104, 105). Notably, ribosomal P0 protein has been identified as an autoantigen recognized by AECAs, with its immunoreactivity showing specific association with SLE disease manifestations (106). Experimental evidence indicates that IgM-class AECAs co-localizing with immune complexes induce endothelial endothelin-1 overexpression, mediating the initiation and progression of microvascular injury in SLE patients (107). Furthermore, anti-phospholipid antibodies and AECAs exhibit functional cross-reactivity. Specific anti-annexin V antibodies bind to membrane-associated epitopes, inducing phosphatidylserine exposure and activating apoptotic pathways in ECs. These mechanisms are implicated in SLE-associated vascular pathology (29, 108).

Pathogenic mechanisms of AECAs in vasculitis

Angiogenesis

Angiogenesis in vasculitis is related to inflammatory factors secreted by ECs. Research has shown that in GCA, when a large amount of carriers of free hemoglobin with angiogenic properties are produced, the levels of TNF-α and IL-6 were increased. In GCA vasculopathy, leukocyte constitutive (PECAM-1, ICAM-1, ICAM-2, and P-selectin) and inducible (E-selectin and VCAM-1) ECs adhesion molecules are overexpressed by ECs of adventitial micro-vessels and neo-vessels (109–111). The interactions of leukocytes with these ligands are responsible for forming inflammatory infiltrates in GCA lesions (112). GCA is characterized by the release of pro-inflammatory cytokines such as IL-1, TNF-α, and IL-6 during the acute systemic phase (113), which influence vascular responses such as vessel occlusion or regeneration and participate in the pathogenesis of GCA inflammatory lesions (114). In KD, ECs of newly formed vessels in coronary aneurysms express E-selectinandVCAM-1, which is involved in leukocyte adhesion to ECs (115). In contrast, luminal ECs of coronary arteries without aneurysms do not express E-selectin and VCAM-1, such as ECs of newly formed vessels in polyarteritis nodosa and GCA (112). In conclusion, angiogenesis is involved in the occurrence and development of vasculitis. Newly formed blood vessels express leukocyte adhesion molecules, such as VCAM-1, ICAM-1, and E-selectin, providing a new location for leukocytes to invade the blood vessel wall (112). In addition, new vessels expand the surface of ECs, providing an additional source of cytokines and chemokines that amplify the inflammatory process (116).

Studies have shown that AECAs induce the activation of ECs and secretion of inflammatory cytokines such as IL-1β and TNF-α, coagulation factors such as vWF, and adhesion molecules such as ICAM-1, VCAM-1, E-selectin, leading to vascular inflammation and occlusion, and participating in the occurrence of vasculitis (117, 118). After AECAs induce vascular damage, minimal proliferation, fibrosis, and thrombosis lead to narrowing or occlusion of the vascular lumen, causing tissue hypoxia and ischemia. The hypoxia-ischemic environment resulting from vascular lumen stenosis or occlusion is a powerful signal for new angiogenesis, ultimately leading to angiogenesis (119).

Mechanical properties

Mechanical properties are significant for the normal functioning of ECs. They determine the integrity and mechanical stress resistance of an EC monolayer and regulate the functions of the endothelium under constant mechanical load from the side of the blood flow. Cells are known to be viscoelastic materials, and the origin of their mechanical properties is determined by the cytoskeleton (120). The cytoskeleton is a multi-hierarchical network structure within the cell with protein fibers as the main component, consisting of three types of protein fibers: actin filaments, tubulin microtubules, and a group of polymers known collectively as intermediate filaments. The cytoskeleton has several broad functions: it spatially organizes cellular contents; it connects the cell physically and biochemically to the external environment; it is involved in intracellular and extracellular transport and signal transduction; it generates coordinated forces that enable cells to move and change shape (121).

Several works reported cytoskeletal remodeling in response to the ligation of AECAs to ECs (122–125). Stimulation of ECs with HLA class I was revealed to activate stress fiber formation via a mechanism that did not include any detectable change in intracellular Ca^{2+} concentration, but induced Myosin light-chain phosphorylation and stress fiber assembly involving myosin light-chain (MLC) kinase and Rho-kinase (ROCK) in an ERK1/2-dependent manner. Molecular aggregation of HLA class I molecules with antibodies leads to the recruitment of integrin ß4 and the subsequent activation of intracellular signals that increase Rho-GTP activity, induce phosphorylation of ROCK, and trigger

the assembly and phosphorylation of focal adhesion kinase, Src and paxillin at the focal adhesions to stimulate actin reorganization (124). The ligation of HLA class II to ECs was shown to induce necrotic cell death via a mechanism of lysosomal membrane permeabilization involving the reorganization of the actin cytoskeleton and the formation of actin stress fibers. The effect was downregulated by the actin polymerization inhibitor cytochalasin D and inhibition of Rho GTPases (125). More early work revealed that autoantibodies from a subset of advanced type 2 diabetes activate ROCK, and induce stress fiber formation and apoptosis in ECs (122). Changes in the stiffness of ECs occur in vascular inflammation (126). The stress fiber formation can increase the EC stiffness by a factor of 2-10 (127).

The mechanical properties of ECs depend also on the mechanical properties of their environment. An increase in substrate rigidity correlates with an overall increase in EC stiffness and apparent viscosity that is associated with the reorganization of actin cytoskeleton. Conversely, the cells on the soft substrate were more deformable and less viscous that is related to actin disordering (128). Inflammation, as a pathological factor of vasculitis, leads to increased vascular stiffness, and vascular stiffness is correlated with the degree of inflammation (129, 130). Inflammatory mediators alter the mechanical properties and permeability of ECs (131, 132). ECs barrier protection mediators, such as prostaglandin (PG) E2, sphingosine 1-phosphate and PGI2, reduce EC stiffness and permeability (131, 133). AECAs bind to specific antigens on the ECs and support to the EC release of mediators such as ICAM-1 and TNF-α which increase EC stiffness and permeability, leading to ECs barrier impairment (126, 134).

Pro-inflammatory cytokines stimulate or inhibit the formation of actin cytoskeletal structures. EC stiffness increases when affected by TNF-α (135). The RhoA pathway regulates TNF-α-induced cytoskeleton rearrangement, leading to increased ECs permeability (134, 136). The RhoA/ROCK pathway can regulate vascular function because changes in the actin cytoskeleton are fundamental to vascular contraction and remodeling, inflammatory cell recruitment, and cell proliferation (137). RhoA has been extensively studied as a regulator of vascular leakage and leukocyte migration through the endothelium. RhoA signals through the activation of ROCK, which inhibits MLC phosphatase and induces the phosphorylation of MLC (p-MLC) (138, 139). This process enhances the formation of actin bundles, fibers, and stretched actin structures and promotes the loss of VE-cadherin mediated cell-cell contacts, leading to vascular leakage (140–142). However, whether AECAs activate the RhoA signaling pathway by binding to antigens on the ECs' surface and producing inflammatory factors, which leads to cytoskeletal rearrangement and increased cell stiffness and permeability, ultimately resulting in the development of vasculitis, has not been investigated and requires follow-up experiments for verification (Figure 4).

Despite the types of AECAs that are already known today (143, 144), there is little information about their specific antigens in ECs. Only a few antigens targeted by AECAs were identified in vasculitis (38). Among these antigens, some antigens are directly related to the cytoskeleton, such as tropomyosin and vimentin. Literature data show that tropomyosin regulates cell stiffness in a complex way via the generation of specific populations of actin filaments containing tropomyosin isoforms (145). Vimentin maintains cell mechanical properties, motility, adhesion, and other signaling pathways that protect against compressive stress and preserve mechanical integrity by enhancing cell elastic behavior (146). Several antigens, like peroxiredoxins and MPO, affect cytoskeletal activity. MPO induces actin cytoskeleton reorganization and affects mechanical stiffness, as found in human platelets (147). Peroxiredoxins interact with collapsing response mediator protein 2 that regulates microtubule structure, for example, during lymphocyte migration and neuronal development (148). Other molecular targets, like HSP60 are associated with mechanisms for regulating the functions and pathways of cell death, such as apoptosis, resulting in decreased arterial elasticity (69, 149, 150). A recent AFM study highlighted the vital role of microtubules in shaping ECs mechanics. It showed that the disruption of microtubules by exposing the cells to colchicine caused the cell to

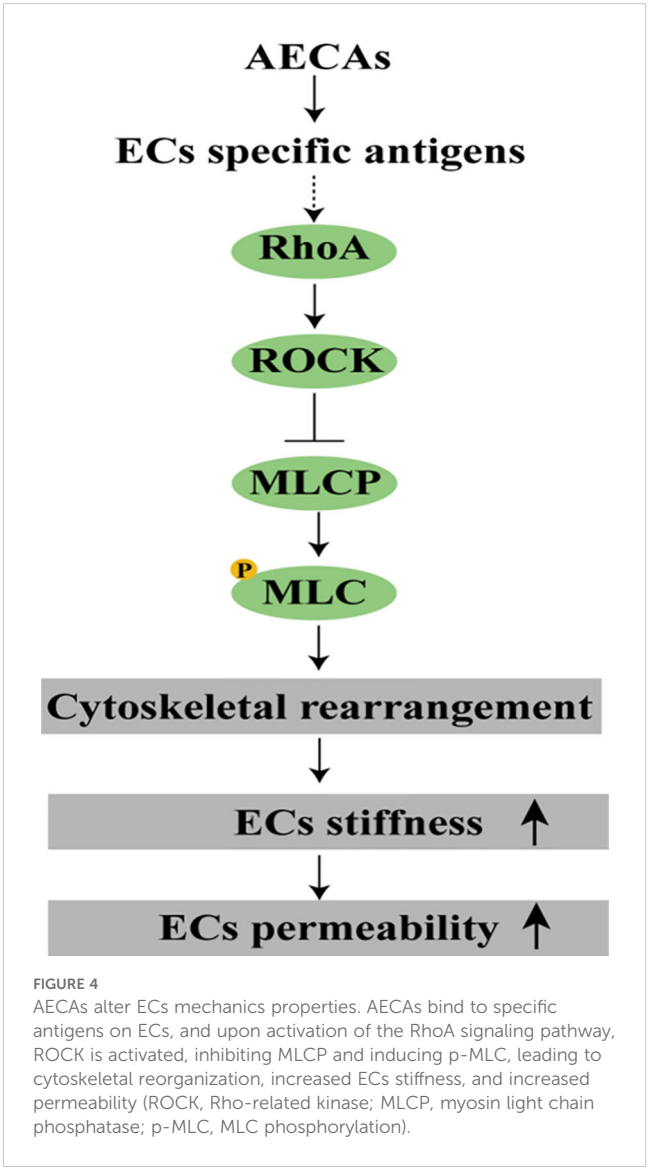


FIGURE 4
AECAs alter ECs mechanics properties. AECAs bind to specific antigens on ECs, and upon activation of the RhoA signaling pathway, ROCK is activated, inhibiting MLCP and inducing p-MLC, leading to cytoskeletal reorganization, increased ECs stiffness, and increased permeability (ROCK, Rho-related kinase; MLCP, myosin light chain phosphatase; p-MLC, MLC phosphorylation).

stiffen, the relaxation times increased, and the adhesion between the tip and cell decreased (151). Actin and vimentin cytoskeleton reorganization and cell stiffening have been recently detected in ECs after blocking CD109 antigen, a regulator of many signaling pathways, using anti-CD109 antibodies (152).

Conclusion

AECAs target diverse antigenic epitopes, including planted antigens, constitutively expressed surface molecules, and cryptic antigens exposed during cellular stress. These interactions can induce ECs injury through ADCC mechanisms. Additionally, AECAs exhibit pro-angiogenic properties and may alter ECs mechanical properties, such as cytoskeletal integrity and intercellular junction stability, thereby promoting vascular hyperpermeability. Collectively, these pathophysiological processes contribute to the pathogenesis of vasculitis. However, AECAs exhibit considerable heterogeneity in their prevalence across vasculitis, and the correlation between antibody titers and clinical disease activity remains inconsistent across studies. Current limitations in their clinical utility stem from suboptimal specificity and the absence of standardized detection protocols. Therefore, methodologically rigorous studies are required to establish reproducible assay systems for AECAs quantification. Such standardization is critical to elucidate the precise mechanistic roles of AECAs in vasculitis progression and to evaluate their potential as therapeutic targets or disease-monitoring biomarkers.

Author contributions

TZ: Conceptualization, Writing – review & editing, Writing – original draft. LL: Writing – review & editing. SH: Writing – review & editing. MS: Writing – review & editing. JL: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the National Nature Science Foundation of China (82241030,82171318 82011530024), Medical and Health Science and Technology Department Project of Shandong (202403020702), State Scientific Research Program "Natural Resources and the Environment"(3.01,2021-2025).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

References

1. Mishra K, Ramcharitar RK, Sharma AM. Vasculitis: when to consider this diagnosis? *Med Clinics North America*. (2023) 107:845–59. doi: 10.1016/j.mcna.2023.05.005

2. Jennette JC. Overview of the 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Clin Exp Nephrol*. (2013) 17:603–6. doi: 10.1007/s10157-013-0869-6

3. Morita T, Trés GFS, Criado RFJ, Sotto MN, Criado PR. Update on vasculitis: an overview and dermatological clues for clinical and histopathological diagnosis - part I. *An Bras Dermatologia*. (2020) 95:355–71. doi: 10.1016/j.abd.2020.01.003

4. Csernok E. The diagnostic and clinical utility of autoantibodies in systemic vasculitis. *Antibodies (Basel Switzerland)*. (2019) 8(2):31. doi: 10.3390/antib8020031

5. Segelmark M, Björck L. Streptococcal enzymes as precision tools against pathogenic igg autoantibodies in small vessel vasculitis. *Front Immunol*. (2019) 10:2165. doi: 10.3389/fimmu.2019.02165

6. Li W, Huang H, Cai M, Yuan T, Sheng Y. Antineutrophil cytoplasmic antibody-associated vasculitis update: genetic pathogenesis. *Front Immunol*. (2021) 12:624848. doi: 10.3389/fimmu.2021.624848

7. Christophe J, Christophe D, Jean-Eric A, Sandrine J, Alain S, Lo?C G, et al. Induction of endothelial cell apoptosis by the binding of anti-endothelial cell antibodies to hsp60 in vasculitis-associated systemic autoimmune diseases. *Arthritis Rheumatol*. (2014) 52:4028–38. doi: 10.1002/art.21401

8. Sebastian JK, Mahr AD, Ahmed SS, Stone JH, Zurina RP, Davis JC, et al. Antiendothelial cell antibodies in patients with wegener's granulomatosis: prevalence and correlation with disease activity and manifestations. *J Rheumatol*. (2007) 34:1027–31.

9. Karasawa R, Yudoh K, Ozaki S, Kato T. Anti-endothelial cell antibodies (Aeca) in patients with systemic vasculitis: our research using proteomics. *Expert Opin Biol Ther*. (2011) 11:77–87. doi: 10.1517/14712598.2011.540234

10. Guilpain P, Mouthon L. Antiendothelial cells autoantibodies in vasculitis-associated systemic diseases. *Clin Rev Allergy Immunol*. (2008) 35:59–65. doi: 10.1007/s12016-007-8069-3

11. Mutoh T, Shirai T, Ishii T, Shirota Y, Fujishima F, Takahashi F, et al. Identification of two major autoantigens negatively regulating endothelial activation in takayasu arteritis. *Nat Commun*. (2020) 11:1253. doi: 10.1038/s41467-020-15088-0

12. Régent A, Dib H, Ly KH, Agard C, Tamby MC, Tamas N, et al. Identification of target antigens of anti-endothelial cell and anti-vascular smooth muscle cell antibodies in patients with giant cell arteritis: A proteomic approach. *Arthritis Res Ther*. (2011) 13:R107. doi: 10.1186/ar3388

13. Sakurai Y. Autoimmune aspects of kawasaki disease. *J Investig Allergol Clin Immunol*. (2019) 29:251–61. doi: 10.18176/jiaci.0300

14. Holmén C, Elsheikh E, Christensson M, Liu J, Johansson AS, Qureshi AR, et al. Anti endothelial cell autoantibodies selectively activate sapk/jnk signalling in wegener's

granulomatosis. *J Am Soc Nephrol: JASN*. (2007) 18:2497–508. doi: 10.1681/asn.2006111286

15. Savage CO, Pottinger BE, Gaskin G, Lockwood CM, Pusey CD, Pearson JD. Vascular damage in wegener's granulomatosis and microscopic polyarteritis: presence of anti-endothelial cell antibodies and their relation to anti-neutrophil cytoplasm antibodies. *Clin Exp Immunol*. (1991) 85:14–9. doi: 10.1111/j.1365-2249.1991.tb05675.x

16. Patterson CC, Ross P Jr., Pope-Harman AL, Knight DA, Magro CM. Alpha-1 anti-trypsin deficiency and henoch-schönlein purpura associated with anti-neutrophil cytoplasmic and anti-endothelial cell antibodies of immunoglobulin-a isotype. *J Cutan Pathol*. (2005) 32:300–6. doi: 10.1111/j.0303-6987.2005.00304.x

17. Cho SB, Ahn KJ, Kim DH, Zheng Z, Cho S, Kang SW, et al. Identification of hnrnp-A2/B1 as a target antigen of anti-endothelial cell iga antibody in behçet's disease. *J Invest Dermatol*. (2012) 132:601–8. doi: 10.1038/jid.2011.397

18. van Paassen P, Duijvestijn A, Debrus-Palmans L, Damoiseaux J, Vroomen M, Tervaert JW. Induction of endothelial cell apoptosis by igg antibodies from sle patients with nephropathy: A potential role for anti-endothelial cell antibodies. *Ann New York Acad Sci*. (2007) 1108:147–56. doi: 10.1196/annals.1422.017

19. Domiciano DS, Carvalho JF, Shoenfeld Y. Pathogenic role of anti-endothelial cell antibodies in autoimmune rheumatic diseases. *Lupus*. (2009) 18:1233–8. doi: 10.1177/0961203309346654

20. Inui N, Matsui T, Suda T, Chida K. Anti-endothelial cell antibodies in patients with sarcoidosis. *Chest*. (2008) 133:955–60. doi: 10.1378/chest.07-0850

21. Del Papa N, Conforti G, Gambini D, La Rosa L, Tincani A, D'Cruz D, et al. Characterization of the endothelial surface proteins recognized by anti-endothelial antibodies in primary and secondary autoimmune vasculitis. *Clin Immunol Immunopathol*. (1994) 70:211–6. doi: 10.1006/clin.1994.1031

22. Belizna C, Tervaert JW. Specificity, pathogenecity, and clinical value of antiendothelial cell antibodies. *Semin Arthritis Rheum*. (1997) 27:98–109. doi: 10.1016/s0049-0172(97)80010-8

23. Shoenfeld Y. Classification of Anti-Endothelial Cell Antibodies into Antibodies against Microvascular and Macrovascular Endothelial Cells: The Pathogenic and Diagnostic Implications. *Cleve Clin J Med*. (2002) 69 Suppl 2:Sii65–7. doi: 10.3949/ccjm.69.suppl_2.sii65

24. Direskeneli H, D'Cruz D, Khamashta MA, Hughes GR. Autoantibodies against endothelial cells, extracellular matrix, and human collagen type iv in patients with systemic vasculitis. *Clin Immunol Immunopathol*. (1994) 70:206–10. doi: 10.1006/clin.1994.1030

25. Delunardo F, Scalzi V, Capozzi A, Camerini S, Misasi R, Pierdominici M, et al. Streptococcal-vimentin cross-reactive antibodies induce microvascular cardiac endothelial proinflammatory phenotype in rheumatic heart disease. *Clin Exp Immunol*. (2013) 173:419–29. doi: 10.1111/cei.12135

26. Sánchez-Zapardiel E, Mancebo E, Díaz-Ordoñez M, de Jorge-Huerta L, Ruiz-Martínez L, Serrano A, et al. Isolated *de novo* antiendothelial cell antibodies and kidney transplant rejection. *Am J Kidney Dis*. (2016) 68:933–43. doi: 10.1053/j.ajkd.2016.07.019

27. Hirohata S. Anti-ribosomal P antibodies and lupus nephritis. *Clin Exp Nephrol*. (2011) 15:471–7. doi: 10.1007/s10157-011-0462-9

28. Yazici ZA, Behrendt M, Cooper D, Goodfield M, Partridge L, Lindsey NJ. The identification of endothelial cell autoantigens. *J Autoimmun*. (2000) 15:41–9. doi: 10.1006/jaut.2000.0391

29. Dieudé M, Senécal JL, Raymond Y. Induction of endothelial cell apoptosis by heat-shock protein 60-reactive antibodies from anti-endothelial cell autoantibody-positive systemic lupus erythematosus patients. *Arthritis Rheum*. (2004) 50:3221–31. doi: 10.1002/art.20564

30. Wen X, Chen S, Li J, Li Y, Li L, Wu Z, et al. Association between genetic variants in the human leukocyte antigen-B/mica and takayasu arteritis in chinese han population. *Int J Rheum Dis*. (2018) 21:271–7. doi: 10.1111/1756-185x.13012

31. Bossi G, Mannarino S, Pietrogrande MC, Salice P, Dellepiane RM, Cremaschi AL, et al. Genetic epistasis between killer immunoglobulin-like receptors and human leukocyte antigens in kawasaki disease susceptibility. *Genes Immun*. (2015) 16:481–7. doi: 10.1038/gene.2015.34

32. Meyer O, Nicaise P, Moreau S, de Bandt M, Palazzo E, Hayem G, et al. Antibodies to cardiolipin and beta 2 glycoprotein I in patients with polymyalgia rheumatica and giant cell arteritis. *Rev Du Rhumatisme (English ed)*. (1996) 63:241–7.

33. Yang YH, Chang CJ, Chuang YH, Hsu HY, Yu HH, Lee JH, et al. Identification and characterization of iga antibodies against B2-glycoprotein I in childhood henoch-schönlein purpura. *Br J Dermatol*. (2012) 167:874–81. doi: 10.1111/j.1365-2133.2012.11068.x

34. Richard Kitching A, Anders H-J, Basu N, Brouwer E, Gordon J, David R, et al. Anca-associated vasculitis. *Nat Rev Dis Primers*. (2020) 6:72. doi: 10.1038/s41572-020-0212-y

35. López-Hoyos M, Alvarez L, Ruiz Soto M, Blanco R, José Bartolomé M, Martínez-Taboada VM. Serum levels of antibodies to chlamydia pneumoniae and human hsp60 in giant cell arteritis patients. *Clin Exp Rheumatol*. (2008) 26:1107–10.

36. Renaudineau Y, Revelen R, Levy Y, Salojin K, Gilburg B, Shoenfeld Y, et al. Anti-endothelial cell antibodies in systemic sclerosis. *Clin Diagn Lab Immunol*. (1999) 6:156–60. doi: 10.1128/cdli.6.2.156-160.1999

37. Renaudineau Y, Grunebaum E, Krause I, Praprotnik S, Revelen R, Youinou P, et al. Anti-endothelial cell antibodies (Aeca) in systemic sclerosis–increased sensitivity using different endothelial cell substrates and association with other autoantibodies. *Autoimmunity*. (2001) 33:171–9. doi: 10.3109/08916930109008045

38. Legendre P, Régent A, Thiebault M, Mouthon L. Anti-endothelial cell antibodies in vasculitis: A systematic review. *Autoimmun Rev*. (2017) 16:146–53. doi: 10.1016/j.autrev.2016.12.012

39. Kreuger J, Phillipson M. Targeting vascular and leukocyte communication in angiogenesis, inflammation and fibrosis. *Nat Rev Drug Discov*. (2016) 15:125–42. doi: 10.1038/nrd.2015.2

40. Kang S, Kishimoto T. Interplay between interleukin-6 signaling and the vascular endothelium in cytokine storms. *Exp Mol Med*. (2021) 53:1116–23. doi: 10.1038/s12276-021-00649-0

41. Chen JX, Huang XY, Wang P, Lin WT, Xu WX, Zeng M. Effects and mechanism of arachidonic acid against tnf-A Induced apoptosis of endothelial cells. *Clin Hemorheol Microcirc*. (2021) 77:259–65. doi: 10.3233/ch-200946

42. Bui TM, Wiesolek HL, Sumagin R. Icam-1: A master regulator of cellular responses in inflammation, injury resolution, and tumorigenesis. *J Leukoc Biol*. (2020) 108:787–99. doi: 10.1002/jlb.2mr0220-549r

43. Singh V, Kaur R, Kumari P, Pasricha C, Singh R. Icam-1 and vcam-1: gatekeepers in various inflammatory and cardiovascular disorders. *Clin Chim Acta*. (2023) 548:117487. doi: 10.1016/j.cca.2023.117487

44. Balta S. Endothelial dysfunction and inflammatory markers of vascular disease. *Curr Vasc Pharmacol*. (2021) 19:243–9. doi: 10.2174/1570161118666200421142542

45. Del Papa N, Raschi E, Moroni G, Panzeri P, Borghi MO, Ponticelli C, et al. Anti-endothelial cell igg fractions from systemic lupus erythematosus patients bind to human endothelial cells and induce a pro-adhesive and a pro-inflammatory phenotype *in vitro*. *Lupus*. (1999) 8:423–9. doi: 10.1177/096120339900800603

46. Carvalho D, Savage CO, Isenberg D, Pearson JD. Igg anti-endothelial cell autoantibodies from patients with systemic lupus erythematosus or systemic vasculitis stimulate the release of two endothelial cell-derived mediators, which enhance adhesion molecule expression and leukocyte adhesion in an autocrine manner. *Arthritis Rheum*. (1999) 42:631–40. doi: 10.1002/1529-0131(199904)42:4<631::Aid-anr5>3.0.Co;2-x

47. Meroni PL, D'Cruz D, Khamashta M, Youinou P, Hughes GR. Anti-endothelial cell antibodies: only for scientists or for clinicians too? *Clin Exp Immunol*. (1996) 104:199–202. doi: 10.1046/j.1365-2249.1996.20707.x

48. Krieglstein CF, Granger DN. Adhesion molecules and their role in vascular disease. *Am J Hypertens*. (2001) 14:44s–54s. doi: 10.1016/s0895-7061(01)02069-6

49. Lee KH, Cho HJ, Kim HS, Lee WJ, Lee S, Bang D. Activation of extracellular signal regulated kinase 1/2 in human dermal microvascular endothelial cells stimulated by anti-endothelial cell antibodies in sera of patients with behcet's disease. *J Dermatol Sci*. (2002) 30:63–72. doi: 10.1016/S0923-1811(02)00062-2

50. Prescott JA, Mitchell JP, Cook SJ. Inhibitory feedback control of nf-Kb signalling in health and disease. *Biochem J*. (2021) 478:2619–64. doi: 10.1042/bcj20210139

51. Mussbacher M, Salzmann M, Brostjan C, Hoesel B, Schoergenhofer C, Datler H, et al. Cell type-specific roles of nf-Kb linking inflammation and thrombosis. *Front Immunol*. (2019) 10:85. doi: 10.3389/fimmu.2019.00085

52. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C, et al. Inflammatory mechanisms contributing to endothelial dysfunction. *Biomedicines*. (2021) 9(7):781. doi: 10.3390/biomedicines9070781

53. Zhong L, Simard MJ, Huot J. Endothelial microrna regulating the nf-Kb pathway and cell adhesion molecules during inflammation. *FASEB J*. (2018) 32:4070–84. doi: 10.1096/fj.201701536R

54. Trimm E, Red-Horse K. Vascular endothelial cell development and diversity. *Nat Rev Cardiol*. (2023) 20:197–210. doi: 10.1038/s41569-022-00770-1

55. Schmaier AA, Anderson PF, Chen SM, El-Darzi E, Aivasovsky I, Kaushik MP, et al. Tmem16e regulates endothelial cell procoagulant activity and thrombosis. *J Clin Invest*. (2023) 133(11):e163808. doi: 10.1172/jci163808

56. Grover SP, Mackman N. Tissue factor: an essential mediator of hemostasis and trigger of thrombosis. *Arterioscler Thromb Vasc Biol*. (2018) 38:709–25. doi: 10.1161/atvbaha.117.309846

57. Shahidi M. Thrombosis and von willebrand factor. *Adv Exp Med Biol*. (2017) 906:285–306. doi: 10.1007/5584_2016_122

58. Manz XD, Bogaard HJ, Aman J. Regulation of vwf (Von willebrand factor) in inflammatory thrombosis. *Arterioscler Thromb Vasc Biol*. (2022) 42:1307–20. doi: 10.1161/atvbaha.122.318179

59. Chang JC. Disseminated intravascular coagulation: new identity as endotheliopathy-associated vascular microthrombotic disease based on *in vivo* hemostasis and endothelial molecular pathogenesis. *Thromb J*. (2020) 18:25. doi: 10.1186/s12959-020-00231-0

60. Martinod K, Wagner DD. Thrombosis: tangled up in nets. *Blood*. (2014) 123:2768–76. doi: 10.1182/blood-2013-10-463646

61. Etulain J, Martinod K, Wong SL, Cifuni SM, Schattner M, Wagner DD. P-selectin promotes neutrophil extracellular trap formation in mice. *Blood*. (2015) 126:242–6. doi: 10.1182/blood-2015-01-624023

62. Shenkman B, Budde U, Angerhaus D, Lubetsky A, Savion N, Seligsohn U, et al. Adamts-13 regulates platelet adhesion under flow. A new method for differentiation between inherited and acquired thrombotic thrombocytopenic purpura. *Thromb Haemost*. (2006) 96:160–6.

63. Bock FJ, Tait SWG. Mitochondria as multifaceted regulators of cell death. *Nat Rev Mol Cell Biol*. (2020) 21:85–100. doi: 10.1038/s41580-019-0173-8

64. Xie J, Li B, Yao B, Zhang P, Wang L, Lu H, et al. Transforming growth factor-B1-regulated fas/fasl pathway activation suppresses nucleus pulposus cell apoptosis in an inflammatory environment. *Biosci Rep*. (2020) 40(2):BSR20191726. doi: 10.1042/bsr20191726

65. Qian QZ, Cao XK, Liu HY, Zheng GY, Qian QQ, Shen FH. Tnfr/tnf-A Signaling pathway regulates apoptosis of alveolar macrophages in coal workers' Pneumoconiosis. *Oncotarget*. (2018) 9:1302–10. doi: 10.18632/oncotarget.18921

66. Lin YS, Lin CF, Lei HY, Liu HS, Yeh TM, Chen SH, et al. Antibody-mediated endothelial cell damage via nitric oxide. *Curr Pharm Des*. (2004) 10:213–21. doi: 10.2174/1381612043453469

67. Gupta S, Knowlton AA. Hsp60, bax, apoptosis and the heart. *J Cell Mol Med*. (2005) 9:51–8. doi: 10.1111/j.1582-4934.2005.tb00336.x

68. Alard JE, Dueymes M, Youinou P, Jamin C. Modulation of endothelial cell damages by anti-hsp60 autoantibodies in systemic autoimmune diseases. *Autoimmun Rev*. (2007) 6:438–43. doi: 10.1016/j.autrev.2007.01.012

69. Jamin C, Dugué C, Alard JE, Jousse S, Saraux A, Guillevin L, et al. Induction of endothelial cell apoptosis by the binding of anti-endothelial cell antibodies to hsp60 in vasculitis-associated systemic autoimmune diseases. *Arthritis Rheum*. (2005) 52:4028–38. doi: 10.1002/art.21401

70. Morikawa Y, Shibata A, Okumura N, Ikari A, Sasajima Y, Suenami K, et al. Sibutramine provokes apoptosis of aortic endothelial cells through altered production of reactive oxygen and nitrogen species. *Toxicol Appl Pharmacol*. (2017) 314:1–11. doi: 10.1016/j.taap.2016.11.003

71. Kahaleh MB, Fan PS. Mechanism of serum-mediated endothelial injury in scleroderma: identification of a granular enzyme in scleroderma skin and sera. *Clin Immunol Immunopathol*. (1997) 83:32–40. doi: 10.1006/clin.1996.4322

72. Holt CM, Lindsey N, Moult J, Malia RG, Greaves M, Hume A, et al. Antibody-dependent cellular cytotoxicity of vascular endothelium: characterization and pathogenic associations in systemic sclerosis. *Clin Exp Immunol*. (1989) 78:359–65.

73. Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: function, dysfunction and human pathology. *Nat Rev Immunol*. (2015) 15:388–400. doi: 10.1038/nri3839

74. Cruz-Muñoz ME, Valenzuela-Vázquez L, Sánchez-Herrera J, Santa-Olalla Tapia J. From the "Missing self" Hypothesis to adaptive nk cells: insights of nk cell-mediated effector functions in immune surveillance. *J Leukoc Biol*. (2019) 105:955–71. doi: 10.1002/jlb.Mr0618-224rr

75. Sgonc R, Gruschwitz MS, Boeck G, Sepp N, Gruber J, Wick G. Endothelial cell apoptosis in systemic sclerosis is induced by antibody-dependent cell-mediated cytotoxicity via cd95. *Arthritis Rheum*. (2000) 43:2550–62. doi: 10.1002/1529-0131(200011)43:11<2550::Aid-anr24>3.0.Co;2-h

76. Jimbo H, Nagai H, Fujiwara S, Shimoura N, Nishigori C. Fas-fasl interaction in cytotoxic T cell-mediated vitiligo: the role of lesional expression of tumor necrosis factor-A and interferon-Γ in fas-mediated melanocyte apoptosis. *Exp Dermatol*. (2020) 29:61–70. doi: 10.1111/exd.14053

77. Wang M, Su P. The role of the fas/fasl signaling pathway in environmental toxicant-induced testicular cell apoptosis: an update. *Syst Biol Reprod Med*. (2018) 64:93–102. doi: 10.1080/19396368.2017.1422046

78. Wang H, Ma J, Wu Q, Luo X, Chen Z, Kou L. Circulating B lymphocytes producing autoantibodies to endothelial cells play a role in the pathogenesis of takayasu arteritis. *J Vasc Surg*. (2011) 53:174–80. doi: 10.1016/j.jvs.2010.06.173

79. Joseph G, Goel R, Thomson VS, Joseph E, Danda D. Takayasu arteritis: jacc focus seminar 3/4. *J Am Coll Cardiol*. (2022) S0735-1097(22)07305-3. doi: 10.1016/j.jacc.2022.09.051

80. Park MC, Park YB, Jung SY, Lee KH, Lee SK. Anti-endothelial cell antibodies and antiphospholipid antibodies in takayasu's arteritis: correlations of their titers and isotype distributions with disease activity. *Clin Exp Rheumatol*. (2006) 24:S10–6.

81. Chauhan SK, Tripathy NK, Nityanand S. Antigenic targets and pathogenicity of anti-aortic endothelial cell antibodies in takayasu arteritis. *Arthritis Rheum*. (2006) 54:2326–33. doi: 10.1002/art.21921

82. Blank M, Krause I, Goldkorn T, Praprotnik S, Livneh A, Langevitz P, et al. Monoclonal anti-endothelial cell antibodies from a patient with takayasu arteritis activate endothelial cells from large vessels. *Arthritis Rheum*. (1999) 42:1421–32. doi: 10.1002/1529-0131(199907)42:7<1421::Aid-anr16>3.0.Co;2-o

83. Muratore F, Kermani TA, Crowson CS, Green AB, Salvarani C, Matteson EL, et al. Large-vessel giant cell arteritis: A cohort study. *Rheumatol (Oxford England)*. (2015) 54:463–70. doi: 10.1093/rheumatology/keu329

84. de Boysson H, Daumas A, Vautier M, Parienti JJ, Liozon E, Lambert M, et al. Large-vessel involvement and aortic dilation in giant-cell arteritis. A multicenter study of 549 patients. *Autoimmun Rev*. (2018) 17:391–8. doi: 10.1016/j.autrev.2017.11.029

85. van der Geest KSM, Sandovici M, Brouwer E, Mackie SL. Diagnostic accuracy of symptoms, physical signs, and laboratory tests for giant cell arteritis: A systematic review and meta-analysis. *JAMA Internal Med*. (2020) 180:1295–304. doi: 10.1001/jamainternmed.2020.3050

86. Saadoun D, Vautier M, Cacoub P. Medium- and large-vessel vasculitis. *Circulation*. (2021) 143:267–82. doi: 10.1161/circulationaha.120.046657

87. Grunebaum E, Blank M, Cohen S, Afek A, Kopolovic J, Meroni PL, et al. The role of anti-endothelial cell antibodies in kawasaki disease - *in vitro* and *in vivo* studies. *Clin Exp Immunol*. (2002) 130:233–40. doi: 10.1046/j.1365-2249.2002.02000.x

88. Suzuki Y, Ichiyama T, Ohsaki A, Hasegawa S, Shiraishi M, Furukawa S. Anti-inflammatory effect of 1alpha,25-dihydroxyvitamin D(3) in human coronary arterial endothelial cells: implication for the treatment of kawasaki disease. *J Steroid Biochem Mol Biol*. (2009) 113:134–8. doi: 10.1016/j.jsbmb.2008.12.004

89. Puéchal X. Granulomatosis with polyangiitis (Wegener's). *Joint Bone Spine*. (2020) 87:572–8. doi: 10.1016/j.jbspin.2020.06.005

90. Régent A, Lofek S, Dib H, Bussone G, Tamas N, Federici C, et al. Identification of target antigens of anti-endothelial cell antibodies in patients with anti-neutrophil cytoplasmic antibody-associated vasculitides: A proteomic approach. *Clin Immunol (Orlando Fla)*. (2014) 153:123–35. doi: 10.1016/j.clim.2014.03.020

91. Pillebout E, Sunderkötter C. Iga vasculitis. *Semin Immunopathol*. (2021) 43:729–38. doi: 10.1007/s00281-021-00874-9

92. Yang YH, Wang SJ, Chuang YH, Lin YT, Chiang BL. The level of iga antibodies to human umbilical vein endothelial cells can be enhanced by tnf-alpha treatment in children with henoch-schönlein purpura. *Clin Exp Immunol*. (2002) 130:352–7. doi: 10.1046/j.1365-2249.2002.01964.x

93. Yang YH, Huang YH, Lin YL, Wang LC, Chuang YH, Yu HH, et al. Circulating iga from acute stage of childhood henoch-schönlein purpura can enhance endothelial interleukin (Il)-8 production through mek/erk signalling pathway. *Clin Exp Immunol*. (2006) 144:247–53. doi: 10.1111/j.1365-2249.2006.03076.x

94. Alibaz-Oner F, Direskeneli H. Update on the diagnosis of behçet's disease. *Diagn (Basel Switzerland)*. (2022) 13(1):41. doi: 10.3390/diagnostics13010041

95. Direskeneli H, Keser G, D'Cruz D, Khamashta MA, Akoğlu T, Yazici H, et al. Anti-endothelial cell antibodies, endothelial proliferation and von willebrand factor antigen in behçet's disease. *Clin Rheumatol*. (1995) 14:55–61. doi: 10.1007/BF02208085

96. Lee KH, Chung HS, Bang D, Lee S. Behçet's disease sera containing antiendothelial cell antibodies promote adhesion of T lymphocytes to cultured human dermal microvascular endothelial cells. *Yonsei Med J*. (1999) 40:152–8. doi: 10.3349/ymj.1999.40.2.152

97. Kwang Hoon L, Hae-Shin C, Hyoung Sup K, Sang-Ho O, Moon-Kyung H, Ja-Hyun B, et al. Human alpha-enolase from endothelial cells as a target antigen of anti-endothelial cell antibody in beh?Et's disease. *Arthritis Rheumatol*. (2003) 48:2025–35. doi: 10.1002/art.11074

98. Lee JH, Cho SB, Bang D, Oh SH, Ahn KJ, Kim J, et al. Human anti-alpha-enolase antibody in sera from patients with behÃ§Et's disease and rheumatologic disorders. *Clin Exp Rheumatol*. (2009) 27:S63.

99. Rossides M, Darlington P, Kullberg S, Arkema EV. Sarcoidosis: epidemiology and clinical insights. *J Internal Med*. (2023) 293:668–80. doi: 10.1111/joim.13629

100. Sgonc R, Gruschwitz MS, Dietrich H, Recheis H, Gershwin ME, Wick G. Endothelial cell apoptosis is a primary pathogenetic event underlying skin lesions in avian and human scleroderma. *J Clin Invest*. (1996) 98:785–92. doi: 10.1172/jci118851

101. Lazar S, Kahlenberg JM. Systemic lupus erythematosus: new diagnostic and therapeutic approaches. *Annu Rev Med*. (2023) 74:339–52. doi: 10.1146/annurev-med-043021-032611

102. Horváthová M, Jahnová E, Nyulassy S. Detection of antiendothelial cell antibodies in patients with connective tissue diseases by flow cytometry and their relation to endothelial cell activation. *Physiol Res*. (2002) 51:613.

103. Perricone C, Pendolino M, Olivieri M, Conti F, Valesini G, Alessandri C. Neuropsychiatric manifestations associated with anti-endothelial cell antibodies in systemic lupus erythematosus. *Israel Med Assoc J Imaj*. (2015) 17:171.

104. Cieślik P, Semik-Grabarczyk E, Hrycek A, Holecki M. The impact of anti-endothelial cell antibodies (Aecas) on the development of blood vessel damage in patients with systemic lupus erythematosus: the preliminary study. *Rheumatol Int*. (2022) 42:791–801. doi: 10.1007/s00296-022-05104-5

105. Kondo A, Takahashi K, Mizuno T, Kato A, Hirano D, Yamamoto N, et al. The level of iga antibodies to endothelial cells correlates with histological evidence of disease activity in patients with lupus nephritis. *PloS One*. (2016) 11:e0163085. doi: 10.1371/journal.pone.0163085

106. Frampton G, Moriya S, Pearson JD, Isenberg DA, Ward FJ, Smith TA, et al. Identification of candidate endothelial cell autoantigens in systemic lupus erythematosus using a molecular cloning strategy: A role for ribosomal P protein P0 as an endothelial cell autoantigen. *Rheumatol (Oxford)*. (2000) 39:1114–20. doi: 10.1093/rheumatology/39.10.1114

107. Yoshio T, Masuyama J, Mimori A, Takeda A, Minota S, Kano S. Endothelin-1 release from cultured endothelial cells induced by sera from patients with systemic lupus erythematosus. *Ann Rheum Dis*. (1995) 54:361–5. doi: 10.1136/ard.54.5.361

108. Matsuda J, Gotoh M, Gohchi K, Kawasugi K, Tsukamoto M, Saitoh N. Anti-endothelial cell antibodies to the endothelial hybridoma cell line (Eahy926) in systemic lupus erythematosus patients with antiphospholipid antibodies. *Br J Haematol*. (1997) 97:227–32. doi: 10.1046/j.1365-2141.1997.d01-2147.x

109. Cid MC, Hernández-Rodríguez J, Esteban MJ, Cebrián M, Gho YS, Font C, et al. Tissue and serum angiogenic activity is associated with low prevalence of ischemic complications in patients with giant-cell arteritis. *Circulation*. (2002) 106:1664–71. doi: 10.1161/01.cir.0000030185.67510.c0

110. Kotulska-Kucharz A, Kopeć-Mędrek M, Kucharz EJ. Serum angiostatin and endostatin levels in patients with granulomatosis with polyangiitis and immune complex small vessel vasculitis. *Reumatologia*. (2018) 56:285–8. doi: 10.5114/reum.2018.79498

111. Hernández-Rodríguez J, García-Martínez A, Casademont J, Filella X, Esteban MJ, López-Soto A, et al. A strong initial systemic inflammatory response is associated with higher corticosteroid requirements and longer duration of therapy in patients with giant-cell arteritis. *Arthritis Rheum*. (2002) 47:29–35. doi: 10.1002/art1.10161

112. Cid MC, Cebrián M, Font C, Coll-Vinent B, Hernández-Rodríguez J, Esparza J, et al. Cell adhesion molecules in the development of inflammatory infiltrates in giant cell arteritis: inflammation-induced angiogenesis as the preferential site of leukocyte-endothelial cell interactions. *Arthritis Rheum*. (2000) 43:184–94. doi: 10.1002/1529-0131(200001)43:1<184::Aid-anr23>3.0.Co;2-n

113. Baumann H, Gauldie J. The acute phase response. *Immunol Today*. (1994) 15:74–80. doi: 10.1016/0167-5699(94)90137-6

114. Hernández-Rodríguez J, Segarra M, Vilardell C, Sánchez M, García-Martínez A, Esteban MJ, et al. Tissue production of pro-inflammatory cytokines (Il-1beta, tnfalpha and il-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. *Rheumatol (Oxford England)*. (2004) 43:294–301. doi: 10.1093/rheumatology/keh058

115. Miura M, Garcia FL, Crawford SE, Rowley AH. Cell adhesion molecule expression in coronary artery aneurysms in acute kawasaki disease. *Pediatr Infect Dis J*. (2004) 23:931–6. doi: 10.1097/01.inf.0000142171.91235.fc

116. Cid MC, Segarra M, García-Martínez A, Hernández-Rodríguez J. Endothelial cells, antineutrophil cytoplasmic antibodies, and cytokines in the pathogenesis of systemic vasculitis. *Curr Rheumatol Rep*. (2004) 6:184–94. doi: 10.1007/s11926-004-0067-3

117. Cacciola R, Gentilini Cacciola E, Vecchio V, Cacciola E. Impact of anti-endothelial cell antibodies (Aecas) in patients with polycythemia vera and thrombosis. *Diagn (Basel Switzerland)*. (2022) 12(5):1077. doi: 10.3390/diagnostics12051077

118. Jackson AM, Sigdel TK, Delville M, Hsieh SC, Dai H, Bagnasco S, et al. Endothelial cell antibodies associated with novel targets and increased rejection. *J Am Soc Nephrol: JASN*. (2015) 26:1161–71. doi: 10.1681/asn.2013121277

119. Maruotti N, Cantatore FP, Nico B, Vacca A, Ribatti D. Angiogenesis in vasculitides. *Clin Exp Rheumatol*. (2008) 26:476–83.

120. Pegoraro AF, Janmey P, Weitz DA. Mechanical properties of the cytoskeleton and cells. *Cold Spring Harbor Perspect Biol*. (2017) 9(11):a022038. doi: 10.1101/cshperspect.a022038

121. Fletcher DA, Mullins RD. Cell mechanics and the cytoskeleton. *Nature*. (2010) 463:485–92. doi: 10.1038/nature08908

122. Zimering MB, Pan Z. Autoantibodies in type 2 diabetes induce stress fiber formation and apoptosis in endothelial cells. *J Clin Endocrinol Metab*. (2009) 94:2171–7. doi: 10.1210/jc.2008-2354

123. Zhang X, Valenzuela NM, Reed EF. Hla class I antibody-mediated endothelial and smooth muscle cell activation. *Curr Opin Organ Transplant*. (2012) 17:446–51. doi: 10.1097/MOT.0b013e328355f1c2

124. Ziegler ME, Souda P, Jin YP, Whitelegge JP, Reed EF. Characterization of the endothelial cell cytoskeleton following hla class I ligation. *PloS One*. (2012) 7:e29472. doi: 10.1371/journal.pone.0029472

125. Aljabri A, Vijayan V, Stankov M, Nikolin C, Figueiredo C, Blasczyk R, et al. Hla class ii antibodies induce necrotic cell death in human endothelial cells via a lysosomal membrane permeabilization-mediated pathway. *Cell Death Dis*. (2019) 10:235. doi: 10.1038/s41419-019-1319-5

126. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol*. (2005) 25:932–43. doi: 10.1161/01.Atv.0000160548.78317.29

127. Satcher RL Jr., Dewey CF Jr. Theoretical estimates of mechanical properties of the endothelial cell cytoskeleton. *Biophys J*. (1996) 71:109–18. doi: 10.1016/s0006-3495(96)79206-8

128. Jannatbabaei A, Tafazzoli-Shadpour M, Seyedjafari E, Fatouraee N. Cytoskeletal remodeling induced by substrate rigidity regulates rheological behaviors in endothelial cells. *J Biomed Mater Res Part A*. (2019) 107:71–80. doi: 10.1002/jbm.a.36533

129. Ucar AK, Ozdede A, Kayadibi Y, Adaletli I, Melikoglu M, Fresko I, et al. Increased arterial stiffness and accelerated atherosclerosis in takayasu arteritis. *Semin Arthritis Rheum*. (2023) 60:152199. doi: 10.1016/j.semarthrit.2023.152199

130. Hussein MA, Ramadan MM, Moneam MAE, Halim HAE, Ghaffar NAE, Fawzy MW. Interleukin 37; a possible marker of arterial stiffness in behçet's disease. *Am J Med Sci*. (2022) 364:425–32. doi: 10.1016/j.amjms.2022.04.013

131. Byfield FJ, Wen Q, Leszczynska K, Kulakowska A, Namiot Z, Janmey PA, et al. Cathelicidin ll-37 peptide regulates endothelial cell stiffness and endothelial barrier permeability. *Am J Physiol Cell Physiol*. (2011) 300:C105–12. doi: 10.1152/ajpcell.00158.2010

132. Okamoto T, Kawamoto E, Takagi Y, Akita N, Hayashi T, Park EJ, et al. Gap junction-mediated regulation of endothelial cellular stiffness. *Sci Rep*. (2017) 7:6134. doi: 10.1038/s41598-017-06463-x

133. Vandenbroucke E, Mehta D, Minshall R, Malik AB. Regulation of endothelial junctional permeability. *Ann New York Acad Sci*. (2008) 1123:134–45. doi: 10.1196/annals.1420.016

134. Thompson PW, Randi AM, Ridley AJ. Intercellular adhesion molecule (Icam)-1, but not icam-2, activates rhoa and stimulates C-fos and rhoa transcription in endothelial cells. *J Immunol (Baltimore Md: 1950)*. (2002) 169:1007–13. doi: 10.4049/jimmunol.169.2.1007

135. Huveneers S, Daemen MJ, Hordijk PL. Between rho(K) and a hard place: the relation between vessel wall stiffness, endothelial contractility, and cardiovascular disease. *Circ Res*. (2015) 116:895–908. doi: 10.1161/circresaha.116.305720

136. McKenzie JA, Ridley AJ. Roles of rho/rock and mlck in tnf-alpha-induced changes in endothelial morphology and permeability. *J Cell Physiol*. (2007) 213:221–8. doi: 10.1002/jcp.21114

137. Sawma T, Shaito A, Najm N, Sidani M, Orekhov A, El-Yazbi AF, et al. Role of rhoa and rho-associated kinase in phenotypic switching of vascular smooth muscle cells: implications for vascular function. *Atherosclerosis*. (2022) 358:12–28. doi: 10.1016/j.atherosclerosis.2022.08.012

138. Chen S, Guo F, Liu X, Xi J, Xue M, Guo Y, et al. Roles of the rhoa-rock signaling pathway in the endothelial H(2)S production and vasodilation in rat cerebral arteries. *ACS Omega*. (2022) 7:18498–508. doi: 10.1021/acsomega.2c00996

139. You LJ, Li PW, Zhang WW, Feng MF, Zhao WP, Hou HM, et al. Schisandrin a ameliorates increased pulmonary capillary endothelial permeability accompanied with sepsis through inhibition of rhoa/rock1/mlc pathways. *Int Immunopharmacol*. (2023) 118:110124. doi: 10.1016/j.intimp.2023.110124

140. Mu X, Tseng C, Hambright WS, Matre P, Lin CY, Chanda P, et al. Cytoskeleton stiffness regulates cellular senescence and innate immune response in hutchinson-gilford progeria syndrome. *Aging Cell*. (2020) 19:e13152. doi: 10.1111/acel.13152

141. Szulcek R, Beckers CM, Hodzic J, de Wit J, Chen Z, Grob T, et al. Localized rhoa gtpase activity regulates dynamics of endothelial monolayer integrity. *Cardiovasc Res*. (2013) 99:471–82. doi: 10.1093/cvr/cvt075

142. Hsieh SL, Wang JJ, Su KH, Kuo YL, Hsieh S, Wu CC. Suppressive effects of the gynura bicolor ether extract on endothelial permeability and leukocyte transmigration in human endothelial cells induced by tnf-A. *Evidence-Based Complement Altern Med: eCAM*. (2020) 2020:9413724. doi: 10.1155/2020/9413724

143. Praprotnik S, Blank M, Meroni PL, Rozman B, Eldor A, Shoenfeld Y. Classification of Anti-Endothelial Cell Antibodies into Antibodies against Microvascular and Macrovascular Endothelial Cells: The Pathogenic and Diagnostic Implications. *Arthritis Rheum*. (2001) 44:1484–94. doi: 10.1002/1529-0131(200107)44:7<1484::Aid-art269>3.0.Co;2-q

144. Belizna C, Duijvestijn A, Hamidou M, Tervaert JW. Antiendothelial cell antibodies in vasculitis and connective tissue disease. *Ann Rheum Dis*. (2006) 65:1545–50. doi: 10.1136/ard.2005.035295

145. Prasad TK, Hack E, Hallberg RL. Function of the maize mitochondrial chaperonin hsp60: specific association between hsp60 and newly synthesized F1-atpase alpha subunits. *Mol Cell Biol*. (1990) 10:3979–86. doi: 10.1128/mcb.10.8.3979

146. Mendez MG, Restle D, Janmey PA. Vimentin enhances cell elastic behavior and protects against compressive stress. *Biophys J*. (2014) 107:314–23. doi: 10.1016/j.bpj.2014.04.050

147. Gorudko IV, Sokolov AV, Shamova EV, Grudinina NA, Drozd ES, Shishlo LM, et al. Myeloperoxidase modulates human platelet aggregation via actin cytoskeleton reorganization and store-operated calcium entry. *Biol Open*. (2013) 2:916–23. doi: 10.1242/bio.20135314

148. Pace PE, Peskin AV, Konigstorfer A, Jasoni CJ, Winterbourn CC, Hampton MB. Peroxiredoxin interaction with the cytoskeletal-regulatory protein crmp2: investigation of a putative redox relay. *Free Radic Biol Med*. (2018) 129:383–93. doi: 10.1016/j.freeradbiomed.2018.10.407

149. Alard JE, Hillion S, Guillevin L, Saraux A, Pers JO, Youinou P, et al. Autoantibodies to endothelial cell surface atp synthase, the endogenous receptor for hsp60, might play a pathogenic role in vasculatides. *PloS One*. (2011) 6:e14654. doi: 10.1371/journal.pone.0014654

150. Ellins E, Shamaei-Tousi A, Steptoe A, Donald A, O'Meagher S, Halcox J, et al. The relationship between carotid stiffness and circulating levels of heat shock protein 60 in middle-aged men and women. *J Hypertens*. (2008) 26:2389–92. doi: 10.1097/HJH.0b013e328313918b

151. Weber A, Iturri J, Benitez R, Zemljic-Jokhadar S, Toca-Herrera JL. Microtubule disruption changes endothelial cell mechanics and adhesion. *Sci Rep*. (2019) 9:14903. doi: 10.1038/s41598-019-51024-z

152. Starodubtseva MN, Liu J, Nadyrov EA, Shkliarava NM, Sadouskaya AU, Starodubtsev IE, et al. Cd109-regulated mechanical properties of endothelial cells. *Cytoskeleton (Hoboken)*. (2023) 80:123–32. doi: 10.1002/cm.21753

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 09 May 2025
DOI 10.3389/fonc.2025.1537825

OPEN ACCESS

EDITED BY
Joshua Daniel Ooi,
Monash University, Australia

REVIEWED BY
Aloukick Kumar Singh,
University of Texas MD Anderson Cancer Center, United States
Michael Shafique,
Moffitt Cancer Center, United States

*CORRESPONDENCE
Valérian Rivet
Valerian.rivet@gmail.com

RECEIVED 01 December 2024
ACCEPTED 17 April 2025
PUBLISHED 09 May 2025

CITATION
Rivet V, Guillon B, Sibaud V, Dion J, Pastissier A, Delavigne K, Cougoul P, Rauzy O and Comont T (2025) Case Report: Acral vasculitis induced by Immune Checkpoint Inhibitors: a case series and literature review. *Front. Oncol.* 15:1537825. doi: 10.3389/fonc.2025.1537825

Case Report: Acral vasculitis induced by Immune Checkpoint Inhibitors: a case series and literature review

Valérian Rivet[1]*, Benoit Guillon[2], Vincent Sibaud[2], Jérémie Dion[1], Andréa Pastissier[1], Karen Delavigne[1], Pierre Cougoul[1], Odile Rauzy[1] and Thibault Comont[1]

[1]Internal Medicine and Immunopathology Department, The Cancer University of Toulouse Oncopole, University Hospital Center of Toulouse, Toulouse, France, [2]Dermatology Department – Medical Oncology, The Cancer University of Toulouse Oncopole, University Hospital Center of Toulouse, Toulouse, France

Introduction: Immune Checkpoint Inhibitors (ICIs) may cause various immune-related Adverse Events (irAEs). Of these events, vascular involvement is still considered an uncommon irAEs and generally concerns large or medium vessels. Acral small-vessel vasculitis can lead to severe digital necrosis.

Case presentation: Herein, we present three cases after treatment with pembrolizumab, nivolumab, and combination nivolumab/ipilimumab for lung adenocarcinoma, renal cell carcinoma, and melanoma, respectively. Two patients had a Raynaud's-like syndrome. All of them presented with digital ischemia of both hands and with severe acral necrosis in the first case. Management consisted in ICI discontinuation, high-dose steroids, and vasodilator agents with good evolution in the three cases. No rechallenge of ICI has been attempted.

Discussion: We found 12 other cases in the literature review to build a cohort of 15 patients, mostly male with a median age of 60 years. Lung cancer and melanoma are the most common tumors. The most frequently used ICI was pembrolizumab. The median time to onset was 8 weeks. The main clinical presentation was a distal and painful necrosis mostly on thehands with bilateral involvement. Toes were affected in only two cases. All cases were severe features with grade $\geq$ 3. Eleven patients were treated with steroids and vasodilator agents. ICI was discontinued permanently in all patients.

Conclusion: ICI-induced small-vessel vasculitis can lead to severe digital ischemia, often in males, and is preceded by a Raynaud's-like syndrome with mostly bilateral and hand involvement. Data are still missing to optimize management of these kinds of patients.

KEYWORDS

acral vasculitis, immune checkpoint inhibitors, immune-related adverse events, nivolumab, pembrolizumab, ipilimumab

Introduction

Immune Checkpoint Inhibitors (ICIs), either alone or in combination, are now used in several advanced malignancies and may cause various immune-related Adverse Events (irAEs) that can affect virtually every organ system. Vascular involvement is still considered an uncommon immune side effect and was not described in early trials. In 2018, a systemic review evaluated 20 cases of vasculitis that occurred after ICIs (1). The main reported type was large-vessel vasculitis (Giant Cell Arteritis) and vasculitis of the central and peripheral nervous system. The predominant cancer was melanoma with a median time to onset of 3 months.

Most cases seemed to be resolved with high-dose systemic steroids and ICI discontinuation. For small vessel involvement, two cases of acral vasculitis are described: one after anti-programmed death-ligand 1 (anti-PD-L1) and one after anti-cytotoxic T-lymphocyte- associated protein 4 (CTLA-4) (1–3). Recently, more published studies have confirmed an association between ICIs and acral small-vessel vasculitis, which can lead to digital severe necrosis with poor response to glucosteroids and which requires surgical amputation (4, 5). The incidence of acral vasculitis seems very low, with only three cases found in 447 patients (0.007%) who developed connective tissue diseases after PD-1/PD-L1 treatment (4).

The pathophysiology is not fully understood, but increasing evidence suggests that the immune checkpoint plays a key role in immune and inflammatory homeostasis of the vasculature (1, 4, 5). ICIs enhance the immune system through blockage of costimulatory signal receptors, inducing hyperstimulation of the immune system against some antigens in healthy tissue and vessels. They can also increase levels of pre-existing autoantibodies (auto-ab) and of inflammatory cytokines, resulting in several irAEs, such as dysthyroidism, colitis, pneumonitis, and, rarely, myocarditis. Some authors have shown that the inhibition of the PD-1/PD-L1 axis induced T-cell hyperactivity in the vessel wall, as well as causing dendritic cell impairment and the production of cytokines and auto-ab that can promote vasculitis (1, 4).

Moreover, ICIs can cause endothelial insult, leading to both atherosclerosis lesions and a procoagulable state (4, 6). Finally, some authors have suggested a relationship to paraneoplastic acral vascular syndrome (PAVS), whose pathomecanism includes hyperviscosity, hypercoagulability, vasospasm, and spontaneous platelet aggregation (7, 8).

Nevertheless, ICI-induced-acral vasculitis (AV-ICI) is still poorly described in both diagnosis and treatment. We propose three more cases and a literature update.

Abbreviations: Auto-ab, Auto-antibodies; ANAs, Antinuclear antibodies; CS, Corticosteroids; ICIs, Immune Checkpoint Inhibitors; IrAEs, Immune-related Adverse Events; Hem-irAEs, hematological irAEs; IS/IM, Immunosuppressive or immunomodulating agents; MMF, Mycophenolate mofetil; PD-1, Anti-programmed death-1 (PD-1); PD-L1, programmed death-ligand 1 (PD- L1); CTLA-4, Anti-cytotoxic T-lymphocyte-associated protein 4; PAVS, Paraneoplastic acral vascular syndrome; PNS, Paraneoplastic syndrome.

Cases presentation

Case 1

A patient in their 60s was initiated on combination chemoimmunotherapy with carboplatin, pemetrexed, and pembrolizumab for metastatic lung adenocarcinoma in June 2022. After four cycles, he was placed on maintenance therapy with pemetrexed and pembrolizumab. In November, after eight cycles of ICI, the patient suffered from a Raynaud's-like syndrome with purple discoloration of all fingers of both hands, including the thumbs. He had no history of acrosyndrome or dysimmune disease but did have a history of smoking, which he had stopped in 2016. In December 2022, the ninth cycle was not completed because of the sudden appearance of painful digital necrosis on both hands (Figures 1A, B). Both chemo and immunotherapy were stopped and the patient was hospitalized. Physical examination showed distal gangrene (sparing the lower limbs) with perinecrotic erythema without any clinical signs of associated rheumatologic/vascular disease or other irAEs. Admission laboratory tests revealed a normal metabolic (including thyroid parameters) and coagulation profile. Immunological tests, including protein electrophoresis, cytoplasmic and perinuclear anti-neutrophil cytoplasmic antibody (ab), complete panel of scleroderma ab, rheumatoid factor, cryoglobulins, cryfibrinogens, anti-phospholipids, anti-extractable nuclear antigen, and anti-DNA ab, were all negative, except for antinuclear ab (ANAs), which were positive at 1:5120. Blood tests were also negative for hepatitis B/C and HIV and spot urine tests revealed no proteinuria. In addition, arterial Doppler of the upper limbs and an echocardiography did not reveal any significant abnormality. Nail fold capillaroscopy showed peri-capillary edema without any associated changes (including a lack of identified megacapillaries). Skin punch biopsy was not performed because of the very high risk of worsening the lesions. A diagnosis of AV-ICI was nonetheless retained considering the clinico-biological features and the absence of a differential diagnosis in our exhaustive comprehensive work-up. ICI perfusions were discontinued.

Prednisone was initiated (1 mg per kg daily for four days), which unfortunately caused worsening of both pain and cutaneous involvement. So, the patient started a three-day course of intravenous (IV) methylprednisone (500 mg per day), calcium blockers, and iloprost to stabilize the extension of the digital necrosis and improve pain. Corticosteroids (CS) were tapered to 1 mg/kg/d. A few days later, he suddenly suffered from respiratory failure that required mechanical ventilation. A CT-scan revealed both A right proximal pulmonary embolism and diffuse interstitial pneumonia (DIP) (Figures 1C, D). Steroid treatment was increased to 2 mg/kg/d without improvement on respiratory parameters. New blood tests did not find any abnormalities once again. Finally, a rescue treatment of tocilizumab infusion (8 mg per kg, IV) was attempted. Progressive recovery led to extubating, weaning of oxygen therapy, and complete stabilization of skin lesions as drying necrosis. A TEP-scan found neoplastic progression of both the lung and metastatic target. After more than two months, the patient was discharged. Contraindication was retained for ICI

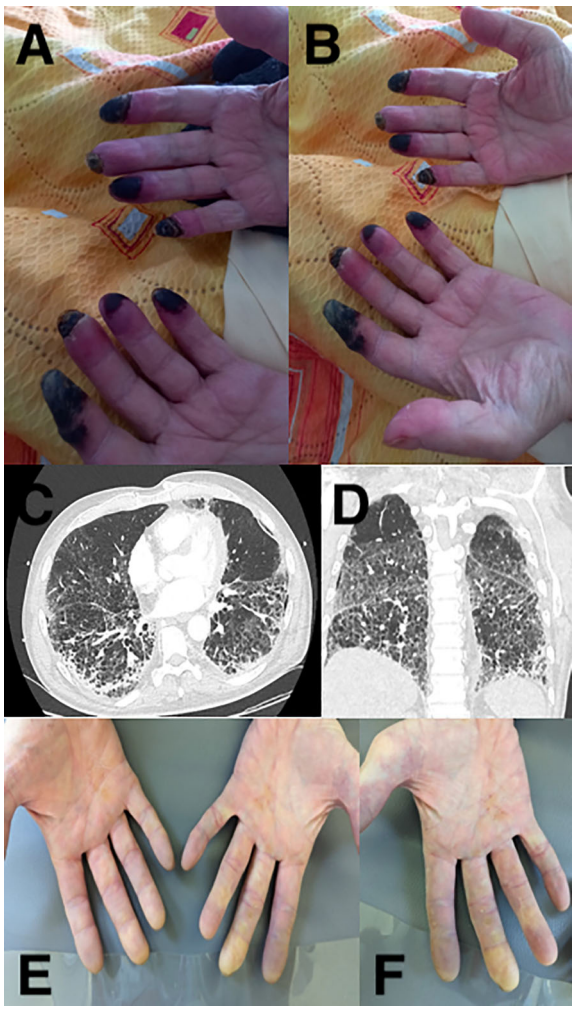


FIGURE 1
Main clinical and imaging features of the case series. Digital necrosis of case 1 **(A, B)**, diffuse interstitial pneumonia of case 1 **(C, D)**, and bilateral digital ischemia of both hands of case 2 **(E, F)**.

treatments. Secondarily, he benefited from surgical amputation. Six months later, there has been no sign of respiratory or cutaneous worsening despite cortisone withdrawal.

Case 2

A man, about 65 years old, with metastatic renal cell carcinoma was treated with nivolumab combined with cabozantinib (an inhibitor of both met receptor tyrosine kinase and the VEGF receptor 2). He had no history of acrosyndrome, dysimmune disease, or smoking. Between September 2022 and February 2024, he received 24 cycles (nivolumab 240 mg every 2 weeks with cabozantinib 40 mg per day). In November 2023, a CT-scan showed a partial response both in primitive lesion and metastatic lymph nodes. After 15 cycles, a systemic blood test revealed grade 3 cytolytic hepatitis and peripheral hypothyroidism, resolved after ICI discontinuation and six weeks of steroids and hormone supplementation. In March 2024, he was hospitalized for painful discoloration of all fingers on both hands. On examination, we found purple discoloration of the bilateral fingers (including the thumbs but sparing the others extremities) without ulceration or necrosis (Figures 1E, F).

Routine blood chemistries, coagulation profiles, and immunological tests were normal. Upper extremity arterial Doppler ultrasound showed only partial and chronic thrombosis of the right ulnar arterial. Nail fold capillaroscopy and skin biopsy were not performed in this patient because of the quick improvement of clinical features after the start of treatment. Both nivolumab and cabozantinib were stopped. The patient started prednisone (1 mg/kg/d). After two days without improvement, iloprost was suggested. After two more days, both acral ischemia and pain clearly improved with complete response and the patient was discharged after eight days. Unfortunately, a new CT-scan revealed worsening of adenopathy and pulmonary metastatic involvement. Because of this oncologic progression and the immune-related vascular toxicity, it was decided to stop ICI perfusions and switch to single-agent lenvatinib (a multi-tyrosine receptor inhibitor). After 3 months, a new CT-scan showed stable oncologic disease in both primitive and metastatic targets, without any recurrence of digital ischemia or vascular involvement.

Case 3

A 60-year-old man, without any smoking history, dysimmune disease, or acrosyndrome, was treated for advanced melanoma with neoadjuvant combination by nivolumab and ipilimumab (respectively 1 mg/kg and 3 mg/kg every 3 weeks) in July 2021. Five days after the second perfusion, he developed a sudden severe Raynaud's-like syndrome associated with paresthesia and cyanosis mostly on both second fingers and the fourth and fifth fingers on the left hand. He did not have myalgia or motor deficiency. In the vascular department, his routine blood chemistries, viral serologies, and coagulation profile were normal.

Immunological tests found only specific anti-Jo1-ab with negative screening of ANA. Bilateral upper extremity arterial Doppler ultrasound was normal and nail fold capillaroscopy showed only non-specific abnormalities. A thoracic CT-scan did not show any vascular abnormalities or interstitial pneumonia. Both elevation on troponin I (194 ng/ml, N < 14) and CPK levels (2156 UI/l, N < 190) were highlighted. Cardiac IRM was normal but an endomyocardic biopsy showed diffuse lymphocytic infiltration and confirmed the immune-related myocarditis. The association of the severe Raynaud's phenomenon, elevated CPK, myocarditis, and positive anti-Jo1 ab suggested an anti-synthetase syndrome triggered by ICIs. An immune-related acral vasculitis was confirmed without histological features in the absence of a differential diagnosis. ICIs were stopped. The patient received three methylprednisone IV perfusions (1g/d) and then prednisone (2 mg/kg) before progressively tapering off, as well as iloprost for 28 days. The patient had complete recovery of both cardiac and vascular involvement. Oncologic follow-up found a complete response of the melanoma. After 6 months, a new tumor

assessment revealed a persistent complete metabolic response and a rechallenge of ICI has not yet been carried out. The patient had no recurrence of acral vascular manifestations despite progressive cortisone withdrawal.

Discussion

Vasculitis has not been documented as an irAE after anti-PD-1/L-1 and/or anti-CTLA4; it is seen in <1% of cases, with large-vessel involvement in most of them (1, 5). Acral vasculitis seems to be an extremely rare manifestation of ICI therapy, with often severe clinical features and still very little data about their management. We described three new cases of small-vessel involvement after ICI. We also found 12 other cases in an update of the literature review to form a cohort of 15 different patients (Table 1).

The median age of this cohort is 60 (min-max 45-73; SD 8,95), with a clear male predominance (only one case involved a woman) (6,7%) (Table 1) (2–5, 7–13). Lung cancer is the most common tumor (five cases, 33%), especially lung adenocarcinoma with melanoma (five cases, 33%). The most frequently used ICI is pembrolizumab (seven; 47%), often associated with chemotherapy. A combination of ICIs is seen in three cases (20%). Nivolumab alone was used in three cases (20%). The median time to onset is eight weeks (SD 17,4), with a quite large variable between only two weeks for the shortest and 17 months for the longest one (11–13). Six patients (40%) suffered from other irAEs, including two with diffuse interstitial pulmonary involvement, including case 1 (2, 3, 5, 13). The main clinical presentation is a distal and painful necrosis mostly on the hands (12/15 cases, 80%) with bilateral involvement (11/15, 73%). Toes were affected only in three cases (20%) (5, 12, 13). The ears and nose can also be affected (five). Interestingly, for six patients (40%), the first clinical phase is described as a Raynaud's-like syndrome, including case 1 (2, 4, 9, 13). All cases have severe features with grade CTCAE (v5.0) ≥ 3. In each case, a large work-up was realized, as recommended to identified etiologies, with large blood samples and at least an arterial Doppler ultrasound test, sometimes completed with a CT chest or arterial angiography (4). Macrovascular disease is sometimes detected but is not sufficient to explain all the clinical signs, like in case 2. (five) (12). When a nail fold capillaroscopy was performed, it did not reveal any pathological findings, like in case 1 and 3 (4, 5, 8, 9). On immunological tests, ANAs were found in six patients (40%), with a median titer of 1:400 (min-max 80-5200), without any speckled pattern in most of them (3–5, 7, 9). Sometimes specific antibodies were found, like anti-RNA pol-III in one patient, anti-SSa with type III cryoglobulin I in another one, and anti-Jo1 in our case 3 (3, 9). None of the patients reported a preexisting autoimmune disease prior to initiating immunotherapy treatment. Biopsy was rarely performed, probably due to risk of worsening lesions and delaying healing; biopsy results are available for only for three (20%) patients (7, 8, 13). Histopathology revealed both thrombosis and perivascular inflammatory infiltrates including lymphocytes, plasma cells, and neutrophils, suggestive of vasculitis (3, 8, 13).

Most patients were treated with steroids, namely 12/15 (80%), sometimes with high doses of IV pulses (5/15) (33%). Only three patients (20%) received one immunosuppressive or immunomodulating agent (IS/IM): mycophenolate mofetil (MMF), rituximab, and tocilizumab, respectively, for each patient (6,7%) (2, 10). Aspirin and anticoagulation were initiated in five (33%) and three (20%) cases, respectively. Seven patients (47%) received at least one calcium blocker. Iloprost was tried in seven cases (47%), prostacyclin analogs in four (27%), and sildenafil in three (20%). Surgical amputation was necessary for four patients (27%) (2, 4, 8, 12). In case 1, surgical amputation was performed late only after stabilization of the digital necrosis. In all cases, ICI was stopped and no rechallenge was attempted. In most cases, CS are not enough to stabilize the ischemia, even with high doses. In the three patients (20%) treated with IS/IM, two had a complete response: one with MMF and our case 1. after tocilizumab perfusion (10). Rituximab did not prevent the third patient from worsening (2). Most patients with a partial or complete response were treated by iloprost or prostacyclin analogs perfusions (3, 7, 10, 11). Calcium blockers are often associated with variable efficiency. Finally, one patient (6,7%) underwent sympathectomy without any improvement of acral necrosis (4). Oncology assessment shows cancer progression in 5/9 (56%) patients. Two patients experienced a complete response and two achieved stable disease (11%).

The pathophysiology of acral vasculitis could be based on the alteration of the immunological homeostasis with activation of the T-cell population or antibodies forming against self-antigens, possibly against endothelial cells (4). Some authors found that blockage of the PD-1/PD-L1 signal initiates T-cell infiltration of the vascular endothelium and can lead to medium/large vessels; blockage of other signals can lead to PD-1 receptor impairment and induce auto-antibodies against shared antigens between tumor and normal tissue in mice models (4, 14). This hypothesis seems to be supported by the positivity of ANAs in a large portion of patients in our cohort and encourage rapid initiation of high-dose CS (9). Similarly, in the case of steroid-refractory vasculitis, we believe that rapid IS/IM agents must be introduced (3–5, 7, 9). Even Franco et al. described a complete response with MMF; we think drugs with a very short onset of action, like tocilizumab used in case 1, are to be preferred., Plasma exchange or anti-JAK (Janus Kinase) therapy could also be viable options, although these were not tried in our cohort (10). Another mechanism to explain acral vasculitis could be a proinflammatory effect caused by ICIs with endothelial injury that could induce either atherosclerosis lesions or a procoagulable state (4). In the same way, several authors discussed a paraneoplastic (PNS) origin as observed on paraneoplastic acral vascular syndrome (PAVS), mostly associated with lung adenocarcinomas and stomach and breast cancers (4, 7–9, 15). PAVS seems to be due to several mechanisms such as hyperviscosity, hypercoagulability, generalized vasospasm, and spontaneous platelet aggregation (8, 15). Le Besnerais et al, found that, of 100 patients with digital ischemia, there was a significantly higher rate of thrombocytosis on cancers patients, demonstrating an indirect measure of hypercoagulability (15). Interestingly, the clinical presentation of patients in our cohort shows some similarities to features found in PAVS, especially a Raynaud's phenomenon that preceded digital ischemia and a bilateral and mostly hands involvement (9, 15). ICIs

TABLE 1 Previously published and current case of Immune Checkpoint Inhibitor-related (ICI) acral vasculitis.

Author Ref (year)	Age/ Gender	Cancer	ICI (ICI-associated therapy)	Onset* (number of perfusion)	Main skin lesions	Systemic symptoms/ other irAEs	Immunological findings	Grade**	Treatment/ Outcome of the irAEs/ Rechallenge
Rivet V, et al. (2025)	60/ Male	Lung ADK	Pembrolizumab (carboplatin/ pemetrexed)	24 (8)	Raynaud-like syndrome and then bilateral severe digital necrosis of both hands	Severe DIP	ANAs (titer 5120, speckled pattern)	4	ICI discontinuation; prednisone; methylprednisolone; calcium blockers; iloprost; tocilizumab; late surgical amputation PR; no rechallenge
	65/ Male	RCC	Nivolumab (cabozantinib)	68 (24)	Painful bilateral ischemia of all fingers without necrosis	Cytolytic hepatitis; peripheral hypothyrodism	None	3	ICI discontinuation; prednisone; iloprost; CR; no rechallenge
	60/ Male	Melanoma	Nivolumab + Ipilimumab	4 (2)	Bilateral Raynaud-like syndrome with severe cyanosis of fingers of both hands	Myocarditis	Anti-Jo1 (negative ANAs)	3	ICI discontinuation; methylprednisolone; iloprost; CR; no rechallenge
Yohannan B, et al. (5) (2023)	60/ Male	Lung ADK	Pembrolizumab (carboplatin/ pemetrexed)	8 (4)	Bilateral Raynaud-like syndrome, acral necrosis of fingertips	Esophagitis; peripheral neuropathy	ANAs (titer 640, speckled pattern)	4	ICI discontinuation; methylprednisolone; aspirin, sildenafil, nitropaste, prostacycline; worsening of irAE; no rechallenge
	72/ Male	ORL SCC	Pembrolizumab (carboplatin, paclitaxel)	24 (8)	Acral necrosis of left arm, right foot, ear and nose	None	None	4	ICI discontinuation; supportive care; no rechallenge
O'Connor P, et al. (9) (2020)	45/ Male	TNBC	Pembrolizumab (carboplatin, docetaxel)	18 (6)	Erythema, edema and tender right 3nd digit and onycholysis, Raynaud-like syndrome	None	ANAs (titer 160, speckled pattern), anti-RNA pol-III	3	ICI discontinuation; anticoagulation; calcium blockers, prednisone; sildenafil; PR; no rechallenge
Franco, F et al. (10) (2019)	46/ Male	RCC	Nivolumab	8 (4)	Pain and ischemia of the all fingers of both hands	None	None	3	ICI discontinuation; methylprednisolone; anticoagulation; aspirin; MMF, iloprost; CR; no rechallenge
Khaddour, K, et al. (4) (2019)	68/Female	Lung ADK	Pembrolizumab	25	Bilateral Raynaud-like syndrome, acral necrosis of all fingers	None	ANAs (titer 80, speckled pattern)	4	ICI discontinuation (late); calcium blockers; prednisone; sympathectomy; worsening of irAE requiring surgical amputation; no rechallenge
Comont T, et al. (7) (2018)	66/ Male	Urothelial bladder cancer	Tremelimumab + Durvalumab	8	Periungual skin necrosis of several digits of both hands	None	ANAs (titer 5200, speckled pattern)	3	ICI discontinuation; prednisone; CR; no rechallenge
Padda A et al. (2) (2018)	52/ Male	Melanoma	Ipilimumab	3 (2)	Raynaud-like syndrome, subungual necrosis on several	Myalgia, athralgia, vision changes, jaw pain, DIP	None	3	ICI discontinuation; methylprednisolone, prednisone, calcium blockers, nitropaste, prostacycline, botulism toxin, sildenafil; rituximab;

(Continued)

10.3389/fonc.2025.1537825

TABLE 1 Continued

Author [Ref] (year)	Age/ Gender	Cancer	ICI (ICI-associated therapy)	Onset* (number of perfusion)	Main skin lesions	Systemic symptoms/ other irAEs	Immunological findings	Grade**	Treatment/ Outcome of the irAEs/ Rechallenge
					upper and lower limb digits, rash				worsening of irAE requiring surgical amputation; no rechallenge
Narvaez J, et al. (11) (2018)	49/ Male	Lung ADK	Nivolumab	2 (1)	Ulceronecrotic lesions of several fingers of both hands	None	None	3	ICI discontinuation; aspirin; prostacyclin; calcium blockers and bosentan; CR; no rechallenge
Leburrel S, et al. (3) (2018)	60/ Male	Melanoma	Anti-PDL1 (anti-MEK/ anti-BRAF)	8	Cyanosis and necrosis of 3 fingers and the heels	Arthralgia, xerostomia, paresthesia of the feet and interstitial pneumonia	ANAs (titer 160, speckled pattern), anti-SSa; cryoglubulinemia (type III)	3	ICI discontinuation; prednisone; calcium blockers; iloprost and aspirin; PR; no rechallenge
Gambicher, T, et al. (8) (2017)	60/ Male	Melanoma	Nivolumab + Ipilimumab	3	Subungual necrosis on the fingertips of both hands, severe gangrene	None	None	4	ICI discontinuation; prednisolone; prostacycline; methylprednisone; nitroglycerin; iloprost; calcium blockers; worsening of irAE requiring surgical amputation; no rechallenge
Thoreau B, et al. (12) (2016)	73/ Male	Melanoma	Pembrolizumab	26	Acute ischemia of the left toes	None	None	4	ICI discontinuation; anticoagulation; iloprost; aspirin; worsening of irAE requiring surgical amputation; no rechallenge
Takada K, et al. (13) (2021)	60/ Male	Lung carcinoma	Pembrolizumab (carboplatin, docetaxel)	2 (1)	Raynaud'like syndrome, bilateral acral necrosis of fingers and toes	Acute renal failure	None	4	ICI discontinuation; prednisone; vasodilatator agents CR; no rechallenge

*Weeks between initiation of immunotherapy and the diagnosis of acral vasculitis.

** Grade of the vascular irAEs according to the CTCAE version 5.0.

ICI, Immune Checkpoint Inhibitor; irAEs, immune-related Adverse Events; ADK, Adenocarcinoma; DIP, diffuse interstitial pneumonia; PR, partial response; ANAs, antinuclear antibodies; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; TNBC, triple-negative breast carcinoma; MMF, mycophenolate mofetil; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events.

10.3389/fonc.2025.1537825

could be triggered by both underlying or a new PAVS. We believe this finding must lead us to try strong vasodilators such as iloprost and stop ICI perfusions earlier. Aspirin may also be useful in reducing the risk of thrombosis (5). However, given the paucity of cases and retrospective data, our conclusions are limited. The absence of uniform diagnostic criteria and histological data in most cases is a damaging point, even if often justified by authors. Similarly, the comprehensive work-up is not homogeneous and not always exhaustive enough to rule out a differential diagnosis to this immuno-related vasculitis. Vascular risk factors like diabetes and smoking have been also reported in some patients who developed digital ischemia (4). This information in clinical cases is not always known and can constitute a bias in the interpretation of our results. Moreover, there is no clear treatment response criteria and a lack of long-term follow up to define the optimal treatment in this situation. Finally, data about rechallenge after vascular irAEs are also missing and contraindication after severe digital ischemia must remain the rule.

Conclusion

ICI-induced vasculitis can concern small vessels and lead to severe digital ischemia, often in males and preceded by a Raynaud's like syndrome with mostly bilateral and hands involvement. Clinicians should be careful about acrosyndrome occurring during treatment and closely monitor for the development of digital necrosis in these patients. We believe that quick high-dose corticosteroids associated with vasodilator agents can lead to real clinical improvement. Immunosuppressive agents are sometimes necessary. If acral vasculitis can be considered as a paraneoplastic syndrome, ICIs must be quickly stopped, although data about rechallenge is currently too limited to try this out. Data are still missing and more studies are necessary to optimize management and specify when rechallenge can be discussed. A better understanding of vasculitis physiopathology would also be important in the choice of second-line immunosuppressive treatments.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

VR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. BG: Investigation, Validation, Writing – review & editing. VS: Supervision, Validation, Writing – review & editing. JD: Supervision, Validation, Writing – review & editing. AP: Validation, Writing – review & editing. KD: Validation, Writing – review & editing. PC: Validation, Writing – review & editing. OR: Validation, Writing – review & editing. TC: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

We thank the patients who agreed to participate in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

References

1. Daxini A, Cronin K. Sreih AG.Vasculitis associated with immune checkpoint inhibitors-a systematic review. *Clin Rheumatol*. (2018) 37:2579–84. doi: 10.1007/s10067-018-4177-0

2. Padda A, Schiopu E, Sovich J, Ma V, Alva A, Fecher L. Ipilimumab induced digital vasculitis. *J Immunother Cancer*. (2018) 12:12. doi: 10.1186/s40425-018-0321-2

3. Le Burel S, Champiat S, Mateus C, Marabelle A, Michot JM, Robert C, et al. Prevalence of immune-related systemic adverse events in patients treated with anti-Programmed cell Death 1/anti-Programmed cell Death-Ligand 1 agents: A single-centre pharmacovigilance database analysis. *Eur J Cancer*. (2017) 82:34–44. doi: 10.1016/j.ejca.2017.05.032

4. Khaddour K, Singh V, Shayuk M. Acral vascular necrosis associated with immune-check point inhibitors: case report with literature review. *BMC Cancer*. (2019) 19:449. doi: 10.1186/s12885-019-5661-x

5. Yohannan B, Truly T, Kala J, Jafri SH. Pembrolizumab-induced acral vasculitis. *J Immunother*. (2023) 46:107–10. doi: 10.1097/CJI.0000000000000457

6. Bu DX, Tarrio M, Maganto-Garcia E, Stavrakis G, Tajima G, Lederer J, et al. Impairment of the programmed cell death-1 pathway increases atherosclerotic lesion development and inflammation. *Arterioscler Thromb Vasc Biol*. (2011) 31:1100–7. doi: 10.1161/ATVBAHA.111.224709

7. Comont T, Sibaud V, Mourey L, Cougoul P, Beyne-Rauzy O. Immune checkpoint inhibitor-related acral vasculitis. *J Immunother Cancer*. (2018) 16:120. doi: 10.1186/s40425-018-0443-6

8. Gambichler T, Struztzman S, Tannapfel A, Susok L. Paraneoplastic acral vascular syndrome in a patient with metastatic melanoma under immune checkpoint blockade. *BMC Cancer*. (2017) 17:327. doi: 10.1186/s12885-017-3313-6

9. O'Connor P, Bhadbhade P, Khan Q, Williamson S. Acral vascular syndrome during an immune checkpoint inhibitor. *BMJ Case Rep*. (2020) 13:e233463. doi: 10.1136/bcr-2019-233463

10. Franco F, Mendez M, Gutierrez L, Sanz J, Calvo V, Provencio M. Nivolumab-associated digital small-vessel vasculitis in a patient with an advanced renal cell carcinoma. *Immunotherapy*. (2019) 11:379–84. doi: 10.2217/imt-2018-0082

11. Narvaez J, Juarez-Lopez P, Lluch J, Narvez JA, Palmero R, Garcia Del Muro X, et al. Rheumatic immune-related adverse events in patients on anti-PD-1 inhibitors: Fasciitis with myositis syndrome as a new complication of immunotherapy. *Autoimmun Rev*. (2018) 17:1040–5. doi: 10.1016/j.autrev.2018.05.002

12. Thoreau B, Gouaillier-Vulcain F, Machet L, Mateus C, Robert C, Ferreira-Maldent N, et al. Acute lower limb ischaemia and diabetes in a patient treated with anti-PD1 monoclonal antibody for metastatic melanoma. *Acta Derm Venereol*. (2017) 97:408–9. doi: 10.2340/00015555-2504

13. Takada K, Hamatake M, Kohashi K, Shimamatsu S, Hirai F, Ohmori S, et al. Limb arteriolar vasculitis induced by pembrolizumab plus chemotherapy in a patient with lung cancer. *Int Cancer Conf*. (2020) 10:83–6. doi: 10.1007/s13691-020-00454-y

14. Zhang H, Watanabe R, Berry GJ, Vaglio A, Liao YJ, Warrington KJ, et al. Immunoinhibitory checkpoint deficiency in medium and large vessel vasculitis. *Proc Natl Acad Sci USA*. (2017) 114:e970–979. doi: 10.1073/pnas.1616848114

15. Le Besnerais M, Miranda S, Cailleux N, Girszyn. Digital ischemia associated with cancer: results from a cohort study. *Medecine (Baltimore)*. (2014) 93:e47. doi: 10.1097/MD.0000000000000047

frontiers | Frontiers in Immunology

TYPE Original Research
PUBLISHED 29 August 2025
DOI 10.3389/fimmu.2025.1624234

OPEN ACCESS

EDITED BY
Alexandre Wagner Silva De Souza,
Federal University of São Paulo, Brazil

REVIEWED BY
Roberto Padoan,
University of Padua, Italy
Harikrishnan Gangadharan,
Government College Kottayam, India
Victor Pimentel-Quiroz,
Hospital Base Guillermo Almenara Irigoyen, Peru

*CORRESPONDENCE
Juan Wang
juan.wang2016@foxmail.com
Sheng Chen
13917556052@139.com

RECEIVED 08 May 2025
ACCEPTED 12 August 2025
PUBLISHED 29 August 2025

CITATION
Wu W, Wang J and Chen S (2025) Reduced-dose obinutuzumab induces remission in refractory ANCA-associated vasculitis: a report of 16 cases.
Front. Immunol. 16:1624234.
doi: 10.3389/fimmu.2025.1624234

Reduced-dose obinutuzumab induces remission in refractory ANCA-associated vasculitis: a report of 16 cases

Wenyi Wu, Juan Wang* and Sheng Chen*

Department of Rheumatology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Objective: Rituximab remains the standard-of-care anti-CD20 therapy for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Obinutuzumab, a next-generation, glycoengineered anti-CD20 monoclonal antibody with enhanced B-cell-depleting capacity, may offer superior efficacy. We evaluated the efficacy and safety of reduced-dose obinutuzumab in 16 patients with active, refractory AAV at a single center in China.

Methods: In this retrospective chart review, we evaluated 16 consecutive patients who received reduced-dose obinutuzumab (most commonly 1,000 mg for induction) after failure to achieve remission with cyclophosphamide (CTX) and/or rituximab (RTX) or who presented with severe, treatment-naïve disease. Primary endpoints were complete remission (CR) rates at 24 and 76 weeks. Secondary endpoints included changes in renal function, inflammatory biomarkers, and immune reconstitution. Adverse events were prospectively recorded.

Results: The median age at obinutuzumab initiation was 44.5 years (IQR 31–54.3); 10 (62.5%) were men. The mean Birmingham Vasculitis Activity Score (BVAS) was 13.5 $\pm$ 6.4. There were 12 patients (75%) who had relapsing disease refractory to CTX/RTX, whereas four treatment-naïve patients presented with multiorgan failure. CR was achieved in 8/16 patients (50%) at week 24 and 13/16 patients (81.3%) at week 76. Obinutuzumab induced rapid clinical remission, suppressed systemic inflammation, achieved peripheral B-cell depletion, rendered ANCA-negative, and improved renal and pulmonary outcomes. No severe infections occurred. Seven patients (43.8%) developed treatment-emergent infections, predominantly respiratory (75%).

Conclusion: Reduced-dose obinutuzumab demonstrates sustained remission in refractory or relapsing active AAV, achieving high long-term remission rates with an acceptable safety profile. No severe invasive infections were observed.

KEYWORDS

ANCA-associated vasculitis, obinutuzumab, efficacy, safety, B cells

Highlights

- Reduced-dose obinutuzumab induced sustained remission in patients with relapsed or refractory ANCA-associated vasculitis.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune condition characterized by necrotizing inflammation of small- to medium-sized blood vessels, frequently resulting in multiorgan involvement. The kidneys are affected in more than 75% of cases, followed by the lungs (50%–70%), the upper respiratory tract, the skin, and, less commonly, the eyes and the peripheral nervous system (1, 2). The clinical course of the disease is typified by rapid progression, cumulative organ damage, and frequent relapses; approximately 40% of patients relapse within 5 years. Renal involvement is particularly ominous, with 20%–40% of patients progressing to end-stage renal disease (ESRD), a complication that substantially worsens the long-term prognosis.

B cells are central to the pathogenesis of AAV. The 2022 EULAR guidelines recommend a combination of glucocorticoids in combination with either rituximab (RTX) or cyclophosphamide (CTX) for life-threatening or organ-threatening AAV (3). However, there is no universally accepted alternative treatment for patients who fail or are intolerant to RTX/CTX, highlighting the need for additional options.

Therapeutic anti-CD20 monoclonal antibodies are classified as Type I or Type II according to their mechanism of action. Obinutuzumab is a humanized, glycoengineered Type II anti-CD20 monoclonal antibody that induces more profound and durable B-cell depletion than Type I agents, such as RTX, via enhanced FcγRIII binding and direct induction of programmed cell death (4–6). Although currently licensed for rituximab-refractory follicular lymphoma, obinutuzumab has demonstrated efficacy in other autoimmune diseases, such as systemic lupus erythematosus and PLA2R-associated membranous nephropathy (7, 8). Preliminary data also indicate renal-protective effects, which are particularly relevant for AAV (9, 10). However, robust evidence for obinutuzumab in AAV is limited. The present study was designed to evaluate obinutuzumab's ability to induce and maintain remission in patients with AAV refractory to CTX and/or RTX or presenting with severe disease activity.

Methods

Study design and patients

This single-center, retrospective chart review enrolled 16 adults with active AAV who either had severe disease activity or were refractory to CTX and/or RTX. Given that ANCA serotype (proteinase 3 [PR3]-ANCA and myeloperoxidase [MPO]-ANCA) is a stronger predictor of clinical presentation, disease course, treatment response, and comorbidities compared with traditional granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) classification, patients were stratified by ANCA subtype. The majority of patients received a single 1,000-mg exploratory induction dose of obinutuzumab; some were maintained on either RTX or obinutuzumab. All underwent 76 weeks of follow-up in the Rheumatology Department at Shanghai Renji Hospital. Baseline characteristics and treatment details are listed in Table 1 and Supplementary Table 1. The study was approved by the Renji Hospital Ethics Committee (IRB no. LY2025 - 197-A), and all patients provided written informed consent.

All patients met the MPA or GPA criteria, as defined by the American College of Rheumatology/European Alliance of Associations for Rheumatology (11, 12) and the Chapel Hill Consensus Conference (13).

Outcome definitions

The primary endpoint was the complete remission (CR) rate at 24 weeks and throughout the 76-week follow-up period. CR was defined as a Birmingham Vasculitis Activity Score (BVAS) of zero and an oral prednisone dose of 10 mg/day or less (14). Response was defined as a ≥50% reduction in BVAS with no new manifestations (3). Relapse was defined as the new emergence or recurrence of one or more BVAS items after remission (15).

Secondary outcomes included changes in laboratory parameters and radiographic improvements on chest imaging. Laboratory parameters included inflammatory markers [C-reactive protein level (CRP), erythrocyte sedimentation rate (ESR)] and immunological markers [ANCA titers (quantified using a commercial MPO/PR3-ELISA kit, positive cutoff ≥1 AU), B-cell counts, and serum immunoglobulin levels]. Renal function was monitored using serum creatinine, estimated glomerular filtration rate (eGFR), and change in proteinuria as a surrogate for long-term renal survival (16).

Adverse events were carefully recorded to assess the safety profile of obinutuzumab treatment. These included infections and infusion-related reactions occurring within 24 h post-administration.

Statistical analysis

Categorical variables are presented as percentages (%), whereas continuous variables are presented as medians with interquartile range (IQR). Statistical significance was determined using a two-sided P-value ≤0.05. All statistical analyses were performed using the R software, version 4.3.2 (R Foundation for Statistical Computing), and GraphPad Prism 8.

Results

Patient characteristics

The baseline characteristics of the 16 enrolled patients are presented in Table 1 and Supplementary Table 1. The median age at the first obinutuzumab infusion was 44.5 years (IQR 31–54.3); 10 participants (62.5%) were men and 6 (37.5%) were women. PR3-

10.3389/fimmu.2025.1624234

TABLE 1 Baseline characteristics of AAV patients who received obinutuzumab.

Characteristics	N=16
Age (years) when started on obinutuzumab, median (IQR)	44.5 (31–54.3)
Age (years) at disease onset, median (IQR)	37 (29.5–53.3)
Duration of the disease (months), median (IQR)	17 (13–20.5)
BVAS, mean (SD)	13.5 (6.42)
Gender	
Male patients	10 (62.5)
Female patients	6 (37.5)
Status	
Newly diagnosed	4 (25)
Relapsing disease	12 (75)
ANCA positivity	
PR3-ANCA+	12 (75)
MPO-ANCA+	4 (25)
System involvement	
Kidney	6 (37.5)
Lung	10 (62.5)
ENT	4 (25)
Nervous	2 (12.5)
Eyes	5 (31.3)
Symptom	
Fever	7 (43.8)
Arthritis	3 (18.8)
Myalgia	3 (18.8)
Oral prednisone at baseline (mg/day)	
15	1 (6.3)
25	1 (6.3)
40	3 (18.8)
50	3 (18.8)
60	8 (50)
Previous therapy	
CTX	10 (62.5)
Mycophenolate mofetil	5 (31.3)
RTX	4 (25)
Methotrexate	6 (37.5)
Azathioprine	4 (25)
Cyclosporin A	1 (6.3)
Leflunomide	1 (6.3)

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; IQR, interquartile range; MPO, myeloperoxidase; PR3, proteinase 3; ANCA, anti-neutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; SD, standard difference; ENT, ear, nose, and throat; CTX, cyclophosphamide; and RTX, rituximab.

ANCA was detected in 12 patients (75%), and the mean BVAS was 13.5 ± 6.4. Multiorgan involvement was observed in 13 patients: renal (37.5%), pulmonary (62.5%), and ear–nose–throat (25%). Fever was documented in seven patients (43.8%). There were 12 patients (75%) who received obinutuzumab for relapsing disease, of whom 11 had been previously treated with CTX and/or RTX. Four patients (all PR3-ANCA-positive) received obinutuzumab as first-line therapy immediately after diagnosis; each exhibited multiorgan disease and markedly elevated disease activity. In this subgroup, two developed acute bilateral profound sensorineural hearing loss accompanied by neuroimaging evidence of central nervous system vasculitis, and one presented with fulminant renal failure requiring urgent dialysis.

Outcomes

Primary outcomes

We assessed both short-term (24 weeks) and long-term (76 weeks) outcomes following obinutuzumab administration. The primary outcomes are summarized in Table 2. All 16 patients completed the 24-week assessment; one patient was subsequently lost to follow-up. Every patient demonstrated a clinical response at both time points. At 24 weeks, 50% achieved CR, with 41.7% of relapsing patients and 75% of newly diagnosed patients achieving this outcome. Nearly 70% attained a BVAS of 0. By week 76, the CR rate had risen to 81.3%, with all patients receiving ≤5 mg/day of oral prednisone and one patient entirely glucocorticoid-free. One relapse occurred at week 36. Detailed treatment regimens are provided in Supplementary Table 1.

Secondary outcomes

Secondary outcomes confirmed marked improvements in both systemic inflammation and immune parameters (Figure 1A and Table 3). Significant reductions in CRP and ESR levels were observed. Renal function, as measured by serum creatinine and eGFR, also notably improved. Although baseline proteinuria was only modestly elevated in our cohort, 24-h urinary protein excretion improved markedly after treatment. Additionally, improvement in lung condition was also observed (Figure 1B). Immunological analyses revealed profound B-cell depletion (median 74.9 × 10^9/L pre-infusion versus 0 post-infusion; $p = 0.0002$) accompanied by a parallel decline in total immunoglobulin levels. The median immunoglobulin G (IgG) level decreased from 10.8 g/L (IQR 9.67–16.7) to 5.81 g/L (IQR 5.09–7.99; $p = 0.0015$), and all patients became ANCA-negative within 24 weeks of the first infusion.

Longitudinal analysis of five key biomarkers (ANCA titers, B-cell counts, IgG levels, eGFR, and serum creatinine) demonstrated durable therapeutic effects through 76 weeks (Figure 2). Rapid clinical improvement was evident within the first 4 weeks of obinutuzumab and persisted for approximately 52 weeks, as reflected by sustained ANCA negativity and profound B-cell depletion. Beyond week 52, a gradual rise in ANCA titers and B-cell repopulation was observed, indicating a potential return to baseline immune status.

10.3389/fimmu.2025.1624234

TABLE 2 Primary outcomes for AAV patients who received obinutuzumab during follow-up.

Time	At week 24			At week 76		
Primary outcomes	Overall (N = 16)	Relapsing (n=12)	Newly diagnosed (n=4)	Overall (N = 16)	Relapsing (n=12)	Newly diagnosed (n=4)
CR rate, n (%)	8 (50)	5 (41.7)	3 (75)	13 (81.3)	10 (83.3)	3 (75)
Prednisone ≤7.5 mg/day	6 (37.5)	4 (33.3)	2 (50)	0	0	0
Prednisone ≤5 mg/day	4 (25)	2 (16.7)	2 (50)	13 (81.3)	10 (83.3)	3 (75)
No prednisone	0	0	0	1 (7.7)	1 (8.3)	0
Response rate, n (%)	16 (100)	12 (100)	4 (100)	16 (100)	12 (100)	4 (100)
Relapse rate, n (%)	0	0	0	1 (6.3)	1 (8.3)	0
BVAS						
BVAS = 0	11 (68.8)	8 (66.7)	3 (75)	13 (81.3)	10 (83.3)	3 (75)
BVAS = 2	2 (12.5)	2 (16.7)	0	0	0	0
BVAS = 4	3 (18.8)	2 (16.7)	1 (25)	2 (12.5)	1 (8.3)	1 (25)

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; CR, complete remission; and BVAS, Birmingham Vasculitis Activity Score.

Adverse events

All patients received sulfamethoxazole–trimethoprim prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) beginning immediately after the first obinutuzumab infusion. No severe infections occurred. Infections occurred in seven patients (43.8%) with a median onset of 12 weeks (range: 5–25 weeks) after infusion. A total of 12 infectious episodes were recorded; four patients experienced recurrent infections. Viral infections predominated (7, 58.3%), followed by fungal (3, 25%) and bacterial (2, 16.7%) infections. Among the viral infections, three

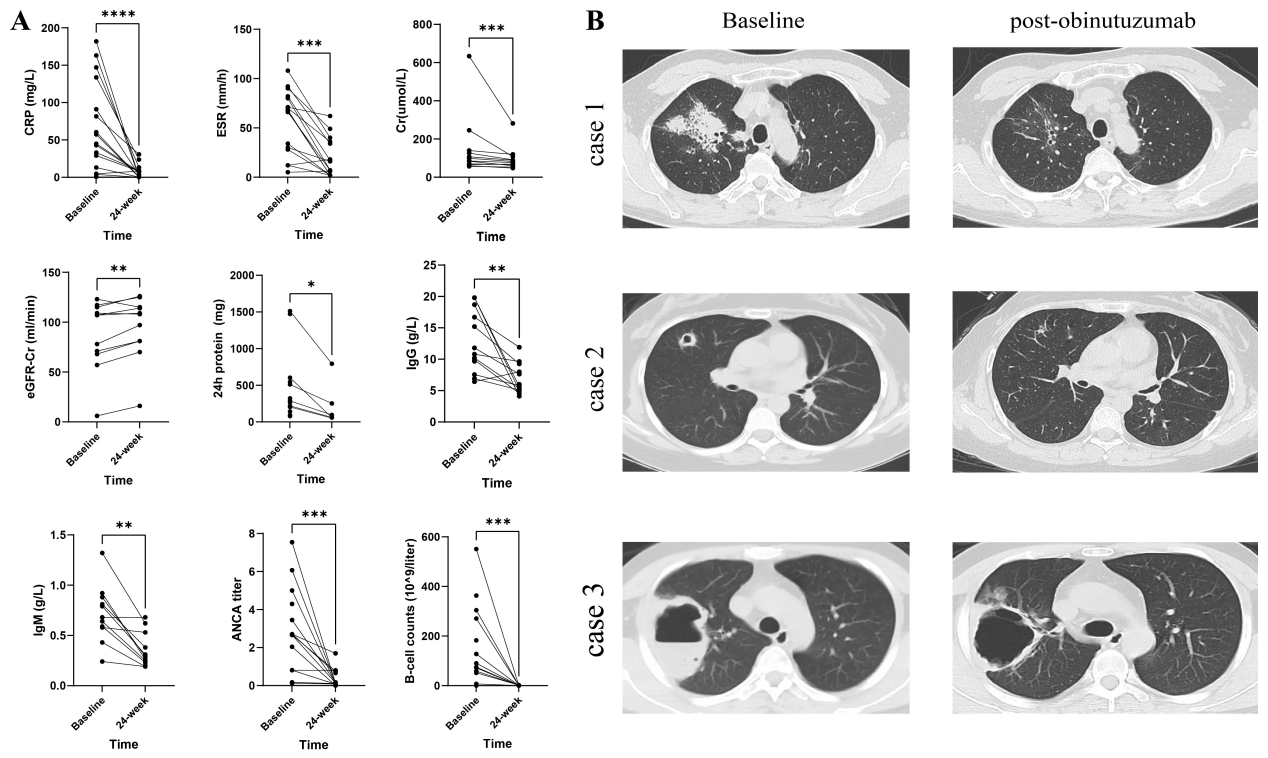


FIGURE 1
Laboratory parameters and chest CT images at baseline and 24 weeks post-obinutuzumab treatment. **(A)** Changes in the laboratory parameters of 16 patients at baseline and 24 weeks after obinutuzumab treatment. **(B)** High resolution CT (HRCT) images at baseline and post-obinutuzumab treatment (4, 8, and 12 weeks) in three cases. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Cr, creatinine; ANCA, antineutrophil cytoplasm antibodies; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; and IgM, immunoglobulin M. *p<0.05 **p<0.01, ***p<0.001 ****p<0.0001.

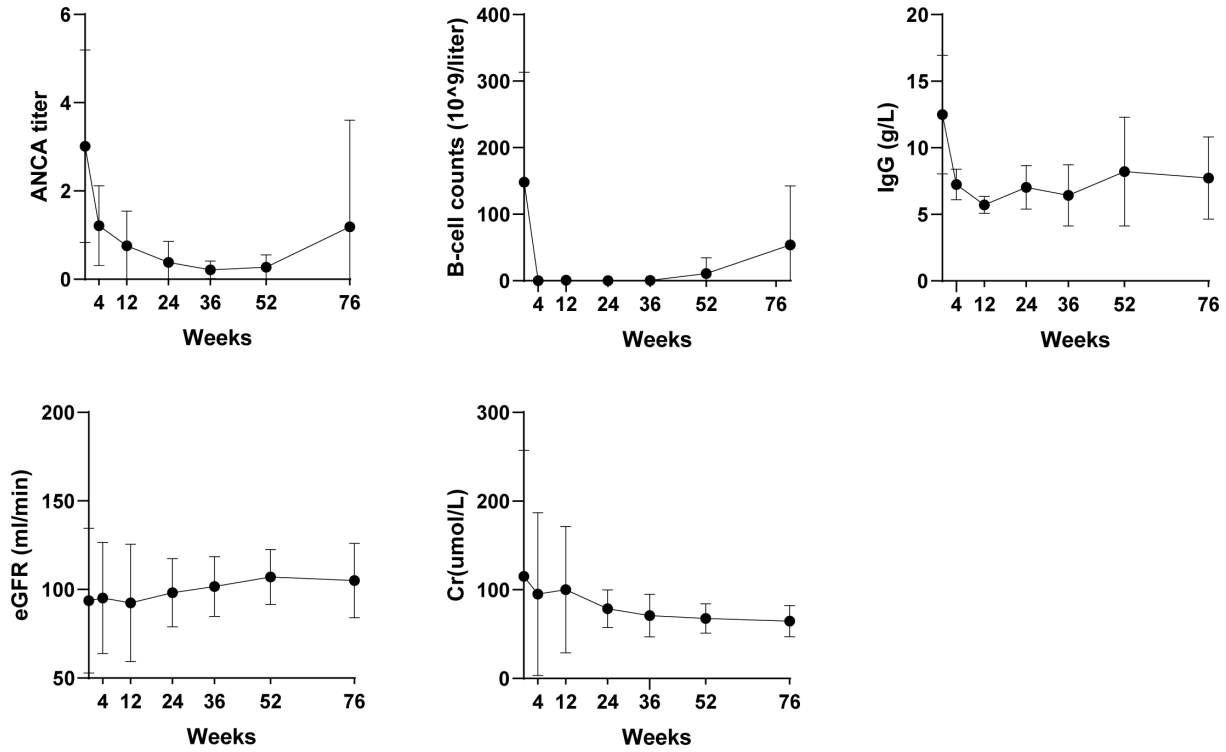


FIGURE 2
Temporal changes in five key laboratory parameters over 76 weeks. ANCA, antineutrophil cytoplasm antibodies; IgG, immunoglobulin G; eGFR, estimated glomerular filtration rate; Cr, creatinine.

were caused by COVID - 19, two by cytomegalovirus (CMV), one by influenza A virus, and one by Epstein–Barr virus (EBV). The respiratory tract was the most common site of infection (9/12, 75%), with COVID - 19 accounting for half of these cases (Table 4).

A subgroup analysis examined potential risk factors for infection, including immunoglobulin levels, concurrent prednisone doses, and prior pulse methylprednisolone therapy (Table 5). Infections occurred predominantly during the induction phase and were associated with significantly higher daily prednisone doses (infected group: mean 55 mg/day vs. non-infected group: mean 18.3 mg/day; $p = 0.0250$), indicating that elevated glucocorticoid exposure increases the risk of infection. However, neither prior pulse methylprednisolone treatment nor immunoglobulin levels at the time of infection differed between the two groups.

Importantly, no patient developed severe hypogammaglobulinemia (IgG <4 g/L) during follow-up; nevertheless, five patients with a marked IgG decline (mean 5.3 g/L) received intravenous immunoglobulin supplementation. Three infusion-related reactions, namely, sinus bradycardia, transient hypertension, and a mild febrile episode, resolved promptly after reducing the infusion rate.

Discussion

Obinutuzumab has already shown benefits for a spectrum of connective-tissue diseases, including systemic lupus erythematosus, anti-Jo1 syndrome, and *Calcinosis cutis*–Raynaud's phenomenon–esophageal dysmotility–sclerodactylia–teleangiectasia (CREST) syndrome (17). In the present cohort, we extended these observations to refractory or relapsing AAV. At 76 weeks, CR was attained by 81% of the patients while successfully tapering prednisone to ≤5 mg/day. This was accompanied by marked reductions in ANCA titers and preservation of renal function. Our results are consistent with a case series in which three rituximab-refractory AAV patients achieved sustained remission after treatment with obinutuzumab (18).

Elevated glucocorticoid exposure is a well-established risk factor for infections. Guided by this principle, we adopted an aggressive tapering strategy: oral prednisone was initiated at 1 mg/kg/day (maximum 60 mg) and reduced to 30 mg/day by week 4 and approximately 15 mg/day by month 3, whenever clinically feasible. In this real-world cohort, the precise schedule remained at the treating physician's discretion. Consequently, attainment of CR (prednisone ≤ 10 mg/day) often took longer than in controlled trials. Consistent with prior reports, infections clustered during the induction period and correlated with significantly higher daily prednisone doses.

Long-term follow-up results revealed that, although ANCA titers and B-cell counts began to rebound after 52 weeks, both Cr and eGFR levels remained stable through 76 weeks. This stability further supports the potential role of obinutuzumab in preserving kidney function. This benefit is especially relevant for the MPA subset, which carries the highest renal risk and is disproportionately

TABLE 3 Comparative analysis of laboratory parameters within 24 weeks.

Variables, median (IQR)	Baseline	24 weeks	P value
CRP, mg/L	51.13 (25.13–101.77)	4.75 (0.28–8.47)	<0.0001
ESR, mm/h	67.50 (29.50–80.50)	11.50 (2–34.50)	0.0002
Serum Cr, μmol/L	92 (68.93–129.73)	79.50 (64.60–95.43)	0.0010
eGFR, mL/min	107 (69.50–112)	108 (81–114.50)	0.0070
24-h protein, mg	277.47 (157.76–538.05)	62.54 (57.14–174.69)	0.0313
IgG, g/L	10.80 (9.67–16.70)	5.81 (5.09–7.99)	0.0015
IgM, g/L	0.74 (0.59–0.83)	0.31 (0.26–0.58)	0.0020
ANCA, AU	2.67 (0.81–3.88)	0.13 (0.09–0.54)[#]	0.0005
B-cell counts, 10^9/L	74.90 (55.30–226.60)	0 (0–0)	0.0002

IQR, interquartile range; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Cr, creatinine; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; IgM, immunoglobulin M; and ANCA, anti-neutrophil cytoplasm antibodies. [#]The cutoff value for a positive ANCA titer was set at ≥1.

prevalent in Asia. In our cohort, all four MPO-ANCA-positive patients, each of whom was previously refractory to CTX or RTX, achieved CR by week 76 while maintained on only 5 mg/day prednisone, highlighting obinutuzumab's superior efficacy in treating this refractory population.

To minimize the risks of adaptive immune dysfunction and susceptibility to opportunistic infections, we administered prophylactic medications, such as sulfamethoxazole-trimethoprim prophylaxis for PJP prevention, isoniazid for tuberculosis prevention, and entecavir for hepatitis B prevention. Additionally, we would recommend vaccination for every patient, although it is not mandatory. Despite pre-medication with intravenous methylprednisolone and paracetamol to mitigate severe infusion reactions, three infusion-related adverse events were documented. All were mild, and each resolved after a transient reduction in infusion rate. Obinutuzumab-induced thrombocytopenia (19) has been well-documented in a previous study. However, this symptom was not observed in our cohort.

A key strength of this study is that it represents the largest real-world cohort of refractory or relapsing AAV patients treated with obinutuzumab to date. Despite this strength, the small sample size constrained the statistical power and limited the generalizability of our findings. Furthermore, the reduced-dose obinutuzumab regimen employed was deliberately more conservative compared with lymphoma protocols, reflecting its status as an exploratory, non-standard approach for AAV. While this lower-dose strategy may potentially reduce adverse effects, it also raises concerns regarding its ability to achieve optimal therapeutic efficacy. The absence of an evidence-based dosing framework for obinutuzumab in AAV underscores the urgent need for well-designed, randomized, controlled trials to establish standardized, effective, and safe treatment protocols. Nonetheless, this exploratory approach represents an important step toward understanding the potential role of obinutuzumab in managing refractory AAV. In our study, CR was achieved when a patient was maintained on a prednisone dosage of ≤10 mg/day. However, more stringent criteria are now favored in current clinical research and practice. The 2022 EULAR update recommends that patients with AAV achieve a dosage of ≤5 mg/day by 4–5 months (3). Furthermore, the TAPIR trial (20) supports the notion that a dosage of ≤5 mg/day, or

TABLE 4 Infections documented during follow-up.

Infection	n, (%)
Patients who were infected	7 (43.8)
Infection times	12
Type	
Virus	7 (58.3)
COVID-19	3 (25)
CMV	2 (16.7)
Influenza A	1 (8.3)
EBV	1 (8.3)
Fungus	3 (25)
Bacterium	2 (16.7)
Site	
Respiratory tract	9 (75)
Urinary tract	1 (8.3)
Blood	2 (16.7)

CMV, cytomegalovirus, and EBV, Epstein–Barr virus.

TABLE 5 Risk factor analysis between the infected and non-infected groups.

Variables, mean (SD)	Infected (n=7)	Non-infected (n=9)	P value
IgG, g/L	6.2 (2.8)	7.4 (1.3)	0.3371
Concurrent prednisone, mg/day	55 (34.1)	18.3 (7.5)	0.0250
Pulse methylprednisolone, n (%)	5 (71.4)	4 (44.4)	0.3575

IgG, immunoglobulin G, and SD, standard difference.

ideally complete glucocorticoid discontinuation, may represent a more contemporary and clinically relevant definition of remission. Nevertheless, this study offers critical real-world evidence supporting obinutuzumab as an experimental treatment option for AAV, leveraging its potent B-cell-depleting activity. Future investigations should prioritize dose optimization strategies, rigorous immune function surveillance, and extended follow-up to definitively establish the therapeutic role of obinutuzumab in AAV.

Conclusions

Reduced-dose obinutuzumab demonstrated rapid and durable efficacy with a favorable safety profile in patients with refractory or relapsing active AAV, establishing it as a promising therapeutic alternative, particularly after RTX or CTX failure.

Data availability statement

The data supporting the findings of this study are available within the article, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Renji Hospital Ethics Committee (IRB no. LY2025 - 197-A) and obtained informed consent from all patients. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

WW: Formal Analysis, Conceptualization, Investigation, Writing – review & editing, Writing – original draft. JW: Writing – review & editing, Conceptualization, Data curation. SC: Resources, Writing – review & editing, Data curation, Supervision, Conceptualization.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2025.1624234/full#supplementary-material

References

1. Geetha D, Jefferson JA. ANCA-associated vasculitis: core curriculum 2020. *Am J Kidney Dis*. (2020) 75:124–37. doi: 10.1053/j.ajkd.2019.04.031

2. Kronbichler A, Bajema IM, Bruchfeld A, Mastroianni Kirsztajn G, Stone JH. Diagnosis and management of ANCA-associated vasculitis. *Lancet*. (2024) 403:683–98. doi: 10.1016/S0140-6736(23)01736-1

3. Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheumatic Dis*. (2024) 83:30–47. doi: 10.1136/ard-2022-223764

4. Abeles I, Palma C, Meednu N, Payne AS, Looney RJ, Anolik JH. B cell–directed therapy in autoimmunity. *Annu Rev Immunol*. (2024) 42:103–26. doi: 10.1146/annurev-immunol-083122-044829

5. Meyer S, Evers M, Jansen JHM, Buijs J, Broek B, Reitsma SE, et al. New insights in Type I and II CD20 antibody mechanisms-of-action with a panel of novel CD20 antibodies. *Br J Haematology*. (2018) 180:808–20. doi: 10.1111/bjh.15132

6. Marinov AD, Wang H, Bastacky SI, van Puijenbroek E, Schindler T, Speziale D, et al. The type II anti-CD20 antibody obinutuzumab (GA101) is more effective than rituximab at depleting B cells and treating disease in a murine lupus model. *Arthritis Rheumatol*. (2021) 73:826–36. doi: 10.1002/art.41608

7. Klomjit N, Fervenza FC, Zand L. Successful treatment of patients with refractory PLA2R-associated membranous nephropathy with obinutuzumab: A report of 3 cases. *Am J Kidney Dis*. (2020) 76:883–8. doi: 10.1053/j.ajkd.2020.02.444

8. McGovern DP, McClure ME, Coates M, Bond S, Martinez Del Pero M, Mynard K, et al. Study protocol for a randomised, phase II, double-blind, experimental medicine study of obinutuzumab versus rituximab in ANCA-associated vasculitis: ObiVas. *BMJ Open*. (2024) 14. doi: 10.1136/bmjopen-2023-083277

9. Dall'Era M, Cisternas MG, Smilek DE, Straub L, Houssiau FA, Cervera R, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. *Arthritis Rheumatol*. (2015) 67:1305–13. doi: 10.1002/art.39026

10. Tamirou F, Lauwerys BR, Dall'Era M, Mackay M, Rovin B, Cervera R, et al. A proteinuria cut-off level of 0.7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN Nephritis Trial. *Lupus Sci Med*. (2015) 2:e000123. doi: 10.1136/lupus-2015-000123

11. Suppiah R, Robson JC, Grayson PC, Ponte C, Craven A, Khalid S, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. *Ann Rheumatic Dis*. (2022) 81:321–6. doi: 10.1136/annrheumdis-2021-221796

12. Robson JC, Grayson PC, Ponte C, Suppiah R, Craven A, Judge A, et al. 2022 american college of rheumatology/european alliance of associations for rheumatology classification criteria for granulomatosis with polyangiitis. *Arthritis Rheumatol*. (2022) 74:393–9. doi: 10.1002/art.41986

13. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. (2013) 65:1–11. doi: 10.1002/art.37715

14. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the birmingham vasculitis activity score (version 3). *Ann Rheum Dis*. (2009) 68:1827–32. doi: 10.1136/ard.2008.101279

15. Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 american college of rheumatology/vasculitis foundation guideline for the management of antineutrophil cytoplasmic antibody–associated vasculitis. *Arthritis Care Res*. (2021) 73:1088–105. doi: 10.1002/acr.24634

16. Furie RA, Rovin BH, Garg JP, Santiago MB, Aroca-Martínez G, Zuta Santillán AE, et al. Efficacy and safety of obinutuzumab in active lupus nephritis. *New Engl J Med*. (2025). doi: 10.1056/NEJMoa2410965

17. Kvacskay P, Merkt W, Günther J, Blank N, Lorenz HM. Obinutuzumab in connective tissue diseases after former rituximab-non-response: a case series. *Ann Rheum Dis*. (2022) 81:744–6. doi: 10.1136/annrheumdis-2021-221756

18. Amudala NA, Boukhlal S, Sheridan B, Langford CA, Geara A, Merkel PA, et al. Obinutuzumab as treatment for ANCA-associated vasculitis. *Rheumatology*. (2022) 61:3814–7. doi: 10.1093/rheumatology/keab916

19. Mechelfekh Y, Pontrucher A, Paillassa J, Temple M, Houot R. Obinutuzumab-induced acute thrombocytopenia: Report of two cases and review of literature. *Br J Haematology*. (2023) 202:168–72. doi: 10.1111/bjh.18826

20. Cronholm PF, Applequist J, Krischer J, Fontenot E, Davis T, Burroughs C, et al. A study of implementation factors for a novel approach to clinical trials: constructs for consideration in the coordination of direct-to-patient online-based medical research. *BMC Med Res Methodol*. (2024) 24:244. doi: 10.1186/s12874-024-02352-w

frontiers | Frontiers in Immunology

TYPE Case Report
PUBLISHED 15 September 2025
DOI 10.3389/fimmu.2025.1618495

OPEN ACCESS

EDITED BY
Poh-Yi Gan,
Monash University, Australia

REVIEWED BY
Graham Wallace,
University of Birmingham, United Kingdom
Mitsuhiro Takeno,
Nippon Medical School Musashi Kosugi Hospital, Japan
Zhang Ning,
Capital Medical University, China

*CORRESPONDENCE
Shuyan Liu
catmi7903@163.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 26 April 2025
ACCEPTED 29 August 2025
PUBLISHED 15 September 2025

CITATION
Zhang P, Zhang W, Xia H, Fan Z, Fan J, Ma H, Zhang C and Liu S (2025) Case Report: A rare case of complex Behçet's disease complicated with acute tubular necrosis and IgA nephropathy, coexists with myelodysplastic syndrome, trisomy 8 and intestinal involvement. *Front. Immunol.* 16:1618495. doi: 10.3389/fimmu.2025.1618495

Case Report: A rare case of complex Behçet's disease complicated with acute tubular necrosis and IgA nephropathy, coexists with myelodysplastic syndrome, trisomy 8 and intestinal involvement

Peipei Zhang[1,2†], Wen Zhang[1,2†], Hong Xia[1,2†], Zhenliang Fan[1,2†], Junfen Fan[1,2], Hongzhen Ma[1,2], Chunli Zhang[3] and Shuyan Liu[4*]

[1]Department of Nephrology, the First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, Zhejiang, China, [2]Zhejiang Key Laboratory of Research and Translation for Kidney Deficiency-Stasis-Turbidity Disease, Zhejiang-Macau International Joint Laboratory of Integrated Traditional Chinese and Western Medicine for Nephrology and Immunology, Hangzhou, Zhejiang, China, [3]Department of Pathology, The First Affiliated Hospital of Zhejiang Chinese Medical University(Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, China, [4]Department of Hematology, The First Affiliated Hospital of Zhejiang Chinese Medical University(Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, China

Behçet's disease (BD) is a rare systemic disease in which small-vessel vasculitis impacts multiple bodily organs. It is typically marked by recurrent oral and genital ulcers, uveitis, and cutaneous lesions. However, peripheral vessels, cardiovascular structures, central nervous system, gastrointestinal tract, joints, lungs, or kidneys may be affected as well. Renal involvement, although uncommon, may manifest as proteinuria, hematuria, and varying degrees of renal insufficiency. Herein, we describe a 35-year-old man with longstanding BD, myelodysplastic syndrome (MDS), and trisomy 8. He presented with cutaneous erythema and gastrointestinal bleeding (requiring colonic resection), later developing acute renal failure. Features of both acute tubular necrosis (ATN) and IgA nephropathy appeared on subsequent biopsy. Following continuous renal replacement therapy and intravenous methylprednisolone treatment, there was gradual recovery of renal function. This scenario represents a rare and severe multisystem presentation of BD with complex comorbidities, attributing the observed kidney injury to combined insults as above. Given the persistent and multifaceted nature of BD, early recognition and targeted management of renal complications are essential to preserve functional capacity and improve patient outcomes.

KEYWORDS

Behçet's disease, acute tubular necrosis, IgA nephropathy, myelodysplastic syndrome, intestinal involvement

Introduction

Behçet's disease (BD) is a multisystem inflammatory disorder characterized primarily by small-vessel vasculitis. Its prevalence is higher in regions along the ancient Silk Road (1). Skin, genitals, and gastrointestinal (GI) tract are most often affected, whereas an association with myelodysplastic syndrome (MDS) is relatively rare (2). Renal involvement in BD is also uncommon. According to past reports, amyloidosis is the prevailing pathology, followed by chronic glomerulonephritis and less frequently by renovascular disease (3). This account serves to document a rare and complex case of severe BD in the context MDS and trisomy 8—one that is complicated by biopsy confirmed acute tubular necrosis (ATN) and IgA nephropathy in the wake of intestinal necrosis.

Case presentation

The patient was 35-year-old man with longstanding BD whose 3-week elevation of serum creatinine (SCr) prompted hospital admission. BD was diagnosed 18 years earlier based on recurrent oral ulcers, persistent high-grade fever, erythema nodosum, and a positive pathergy test. Prednisone (30 mg/day) and thalidomide were given at the time and seemed advantageous, conferring clinical benefit. Although prednisone tapering and discontinuation took place after 1 year of therapy, single doses were still warranted on occasion to manage intermittent bouts of low-grade fever and oral ulcers.

One year previously, the patient again experienced recurrent high fever (recorded maximum, 40.5°C), with relapse of oral ulcers, pharyngalgia, and headaches. Laboratory testing revealed pancytopenia (white blood cell [WBC] count, 0.7 × 10^9/L; hemoglobin [Hgb], 46 g/L; platelet count, 47 × 10^9/L) and remarkably high C-reactive protein (CRP, 91.88 mg/L). Empiric antimicrobial therapy and blood transfusion proved ineffective, but myelodysplastic syndrome (MDS) and trisomy 8 were diagnosed through fluorescence *in situ* hybridization and tumor mutational burden analyses of aspirated bone marrow.

Approximately 11 months prior, the patient claimed onset of hematochezia, reported as dark-red, jelly-like stools. Colonoscopy revealed severe ileocolonic changes likely stemming from BD. Treatment included intravenous (IV) methylprednisolone (80 mg/day) and immunoglobulin (10 g/day, 3 consecutive days), plus oral thalidomide (100 mg nightly). Unfortunately, the bleeding did not abate, instead culminating in massive GI hemorrhage and shock. The resultant fall in Hgb level to 59 g/L necessitated total colectomy and ileostomy on an emergency basis.

Histologic sections of resected colon confirmed vasculitis-associated intestinal necrosis. Full-thickness chronic inflammatory cell infiltrates were evident at ulcerative sites, in addition to necrosis and granulation tissue formation. Some blood vessels showed inflammatory mural infiltrates and visible thromboses, with luminal narrowing or complete obliteration (Figure 1).

During postoperative recovery, episodic seizures, with no abnormalities detected on brain MRI or CSF analysis, were successfully managed with oral sodium valproate. Ultimately, infliximab was administered at 250–300 mg (5 mg/kg) on Weeks 0, 2, and 6. This was followed by maintenance infusions at 8-week intervals. Thalidomide (100 mg/day) and cyclosporine (35 mg twice daily) were also added to the immunosuppressive regimen.

The patient had now presented with mild SCr elevation (up to 124 μmol/L) over a 3-week period. Urinary output was unfazed (~1,500 mL/day), but anorexia, nausea, and vomiting arose 3 days before admission, along with an upsurge in SCr (up to 1113 μmol/L) and hyperkalemia (6.1 mmol/L) (Figure 2). After concurrent initiation of volume resuscitation and potassium-lowering therapies, sinus bradycardia became problematic, registering a heart rate (HR) between 35 and 45 beats/min that required temporary transvenous pacemaker implantation (see corresponding electrocardiogram tracings of Figure 3). Once achieved, continuous renal replacement therapy (CRRT) began immediately, and renal biopsy was obtained when conditions permitted. In histologic sections, both IgA nephropathy and acute tubulointerstitial injury

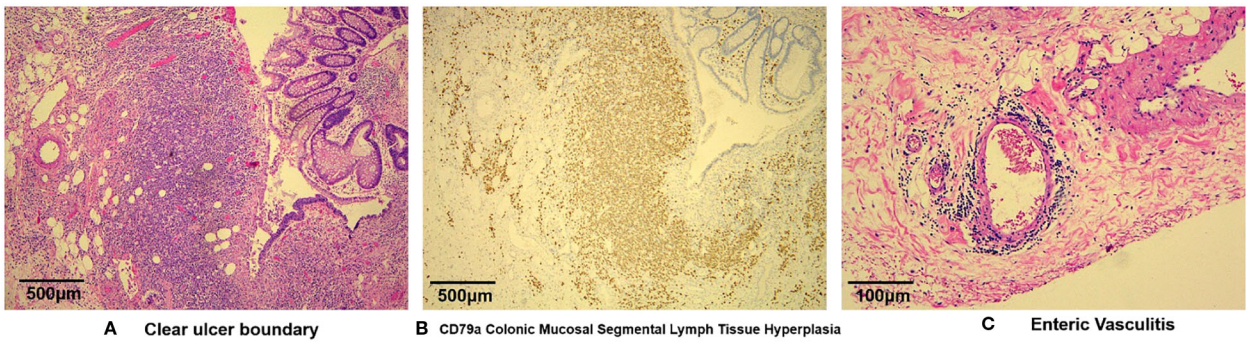


FIGURE 1
Microscopic views of vasculitis-induced intestinal necrosis: **(A)** full-thickness infiltration by chronic inflammatory cells at ulcer site, with necrosis and granulation tissue formation (H&E, 40X); **(B)** polyclonal proliferation of B lymphocytes differentiated from plasma cells (CD79a, 40X); and **(C)** mural infiltration of vessels by inflammatory cells and visible thrombosis, with luminal narrowing or obliteration—note partial arterial wall disruption and prominent histiocytic aggregates inside venous channels at ulcer base (H&E, 200X).

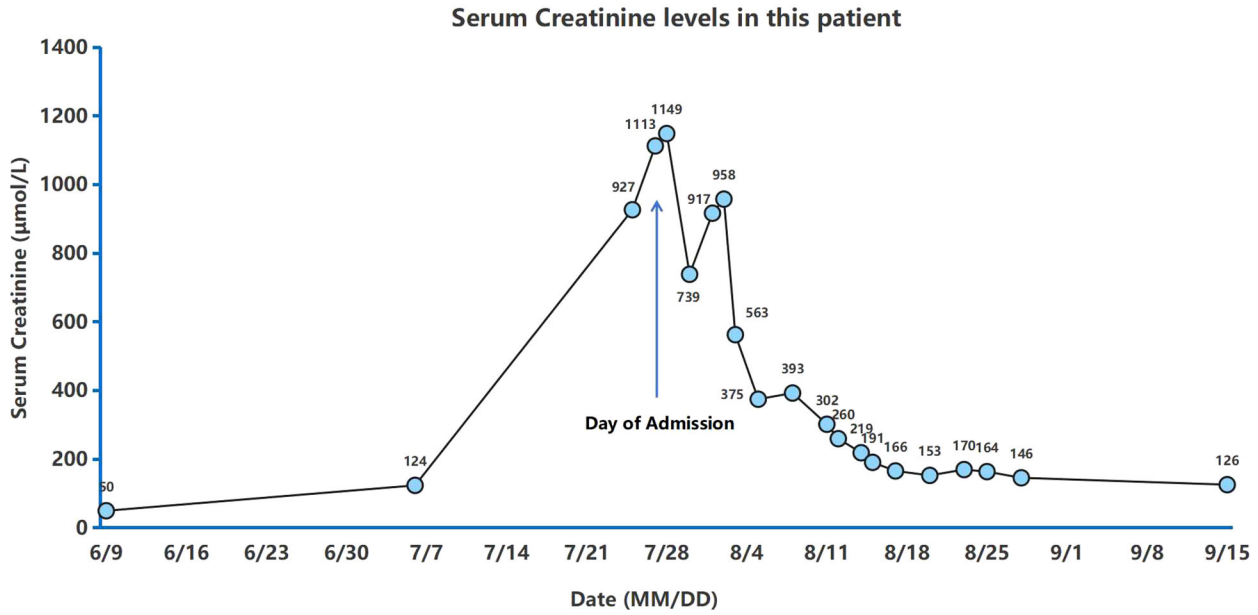


FIGURE 2
Dynamic changes in serum creatinine levels during patient's clinical course.

were identifiable. Chronic changes were also noted, including partial tubular necrosis. Moreover, birefringent disc-shaped crystals or basophilic deposits were discovered found within three tubular lumina under polarized light. The Oxford Classification of IgA nephropathy was M1 E0 S1 T0 C1 (Figure 4).

Renal replacement therapy continued, while administering IV methylprednisolone (80 mg/day) for 1 week. The patient gradually regained a normal heart rate (70 beats/min) in sinus rhythm, enabling pacemaker removal. After 3 weeks of treatment, he was discharged on prednisone tapered to 24 mg/day, with SCr at 166 μmol/L. Owing to a history of hepatitis B virus infection, antiviral therapy (tenofovir propofol fumarate, 25 mg/day) was additionally ongoing.

Course of treatment

Upon admission, the patient underwent continuous blood purification therapy. Cyclosporine was discontinued, and intravenous methylprednisolone (80 mg/day) was administered for 1 week. The patient's renal function gradually improved, with urine output increasing to 1,500-2,000 mL/day. Once stabilized, dialysis was terminated, and the dialysis catheter was removed.

Prognosis and follow-up

At 1-year follow-up, a regimen of prednisone (7.5 mg, once daily), mycophenolate mofetil (250 mg, twice daily), and thalidomide (50 mg, once nightly) was in place. The most recent hematologic measures were as follows: WBC count, 1.9 × 10^9/L; Hgb, 103 g/L; platelet count, 43 × 10^9/L; and reticulocytes, 2.51%. CRP values had normalized, and proteinuria was absent on urinalysis, which did show 8.4 erythrocytes per high-power microscopic field. Uric acid (583 μmol/L), SCr (108 μmol/L), cystatin C (1.52 mg/L), and estimated glomerular filtration rate (eGFR, 79.15 mL/min/1.73 m^2) were all within or near acceptable levels, reflecting adequacy of renal function.

Discussion

Renal involvement in patients with BD

BD is a chronic, relapsing, and multisystem autoimmune disorder with distinctive clinical features, including recurrent oral and genital ulcers, uveitis, and GI lesions (4). The diagnosis remains challenging due to lack of specific serologic markers, and disease severity may vary substantially among patients. Certain inflammatory cytokines, such as interleukin-6 (IL-6), have been proposed as auxiliary markers of disease activity (5). The sequence of events in our patient, marked by episodic oral ulcers and fever, diagnosis of MDS, catastrophic intestinal bleeding, seizure activity, acute renal failure, hyperkalemia, and obligatory temporary pacemaker implantation, was especially complex and overall proved quite daunting for clinical management.

The reported prevalence of renal involvement in BD varies widely across studies, ranging from 0-55% (3). These data may reflect differences in study populations, geographic regions, genetic predispositions, and diagnostic criteria, all of which influence accuracy and consistency of prevalence estimates. Abnormal

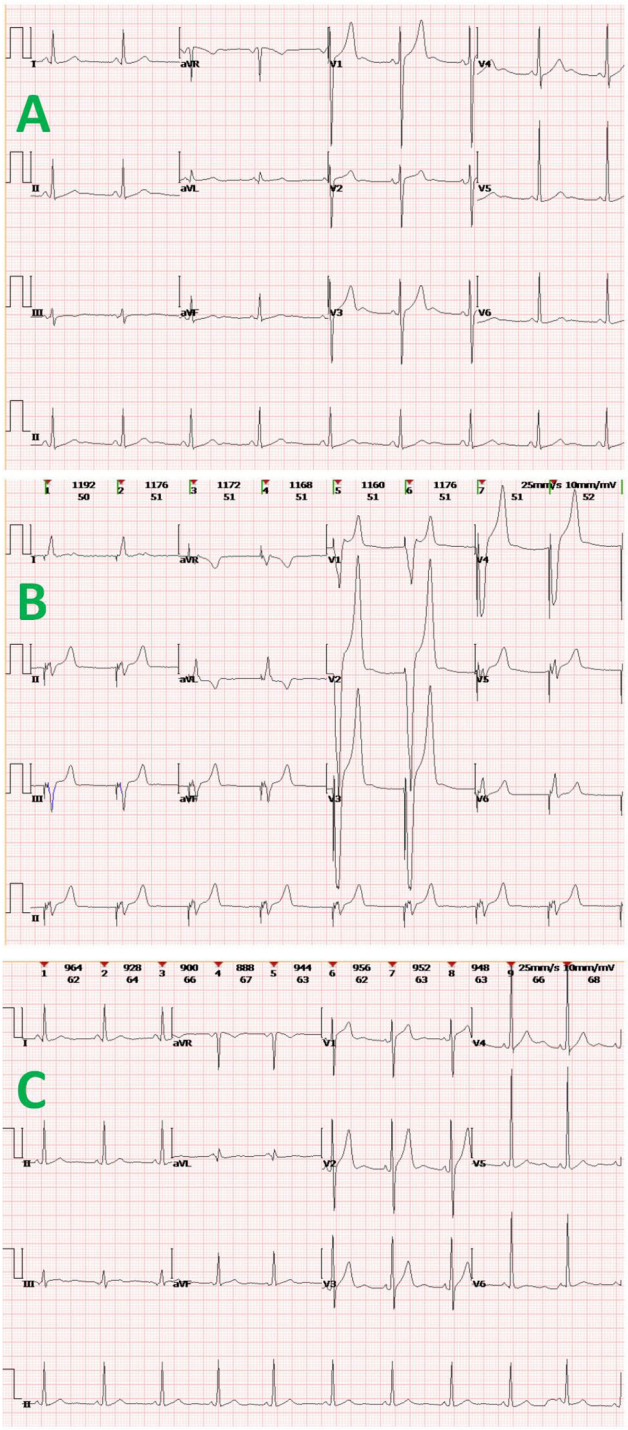


FIGURE 3
Electrocardiogram tracings at various clinical time points: **(A)** sinus bradycardia and mild QT-interval prolongation shown during acute renal failure; **(B)** post-implantation pacing in VVI mode, with broad/deformed QRS-T complexes following "spike-like" pacing signals; and **(C)** return to normal sinus rhythm.

urinalysis (i.e., proteinuria and microscopic hematuria) is the most frequent indicator of renal injury. Elevated SCr and blood urea nitrogen levels are reported in only a minority of cases (6), A subset of patients may also present with hypertension, often exhibiting malignant hypertension secondary to BD-related renal artery stenosis (7, 8). Histologic findings in renal biopsies from patients with BD have exposed an array of disease processes. Renal amyloidosis is most commonly reported, followed by chronic glomerulonephritis; and although rare, IgA nephropathy has been documented as well (9–11).

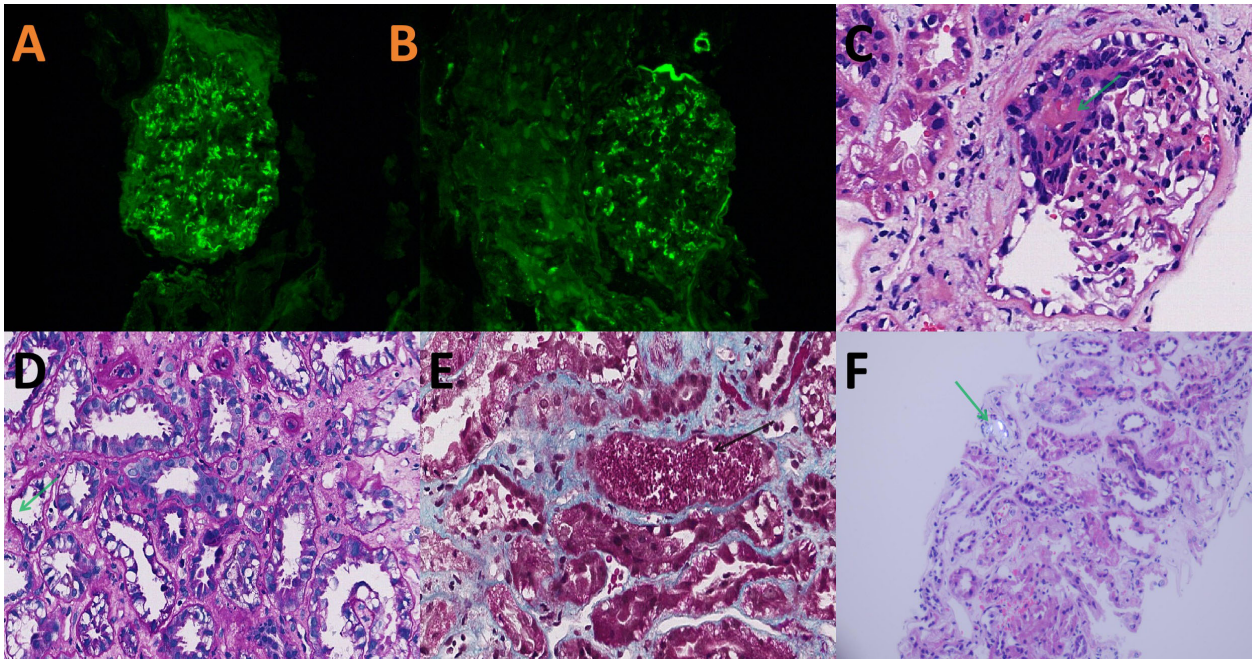


FIGURE 4
Renal biopsy findings: **(A, B)** acute tubulointerstitial lesions of IgA nephropathy clearly positive for IgA (+++) and C3 (++) by immunofluorescence microscopy, appearing as comma-shaped granular deposits in glomerular mesangial region and segmental capillary loops; **(C)** small cellular crescent containing fibrinoid exudate (arrow) (H&E, 200X); **(D)** vacuolar and granular degeneration of tubular epithelial cells, patchy tubular dilation, brush border loss, epithelial desquamation, and denuded basement membranes (green arrow) (PAS, 200X); **(E)** focal tubular necrosis and red blood cell casts (black arrow) (Masson, 200X); and **(F)** disc-shaped crystals within tubular lumen displaying white birefringence under polarized light (arrow) (H&E, 100X).

Acute tubulointerstitial injury in relation to BD

Acute tubulointerstitial injury is an uncommon manifestation of BD. To date, this is the first reported case of BD to show concurrent ATN and IgA nephropathy in the setting of MDS. As a chronic, relapsing autoimmune disorder, BD typically calls for long-term immunosuppressive therapy using corticosteroids, conventional immunosuppressants, or biologic agents. However, a number of these are actually implicated in renal injury. Prolonged use of cyclosporine is associated with acute and chronic tubulointerstitial injury, including interstitial fibrosis (12). Biologic agents, such as adalimumab and infliximab, have also been linked to onset and progression of IgA nephropathy in some patients (13, 14). Rarely, BD-related acute kidney injury (AKI) may be pronounced, causing rapid elevations of SCr and life-threatening hyperkalemia. It is exceedingly rare for patients with BD to require both temporary cardiac pacing and CRRT, as we have detailed.

In our patient, calamitous GI bleeding created a surgical emergency. Still, intestinal resection and the functional impairment entailed are recognized risk factors for secondary oxalate nephropathy. Inflammatory bowel disease is known to increase intestinal binding of calcium to the surplus of unabsorbed fatty acids produced, thereby reducing fecal excretion of calcium oxalate. Hyperoxaluria is thus promoted through enhanced oxalate absorption. At this same time, decreased urinary excretion of citrate and magnesium—both inhibitors of calcium oxalate crystallization—further increases the risk of nephrolithiasis. Hence, intestinal surgery (ileostomy mostly) is an independent risk factor for urinary stone formation, due to chronic dehydration, bicarbonate loss, and resultant urine acidification (15).

Upon histologic examination, renal tubules in this patient harbored apparent oxalate deposits. Disc-shaped crystals showing white birefringence under polarized light were visible within the lumina, possibly contributing to tubular obstruction and exacerbating the acute kidney injury (Figure 4). In previously reported cases of BD-related renal compromise, glomerular pathology occasionally revealed crescent formation, which is associated with rapid disease progression and poor urinary outcomes (3, 16). However, glomerular involvement was mild in this instance, with renal injury largely confined to ATN and interstitial inflammation. Corticosteroid therapy is known to accelerate recovery from ATN. In addition to high-dose corticosteroids, CRRT likely helped to improve renal function.

Intestinal involvement in patients with BD

Intestinal effects are inherent in BD, compelled by the systemic inflammatory nature of this disorder (17). Pertinent clinical symptoms commonly include abdominal pain, diarrhea, and hematochezia. In more severe cases, intestinal obstruction, perforation, or necrosis may emerge as complications. Management strategies for such involvement rely on both

pharmacologic and surgical interventions. Immunosuppressive therapy, namely corticosteroids and calcineurin inhibitors, remain the cornerstone of medical treatment, aiming to control inflammation and alleviate GI symptoms (12). For disease refractory to conventional immunosuppressants, surgical remedies (ie, bowel resection and enterostomy) may be inevitable. Biologic agents targeting tumor necrosis factor-alpha (TNF-α), particularly infliximab and adalimumab, have demonstrated efficacy in those with intractable intestinal BD, facilitating symptom control and healing of extreme mucosal damage (18). Our patient's uncontrolled GI bleeding and necrosis did not respond to therapy (corticosteroids, IV immunoglobulin, thalidomide, and cyclosporine), rendering surgical resection and ileostomy unavoidable. Infliximab administration in the aftermath finally brought clinical improvement and resolution of GI symptoms.

Pathogenetic interplay between BD, MDS, and trisomy 8

The coexistence of BD and MDS represents a clinically significant entity characterized by overlapping pathophysiology. MDS comprises heterogeneous clonal hematopoietic stem cell disorders featuring ineffective hematopoiesis, peripheral cytopenia, and risk of leukemic transformation. Notably, epidemiologic studies report a 0.4-3.1% prevalence of MDS among BD patients (19–21), suggesting potential bidirectional pathogenetic links. Chronic immune dysregulation inherent to BD may drive clonal expansion of hematopoietic stem cells, while MDS-related immunosuppression can manifest as BD-like features including recurrent mucocutaneous ulcers. This clinical convergence complicates diagnosis and often delays appropriate intervention, particularly given the heightened gastrointestinal involvement observed in concurrent BD-MDS cases compared to isolated BD.

Central to this interplay may be trisomy 8, a cytogenetic aberration present in 7–9% of MDS patients with detectable chromosomal abnormalities (22, 23). Mechanistically, trisomy 8 drives overexpression of proinflammatory cytokines including transforming growth factor-β, IL-6, and interleukin-7 receptor in MDS (24), mirroring elevated IL-6, granulocyte colony-stimulating factor, and TNF-α levels in trisomy 8-positive BD patients. This shared cytokine dysregulation disrupts immune homeostasis, damages hematopoietic stem cells, and promotes both bone marrow failure and autoinflammatory manifestations. Critically, trisomy 8 constitutes a high-risk marker for BD-to-MDS progression (25) and correlates with severe gastrointestinal involvement. Systematic evidence confirms trisomy 8-positive patients exhibit significantly higher mortality (OR 11.74), gastrointestinal manifestations (76.1% vs. 17.2% in classical BD), and treatment-refractory inflammation, underscoring its distinct clinico-pathologic identity (26).

Therapeutic implications emerge from this unified pathogenic model: hematopoietic stem cell transplantation demonstrates disease-modifying potential in BD patients with concurrent trisomy 8-positive MDS (27), while conventional immunosuppressants and corticosteroids remain first-line options. Future research should clarify precise molecular pathways linking trisomy 8, cytokine networks, and hematopoietic clonality to optimize risk stratification and targeted therapies.

Renal implications of MDS

MDS is a serious but rare clonal hematopoietic disorder. Assorted renal pathologies documented in conjunction with MDS include acute tubulointerstitial nephritis, ANCA-negative pauci-immune necrotizing and crescentic glomerulonephritis, membranous nephropathy, and IgA nephropathy (28–30). Among these, acute tubulointerstitial nephritis and membranous nephropathy are most common. Because the risk of renal biopsy is heightened in patients with MDS (due to cytopenia), biopsy proven cases are scarce. Past reports have thus failed to properly record simultaneous occurrences of BD, MDS, and renal pathology. The present account is the first to address coexistence of these three conditions, highlighting an unusual and complex clinical scenario.

Conclusion

This report details a rare and severe case of BD leading to intestinal necrosis and subsequent acute renal injury (due to ATN, IgA nephropathy) in a patient with MDS and trisomy 8. It underscores the need for timely recognition and management of renal involvement in patients with BD, serving to preserve kidney function and improve clinical outcomes. Given the multisystem nature of BD, with potential overlap of hematologic and GI complications, a multidisciplinary approach to diagnosis and management is essential. Early detection, individualized treatment strategies, and continuous follow-up are critical for optimizing outcomes under such complex circumstances.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

PZ: Writing – review & editing, Writing – original draft. WZ: Writing – original draft, Writing – review & editing. HX: Writing – review & editing, Writing – original draft. ZF: Writing – review & editing. JF: Writing – review & editing. HM: Writing – review & editing. CZ: Writing – review & editing, Resources. SL: Writing – review & editing, Writing – original draft.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. This research was supported by the National Natural Science Foundation of China (Grant Nos. 82274432, 82204999), the Scientific Research Fund Project of the Zhejiang Administration of Traditional Chinese Medicine (Grant Nos. 2021ZB093, 2022ZB103), and the Zhejiang Medical and Health Science and Technology Program (Grant No. 2022KY925).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2025.1618495/full#supplementary-material

References

1. Fazaa A, Makhlouf Y, Ben Massoud F, Miladi S, Boussaa H, Ouenniche K, et al. Behçet disease: epidemiology, classification criteria and treatment modalities. *Expert Rev Clin Immunol.* (2024) 20:1437–48. doi: 10.1080/1744666x.2024.2388693

2. Emmi G, Bettiol A, Hatemi G, Prisco D. Behçet's syndrome. *Lancet.* (2024) 403:1093–108. doi: 10.1016/s0140-6736(23)02629-6

3. Akpolat T, Akkoyunlu M, Akpolat I, Dilek M, Odabas AR, Ozen S. Renal behçet's disease: A cumulative analysis. *Semin Arthritis Rheumatism.* (2002) 31:317–37. doi: 10.1053/sarh.2002.31721

4. Yazici Y. Management of behçet syndrome. *Curr Opin Rheumatol.* (2020) 32:35–40. doi: 10.1097/bor.0000000000000666

5. Hirahara L, Kirino Y, Soejima Y, Iizuka Y, Yoshimi R, Fujieda Y, et al. Association of high disease activity and serum il-6 levels with the incidence of inflammatory major organ events in behçet disease: A prospective registry study. *Front Immunol.* (2024) 15:1354969. doi: 10.3389/fimmu.2024.1354969

6. Shahram F, Davatchi F, Nadji A, Jamshidi A, Akbarian M, Gharibdoost F, et al. Urine abnormalities in behçet's disease. Study of 4704 cases. *Adv Exp Med Biol.* (2003) 528:477–8. doi: 10.1007/0-306-48382-3_97

7. Wang X, Zhou Z, Li J, Su G, Li X. Hypertension as a prominent manifestation secondary to renal artery lesions in pediatric behcet's disease. *Pediatr Rheumatol.* (2024) 22:19. doi: 10.1186/s12969-023-00932-6

8. Kinguchi S, Tamura M, Furuta R, Toyota K, Ishiga K, Kanaoka T, et al. Behcet's disease presenting as Malignant hypertension induced by renovascular hypertension. *CEN Case Rep.* (2025) 14:135–40. doi: 10.1007/s13730-024-00918-7

9. Liao Y, Hong Q, Wang Y, Su F, Gan C, Hu J. A patient with behcet's disease and iga nephropathy in China. *BMC Nephrol.* (2024) 25:310. doi: 10.1186/s12882-024-03748-y

10. Akpolat T, Diri B, Oguz Y, Yilmaz E, Yavuz M, Dilek M. Behcet's disease and renal failure. *Nephrol Dialysis Transplant.* (2003) 18:888–91. doi: 10.1093/ndt/gfg084

11. Fernandes BM, Garcia S, Rato M, Pinheiro F, Pimenta S, Mariz E, et al. Renal involvement in behçet´S disease: A rare clinical challenge. *ARP Rheumatol.* (2022) 1:174–6.

12. Kawaguchi T, Fukata M, Omori T. Efficacy of calcineurin inhibitors for induction of remission in intestinal behçet's disease. *Crohns Colitis 360* (2022) 4: otac017. doi: 10.1093/crocol/otac017

13. Bhagat Singh AK, JeyAruban AS, Wilson GJ, Ranganathan D. Adalimumab-induced iga nephropathy. *BMJ Case Rep.* (2019) 12:e226442. doi: 10.1136/bcr-2018-226442

14. Segawa Y, Ishida R, Kanehisa F, Nakai K, Morimoto M, Seno M, et al. Iga nephropathy in a patient receiving infliximab for generalized pustular psoriasis. *BMC Nephrol* (2020) 21:366. doi: 10.1186/s12882-020-02015-0

15. Bianchi L, Gaiani F, Bizzarri B, Minelli R, Cortegoso Valdivia P, Leandro G, et al. Renal lithiasis and inflammatory bowel diseases, an update on pediatric population. *Acta bio-medica: Atenei Parmensis.* (2018) 89:76–80. doi: 10.23750/abm.v89i9-S.7908

16. Akpolat T, Dilek M, Aksu K, Keser G, Toprak O, Cirit M, et al. Renal behçet's disease: an update. *Semin Arthritis Rheum.* (2008) 38:241–8. doi: 10.1016/j.semarthrit.2007.11.001

17. Gonçalves JC, Rosa B, Cotter J. Small bowel vasculitis? What a gastroenterologist should know - from diagnosis to management. *Curr Opin Gastroenterol.* (2025) 41:132-8. doi: 10.1097/mog.0000000000001087

18. Talarico R, Italiano N, Emmi G. Efficacy and safety of infliximab or adalimumab in severe mucocutaneous behçet's syndrome refractory to traditional immunosuppressants: A 6-month, multicentre, randomised controlled, prospective, parallel group, single-blind trial. *Ann Rheum Dis.* (2024). doi: 10.1136/ard-2024-226113

19. Ahn JK, Oh JM, Lee J, Koh EM, Cha HS. Behcet's disease associated with Malignancy in korea: A single center experience. *Rheumatol Int.* (2010) 30:831–5. doi: 10.1007/s00296-009-1319-3

20. Lin Y, Li G, Zheng W, Tian X, Zhang F. Behcet's disease associated with Malignancy: A report of 41 chinese cases. *Int J rheumatic Dis.* (2014) 17:459–65. doi: 10.1111/1756-185x.12269

21. Shen Y, Ma HF. High incidence of gastrointestinal ulceration and cytogenetic aberration of trisomy 8 as typical features of behçet's disease associated with myelodysplastic syndrome: A series of 16 consecutive chinese patients from the

shanghai behçet's disease database and comparison with the literature. *Biomed Res Int*. (2018) 2018:8535091. doi: 10.1155/2018/8535091

22. Solé F, Espinet B, Sanz GF, Cervera J, Calasanz MJ, Luño E, et al. Incidence, characterization and prognostic significance of chromosomal abnormalities in 640 patients with primary myelodysplastic syndromes. *Grupo Cooperativo Español Citogenética Hematológica. Br J haematology*. (2000) 108:346–56. doi: 10.1046/j.1365-2141.2000.01868.x

23. Bernasconi P, Klersy C, Boni M, Cavigliano PM, Calatroni S, Giardini I, et al. Incidence and prognostic significance of karyotype abnormalities in *de novo* primary myelodysplastic syndromes: A study on 331 patients from a single institution. *Leukemia*. (2005) 19:1424–31. doi: 10.1038/sj.leu.2403806

24. Chen G, Zeng W, Miyazato A, Billings E, Maciejewski JP, Kajigaya S, et al. Distinctive gene expression profiles of cd34 cells from patients with myelodysplastic syndrome characterized by specific chromosomal abnormalities. *Blood*. (2004) 104:4210–8. doi: 10.1182/blood-2004-01-0103

25. Kawabata H, Sawaki T, Kawanami T, Shimoyama K, Karasawa H, Fukushima T, et al. Myelodysplastic syndrome complicated with inflammatory intestinal ulcers: significance of trisomy 8. *Internal Med (Tokyo Japan)*. (2006) 45:1309–14. doi: 10.2169/internalmedicine.45.1718

26. Ichikawa K, Adachi S, Takase-Minegishi K, Nakayama Y, Nagasawa Y, Iizuka Y, et al. Distinct features of trisomy 8-associated autoinflammatory disease from behçet's disease: case series and systematic review. *Clin Exp Rheumatol*. (2025). doi: 10.55563/clinexprheumatol/8j7rbr

27. Yilmaz U, Ar MC, Esatoglu SN, Bavunoglu I, Erzin YZ, Hatemi AI, et al. How to treat myelodysplastic syndrome with clinical features resembling behçet syndrome: A case-based systematic review. *Ann Hematol*. (2020) 99:1193–203. doi: 10.1007/s00277-020-03951-5

28. Schwotzer N, Provot F, Ville S, Daniel L, Le Fur A, Kissling S, et al. Spectrum of kidney involvement in patients with myelodysplastic syndromes. *Kidney Int Rep*. (2021) 6:746–54. doi: 10.1016/j.ekir.2020.12.030

29. Apostolou T, Sotsiou F, Pappas C, Rontoianni D, Apostolidis J, Nikolopoulou N. Atheroembolic renal disease and membranous nephropathy, in a patient with myelodysplastic syndrome, eosinophilia, and trisomy 8. *Nephrology dialysis transplantation: Off Publ Eur Dialysis Transplant Assoc - Eur Renal Assoc*. (2002) 17:1336–8. doi: 10.1093/ndt/17.7.1336

30. Ko KI, Lee MJ, Doh FM, Koo HM, Kim CH, Shin DH, et al. Membranous glomerulonephritis in a patient with myelodysplastic syndrome-refractory cytopenia with multilineage dysplasia. *Kidney Res Clin Pract*. (2013) 32:134–7. doi: 10.1016/j.krcp.2013.06.001

frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 18 September 2025
DOI 10.3389/fimmu.2025.1655326

OPEN ACCESS

EDITED BY
Joshua Daniel Ooi,
Monash University, Australia

REVIEWED BY
Chrysoula Gialouri,
National and Kapodistrian University of Athens, Greece
Chaïmaâ Zeroual,
Centre Hospitalier Universitaire Ibn Rochd, Morocco

*CORRESPONDENCE
Federico Alberici
federico.alberici@gmail.com

RECEIVED 27 June 2025
ACCEPTED 18 August 2025
PUBLISHED 18 September 2025

CITATION
Alberici F, Flossmann O, Lamprecht P, Loudon KW, Padoan R, Popov T, Salvarani C and Mohammad AJ (2025) Antineutrophil cytoplasmic antibody-associated vasculitis: insights into relapse risk and future management directions.
Front. Immunol. 16:1655326.
doi: 10.3389/fimmu.2025.1655326

Antineutrophil cytoplasmic antibody-associated vasculitis: insights into relapse risk and future management directions

Federico Alberici[1]*, Oliver Flossmann[2], Peter Lamprecht[3], Kevin W. Loudon[4,5], Roberto Padoan[6], Tamara Popov[7], Carlo Salvarani[8] and Aladdin J. Mohammad[9,10,11]

[1]Nephrology Unit, University of Brescia, ASST Spedali Civili, Brescia, Italy, [2]Renal Unit, Royal Berkshire Hospital, Reading, Berkshire, United Kingdom, [3]Department of Rheumatology and Clinical Immunology, University of Lübeck, Lübeck, Germany, [4]Molecular Immunity Unit, Department of Medicine, University of Cambridge, Cambridge, United Kingdom, [5]Cambridge University Hospitals NHS Foundation Trust, NIHR Cambridge Biomedical Research Centre, Cambridge, United Kingdom, [6]Rheumatology Unit, Department of Medicine (DiMed), University of Padua, Padua, Italy, [7]CSL Vifor, Glattbrugg, Switzerland, [8]Rheumatology Unit, Azienda USL-IRCCS di Reggio Emilia, Università di Modena e Reggio Emilia, Reggio Emilia, Italy, [9]Department of Rheumatology, Skåne University Hospital, Lund, Sweden, [10]Clinical Sciences, Rheumatology, Lund University, Lund, Sweden, [11]Department of Medicine, University of Cambridge, Cambridge, United Kingdom

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) has a relapsing-remitting course and, even with the availability of effective maintenance therapies such as rituximab, relapse rates remain high. Relapse is associated with the accrual of organ damage stemming from both the underlying disease and from the effects of AAV treatments; thus, early detection and proactive prevention are crucial. AAV study populations typically include mixed cohorts of patients with new-onset and relapsing disease. Although data specifically addressing re-induction of remission after relapse are limited, available evidence suggests high remission rates when rituximab is combined with glucocorticoids. However, the balance between effective disease control and the potential treatment-related side effects must be carefully considered, and new therapeutic options may help improve this tradeoff. The aim of this review is to explore what is known about relapse risk and relapse management while considering emerging pathogenic and therapeutic paradigms.

KEYWORDS

antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, AAV relapse, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), remission re-induction

1 Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of autoimmune necrotizing small vessel vasculitides that causes potentially life-threatening ischemic and inflammatory organ damage (1–3). The three subsets of AAV are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Patients with GPA predominantly have ANCA directed against proteinase 3 (PR3), whereas, in MPA, 60 – 80% of patients have ANCA specific for myeloperoxidase (MPO) (4, 5). In EGPA, MPO-ANCA are detected in 30 – 40% of patients, whereas PR3-ANCA are rare. GPA is the most common AAV subtype with a global incidence of 9 per million person-years (6). Due to the distinct nature and genetic background of EGPA, it is often excluded from AAV clinical trials and will not be discussed in this paper.

Treatment of AAV with cytotoxic agents, immunosuppressive therapies, and biologics (particularly the monoclonal anti-CD20 antibody rituximab) have improved prognosis by effectively addressing active disease which, if untreated, can lead to impaired organ structure and/or function (organ damage) (7, 8). Although AAV is associated with premature mortality relative to the general population (9, 10), treatment-related improvements in survival together with a greater awareness of AAV leading to improved diagnosis have led to a rise in the overall prevalence of AAV (6, 11, 12).

These conditions, which were once fatal in nearly all patients, are now considered as chronic relapsing disorders with peaks and troughs in disease activity (13). Although relapses (defined as the return of active disease after remission) are common and can be clinically significant, it is not possible to reliably predict when they will occur. Re-establishing control of disease activity (re-induction) promptly in patients with relapse is important to prevent or minimize organ damage. However, the optimal treatment for AAV relapse remains to be determined (14).

This paper summarizes the risk factors for AAV relapse, evaluates the effectiveness of available and exploratory biomarkers for predicting relapse, explores factors that might help inform relapse prevention strategies, and assesses the available treatment options for re-inducing remission.

2 Pathophysiology of AAV

Immune dysfunction is fundamental to the development of characteristic inflammatory lesions in blood vessels and affected organs in AAV (2, 3). In patients with impaired immunological self-tolerance and a genetic predisposition, the production of ANCA plays a key role in AAV pathogenesis by promoting inflammatory responses (4, 15, 16). The binding of ANCA to MPO and PR3 exposed on neutrophils primed by complement fragment C5a and cytokines enhances leukocyte-endothelial interactions triggering neutrophil extracellular trap (NET) formation (17) as well as a strong inflammatory response. This process is part of a broader immune dysfunction which exacerbates endothelial injury, with C5a further amplifying inflammation by enhancing the generation of antibodies and the activation of phagocytic cells (18). Complement activation thus plays a key role in disease pathogenesis and therefore in the development of organ injury (19–22). Of note, pathophysiological studies in AAV have historically not distinguished between the mechanisms driving disease onset and those involved in relapse. Although these processes are likely to overlap, definitive evidence supporting this assumption is currently lacking.

3 AAV disease course

AAV can develop at any time, but incidence increases with age (23). This complex disease has heterogenous phenotypes resulting in different treatment priorities in different patients (Figure 1).

The early stages of AAV typically present with a range of non-specific symptoms suggestive of chronic inflammation, including fatigue, weight loss, fever, myalgia, and polyarthralgia (23). Patients with more advanced disease may show signs and symptoms of damage to the ears, nose and throat (ENT) (e.g., chronic rhinosinusitis, nasal bleeding and hearing loss (23, 24)), lung fibrosis (e.g., persistent cough and breathlessness (23)), and/or chronic kidney disease (CKD) (e.g., microscopic hematuria and reduced estimated glomerular filtration rate [eGFR] (23)). In addition, prolonged active disease can result in inflammation-related comorbidities, such as cardiovascular disease (25, 26). The longer AAV remains undiagnosed and untreated, the greater the risk of AAV-related comorbidities and irreversible organ damage.

AAV is a relapsing-remitting disease making increases in disease activity part of the natural disease course. However, there is considerable variability in the duration of remission between relapses (27, 28), with some patients never experiencing a relapse. These disparities may be partly explained by differences between patients in immune system characteristics and response to immunosuppressive treatment (29, 30).

Each relapse increases the risk of potentially fatal organ damage due to increased inflammatory disease activity and the use of higher-dose (more toxic) re-induction treatments (31). Mortality is also affected by treatment-related toxicities (in particular serious infections) and comorbidities, including cardiovascular disease (26). Although treatment effectively improves survival in most patients, survival rates are typically lower in older patients and in those with more severe kidney involvement and more active disease (32). Despite improvements in survival rates over recent decades, mortality remains approximately 2.7 times higher in patients with AAV than in the general population (26).

4 Treatment of AAV

The aim of AAV treatment is to control active disease whilst limiting treatment-related toxicities, thereby preventing or minimizing the risk of tissue damage. Treatment includes

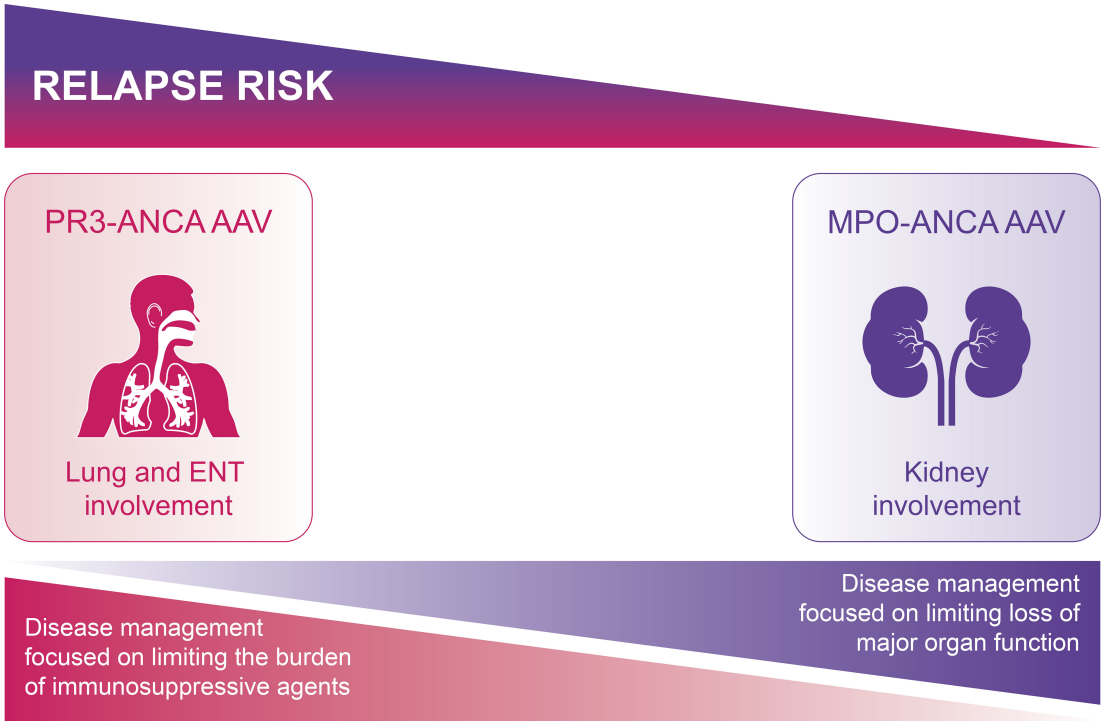


FIGURE 1
Aims of treatment differ according to AAV phenotype. For PR3-ANCA AAV, the relapse rate is higher, but the risk of major organ damage is lower, and so limiting the burden of re-treatment is the main aim of disease management. For MPO-ANCA AAV, although the relapse risk is lower, the higher chance of residual organ damage from the first relapse means there is higher risk of further progression of organ damage towards end-stage disease; the aim of disease management is thus to limit disease activity and reduce the risk of further loss of major organ function. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

intensive induction therapy (typically high-dose glucocorticoids with rituximab or cyclophosphamide) to gain rapid disease control and, once this is achieved, less toxic maintenance strategies to sustain remission (14).

The choice of treatment is not straightforward and may be restricted by the presence of disease-induced organ damage and co-morbidities. Treatments should ideally be tailored according to disease activity, risk factors, age, and existing comorbidities, e.g., CKD and lung disease (14, 33). The risk of treatment-induced comorbidities, such as infertility, diabetes, osteoporosis and infections, must also be considered. Ongoing monitoring of risk factors and signs of relapse is recommended throughout remission, as relapse risk can fluctuate over time due to inherent factors and cumulative events. The ideal scenario would be to have reliable tools for predicting relapses so, where necessary, treatment can be intensified early.

Over the last 30 years, expanding AAV treatment options have led to a shift from high-dose glucocorticoids supplemented with cyclophosphamide to less toxic approaches (34–36). For example, cyclophosphamide is often replaced or supplemented with rituximab to reduce the cumulative dose (14, 33). The current consensus is that rituximab is the most effective treatment for maintaining remission (37–39), and a combination of rituximab and glucocorticoids is recommended for the treatment of relapsing disease in most settings (14, 33). According to treatment guidelines, once remission is established, glucocorticoids should be tapered to the lowest effective dose (typically ≤5 mg/day within 4 to 5 months) or completely withdrawn to limit treatment toxicity (14, 33).

Recent studies, including the phase 3 randomized controlled ADVOCATE trial (40), demonstrate that the complement 5a receptor 1 (C5aR1) antagonist, avacopan, can improve remission rates, sustain remission over time, and (in patients with ANCA-associated glomerulonephritis) improve kidney function in patients with new-onset or relapsing AAV treated with rituximab or cyclophosphamide and reduced glucocorticoid exposure (37, 39–44). The use of avacopan with a low-dose glucocorticoid regimen is associated with a lower incidence of toxicities, including serious infections, than standard (non-avacopan) treatment (45). Based on results from the ADVOCATE trial (40), EULAR and KDIGO guidelines recommend using avacopan to reduce glucocorticoid exposure in patients receiving standard treatment for GPA or MPA (14, 33).

5 Challenges in maintaining remission

The optimal maintenance regimen has yet to be defined for patients achieving remission. Based on results from the MAINRITSAN trial (Table 1) (39), the recommended regimen includes pre-emptive rituximab doses of 500 mg every six months for 24 months (14, 53). However, the RITAZAREM trial found that a rituximab-based regimen of 1000 mg every 4 months was also

10.3389/fimmu.2025.1655326

TABLE 1 Summary of key data from randomized clinical trials in patients with relapsing AAV.

Trial	Study treatment	Follow-up	Remission assessment	Relapse assessment	Incidence of infection
Rituximab					
RAVE (37, 46) N=188 • Around half of patients had relapsing AAV • Excluded patients with severe kidney involvement	Arm 1: RTX 375 mg/m^2/ week×4 (n=99). No active treatment after achieving remission (n=61) to Month 18 Arm 2: Daily CYC 2 mg/kg (n=98). On achieving remission (n=63) AZA 2 mg/ kg to Month 18	18 months	Rate of remission at 6 months in relapsing AAV: RTX 67% p=0.01 CYC/AZA 42%.	Number of major relapses at: 12 months • 7 RTX group • 15 CYC/AZA group p=0.03 18 months • 1 RTX group • 17 CYC/AZA group p=0.19	Rate of grade ≥3 infections similar for both treatment groups (12% vs 11%) Leukopenia grade ≥2 was less common in RTX group (5 vs 23%, P<0.001)
RAVE re-induction (47) N=26 (15 RTX; 11 CYC/AZA • Patients from RAVE who experienced severe relapse Months 6 – 18 • 16 patients had relapsing AAV on starting RAVE	Open-label RTX (375 mg/m^2/ week for four weeks) plus GC (1mg/kg, tapered to discontinuation during remission)	12 months	Remission restored with RTX and GC re-induction treatment in 88% of patients 13/15 RTX group 10/11 CYC/AZA group Complete remission (zero GC) 40% RTX group 64% CYC/AZA group Mean time to remission: 56 days RTX group 36 days CYC/ AZA group	Relapse rate at 12 months: • 2 limited relapses RTX group • 2 severe relapse CYC/ AZA group	13 infections, of which 10 (77%) involved the ears, nose and upper respiratory tract. 2 grade 3 infections (gastroenteritis and sinusitis)
MAINRITSAN-1 (39) N=115 • Patients with AAV in remission • 20% had relapsing disease	Arm 1: Fixed RTX 500 mg infusion every 6 months for 18 months (n=57) Arm 2: Azathioprine 1 – 2 mg/kg/day for 22 months (n=58)	28 months	Prior to enrolment, remission was achieved using CYC plus GC and obtained after a mean of 4.6 months	Rate of major relapse Month 28: • 5% RTX group • 29% AZA group p= 0.002 4 AZA patients switched to RTX. In the AZA group 8 major relapses occurred within the first 12 months of maintenance therapy. One major relapse in the RTX group occurred at Month 8, and the 2 others occurred after the last infusion (Month 22 and Month 24)	Severe infections: • 19% RTX group • 14% AZA group Fatal sepsis in 1 AZA patient
MAINRITSAN-1 follow-up (48) N=115 • Patients with AAV in remission • 20% had relapsing disease	Arm 1: Fixed RTX 500 mg infusion every 6 months for 18 months (n=57) Arm 2: Azathioprine 1 – 2 mg/kg/day for 22 months (n=58)	60 months		At month 60, the major relapse-free survival rates were: 71.9% RTX group 49.4% AZA group p=0.003 RTX patients had 12.6 months more without relapse or toxicity than AZA patients	Severe infections: • 26% RTX group • 28% AZA group More bronchitis events with RTX v AZA (10 vs 1)
MAINRITSAN-2 (49) N=115 • Patients with AAV in remission • Tailored group 35% relapsing AAV • Fixed group 37% relapsing AAV	Arm 1: RTX 500 mg infusion + further RTX reinfusion when CD19+B lymphocytes reappeared or ANCA titre rose markedly (tailored group; n=81) Arm 2: Fixed RTX 500 mg infusion on days 0 and 14, then 6, 12 and 18 months after the first infusion (Fixed group; n=81)	28 months		Withdrawal due to major relapse by Month 18: • Tailored group: 3 • Fixed group: 2 Relapse rate Month 28: • Tailored: 17.3% • Fixed: 9.9% p=0.22 Major relapse rate Month 28: • Tailored: 83.8% • Fixed: 86.4% p=0.23	Each group had 18 infections. Infectious complications: • 11% tailored RTX • 20% fixed RTX group

(Continued)

10.3389/fimmu.2025.1655326

TABLE 1 Continued

Trial	Study treatment	Follow-up	Remission assessment	Relapse assessment	Incidence of infection
Rituximab					
MAINRITSAN-3 (50) • 68 patients in complete remission from MAINRITSAN - 2 • 41% relapsing disease	Arm 1: RTX every 6 months for 18 months (4 infusions) (n=50) Arm 2: Placebo infusion every 6 months for 18 months (4 infusions) (n=47)	≤36 months		Relapse-free survival Month 28 Any: • RTX: 96% • Placebo: 74% p=0.008 Major: • RTX: 100% • Placebo: 87% p=0.009 Month 48 relapse rates Any: • RTX: 4% • Placebo: 26% Major: • RTX: 0% • Placebo: 13%	Incidence of serious infection • 12% RTX group • 9% placebo group
MAINRITSAN Pooled (8) N=277 • 29% relapsing AAV	Group 1: 18-month fixed-dosing RTX (n=97) Group 2: 18-month tailored RTX (n=40) Group 3: 36-month tailored/fixed RTX (n=42) Group 4: 36-month fixed/fixed RTX (n=41) Group 5: AZA (n=58)	84 months		Major relapse risk Month 84: 18-month fixed RTX superior to AZA (HR 0.38) 18-month fixed RTX superior to tailored RTX (HR 2.92) Similar for 36-month fixed/fixed RTX and 18-month fixed RTX (HR 0.69) Median time to major relapse was 25 months with AZA group, and 36 months with RTX	Infections were the most frequent serious adverse event with 75 (27%) patients having ≥1 serious infection
RITAZAREM (51, 52) N=188 • Patients with relapsing AAV recruited at time of relapse • 63% of relapses had ≥1 major disease activity item	Re-induction with weekly RTX and GCs (N = 187) followed by: Arm 1: maintenance with fixed-dose RTX 1000 mg every 4 months, through month 20 (n=85) Arm 2: Daily AZA for 24 months (n=85)	48 months	Re-induction of remission was successful within 4 months in 90% of patients Of the 17 patients who did not achieve remission by Month 4, 13 (76%) had PR3-ANCA AAV and 10 (59%) had ENT involvement at baseline	RTX was superior to AZA in preventing any relapse (HR 0.41; p<0.001) and major relapse was (HR 0.36; p=0.004). 38 RTX patients (45%) had 52 relapses (11 major). 60 AZA patients (71%) had 89 relapses (28 major).	Induction phase 5/13 severe infections occurred within 4 weeks of the first RTX induction dose. There were 86 non-severe infections 2 patients died in the induction phase due to pneumonia Maintenance phase 19 serious infections in the RTX group and 24 in the AZA group.
Avacopan					
Phase II trial (43) N=67 Relapsing AAV: • GC group: 22% • GC+AVA group: 32% • AVA group: 27%	CYC or RTX plus GC 60 mg/day or GC 20 mg/day and AVA 30 mg bid or AVA 30 mg bid	12 weeks	Remission at Week 12: • GC group: 40% • GC+AVA group: 45% • AVA group: 33%	Remission at Week 4 sustained to Week 12: • GC group: 5% • GC+AVA group: 14% • AVA group: 29% (p<0.05 vs GC group)	Serious infection: • GC group: 4% • GC+AVA group: 5% • AVA group: 5%
ADVOCATE (40) N=331 Relapsing AAV: • GC group: 30.5% • AVA group: 30.7%	AVA 30 mg bid (n=166) or Tapered prednisone (n=165) Along with RTX as single cycle at the time of induction or CYC followed by AZA	52 weeks	AVA was non-inferior to prednisone in achieving remission at Week 26 (72.3% vs 70.1%; p<0.0001)	AVA was superior to prednisone in maintaining remission at Week 52 (65.7% vs 54.9%; p=0.0066) The risk of relapse at 52 weeks was 54% lower with AVA vs prednisone	Serious infection: • AVA group: 13.3% • GC group: 15.2% Death due to infection: • AVA group: 0.6% • GC group: 1.2%

AZA, azathioprine; AVA, avacopan; CYC, cyclophosphamide; ENT, ear, nose and throat; GC, glucocorticoid; HR, hazard ratio; RTX, rituximab.

effective in patients with relapsing disease (51) leading guidelines to suggest using the higher dose in patients who relapse on the 500 mg regimen (14).

Defining the optimal duration of rituximab treatment is particularly challenging due to the increased risk of adverse effects, including infection, hypogammaglobulinemia, and impaired vaccine response. The recommended duration of rituximab therapy varies between guidelines, with EULAR guidelines recommending continuing treatment for 24 to 48 months (14) and KDIGO guidelines recommending 18 to 48 months (33). Of note, the MAINRITSAN-3 trial demonstrated fewer relapses in patients receiving rituximab for 36 months versus 18 months (50). Although subsequent pooled analyses failed to show an improvement in relapse-free survival with extended dosing (8), results suggest that extending maintenance therapy may be beneficial in some contexts (54).

Rituximab maintenance treatment is generally effective in sustaining remission and is typically well-tolerated. However, this is not the case for all patients and several factors may limit its' use. These include a reduced response to rituximab in some patients, which may be a consequence of high interpatient variability of serum rituximab levels due to genetic polymorphisms and/or (in patients with repeated rituximab exposure) neutralization of rituximab activity by anti-rituximab antibodies (55–57). Furthermore, the use of rituximab is associated with an increased risk of infection, as demonstrated by both the MAINRITSAN and RITAZAREM trials (Table 1) (39, 52). The observation that infection rates improved using an individually tailored approach with reduced rituximab exposure (49) raises the question of whether decisions abouts re-dosing and the duration of maintenance treatment should always be pre-emptive or whether they should be reduced in people with low relapse risk (e.g., those who remain MPO-ANCA negative or experience sustained B-cell depletion after rituximab treatment) (Table 2) (62, 63).

The risk of infection tends to increase in patients with hypogammaglobulinemia during the first year of rituximab induction. This is more prevalent among patients with low baseline IgG levels and is primarily linked to older age and glucocorticoid dose (72–75). Although hypogammaglobulinemia is not definitively linked to an increased risk of infection during maintenance treatment, patients receiving re-induction therapy after relapse may experience further decreases in IgG levels due to repeated rituximab administration (75, 76). Similarly, the diminished response to vaccines in patients undergoing B-cell depletion—a common phenomenon in rituximab-treated patients—may have important clinical implications, potentially heightening the risk of infection (77, 78).

The high risk of severe infections and other complications with glucocorticoids, even at low doses, means their use requires careful risk-benefit assessment, particularly in terms of co-morbidities (31). Whilst pre-rituximab data suggest that the extended use of glucocorticoids is associated with fewer relapses (79), a retrospective study in rituximab-treated patients found that extending the use of high-dose glucocorticoids for more than six months increased the risk of severe infection and other adverse effects (e.g., diabetes and cardiovascular complications) without reducing relapse risk (80). The long-term use of low-dose glucocorticoids for the prevention of relapse has not been specifically evaluated in randomized controlled trials. However, the TAPIR trial found that the risk of major relapse in rituximab-treated patients with GPA remained low irrespective of whether patients received low-dose or no glucocorticoids and that the benefits of low-dose glucocorticoids to prevent minor relapses were only observed among patients treated with non-rituximab-based regimens (81). This suggests that maintenance treatment with rituximab and little or no glucocorticoids may be possible in some patients.

6 Relapse in AAV

Relapse is classified according to the level of disease activity and the extent of organ involvement, assessed using the Birmingham Vasculitis Activity Score (BVAS) Version 3 (14, 82) or the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS-WG) (83). A relapse is typically deemed major if it affects key organs, such as the neurological system or the kidneys. Minor relapses are usually characterized by constitutional symptoms either in isolation or in association with non-life or non-organ-threatening manifestations. However, classification is often complicated by limitations in assessing disease activity. For example, kidney disease relapse does not have a generally accepted and shared definition, and there is no standardized modality for assessing kidney disease activity in patients with relapsing AAV.

ANCA testing is a central component of AAV diagnosis and is increasingly used to help define disease status, including remission and relapse. A negative serum ANCA assay characterizes serological remission while ANCA return suggests serological relapse. However, since ANCA titers do not necessarily reflect AAV activity, they are an imperfect indicator of relapse (78).

In the pre-rituximab era, the likelihood of relapse within the first five years was 40%–55% (82, 84). While the use of rituximab as maintenance therapy has significantly reduced this risk, relapse rates are not negligible and tend to increase significantly after maintenance treatment is withdrawn (8).

6.1 Relapse risk

Accurate risk assessment is essential for the prevention or early detection of relapse (31). Consequently, guidelines recommend continuously assessing patients throughout their journey (14, 33). Several factors determine the likelihood of relapse (Table 2). Generally, relapse is less common in patients with MPA (27), MPO-ANCA associated disease (27, 61), severe kidney disease (69), and older age (>75 years old) (58), while it is more common in those with GPA (27), PR3-ANCA associated disease (27, 59–61), and ENT involvement (66, 68, 70, 85–87). Other risk factors for relapse include infection (70, 71), relapse history (27),

10.3389/fimmu.2025.1655326

TABLE 2 Risk factors for AAV relapse.

Factor	Associated relapse risk	Additional remarks
Patient clinical characteristics		
Older age (58)	↓	Patients with AAV after the age of 75 years have a lower relapse risk than patients aged 65 – 75 years
Molecular characteristics		
HLA-DPB1*04:01 (59)	↑	Homozygosity for this allele, which is mainly found in PR3-ANCA positive disease, is associated with a higher relapse risk
Leukocyte PRTN3 expression (60)	↑	Mainly found in PR3-ANCA positive disease
Low levels of endogenous anti-C5aR1 antibodies (22)	↑	Good correlation with disease activity
Baseline disease characteristics		
MPO-ANCA positive (27, 61)	↓	
PR3-ANCA positive (27, 59–61)	↑	
Disease characteristics during treatment		
Persistently negligible ANCA levels (for MPO-ANCA positive patients) (62)	↓	Patients who remain ANCA negative were found to remain relapse-free
Persistent B-cells depletion (63)	↓	Patients who remain sustained B-cell depleted after rituximab were found to remain relapse-free
Serological remission (64)	↓	Achieving serological remission (negative ANCA assay) within 180 days of induction was associated with a lower 5-year cumulative incidence of relapse (9.4 per 100 patients vs 18.3)
History of relapse (27)	↑	Once a patient has experienced a relapse, they are more likely to do so again
Increasing ANCA concentrations (65)	↑	A two-fold increase in ANCA levels was found to be associated with a significantly increased relapse risk
Seroconversion from negative to positive ANCA (62, 64, 66, 67)	↑	Several trials have reported that a change from negative to positive ANCA titre is associated with increased relapse risk
ANCA positivity (66, 67)	↑	Persistent ANCA positivity, despite being in remission is associated with an increased relapse risk
Increase in peripheral B-cells (63, 68)	↑	The return of peripheral B-cells following rituximab-induced B cell depletion is associated with an increased risk of relapse
Maintenance treatment employed		
Rituximab based maintenance treatment (39, 52)	↓	Compared to the historical standard of care (azathioprine)
Morbidities		
End-stage kidney disease (69)	↓	End-stage kidney disease is generally associated with a low risk of relapse, but it can increase the risk of infection that raises relapse rate
Infection (70, 71)	↑	Infection can promote AAV activity, increasing the risk of relapses

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

seroconversion to ANCA positivity and (possibly) rising ANCA titers during treatment (62, 64–67) (Table 2). In contrast, persistent ANCA negativity (especially in rituximab-treated patients with sustained B-cell depletion) is strongly predictive of a patient remaining relapse-free (62, 63, 68).

When assessing relapse risk in patients with AAV, the therapeutic regimen employed should also be taken into account. While robust evidence has established that a rituximab-based maintenance regimen is superior to azathioprine in preventing relapses (39, 52), emerging data suggest that the induction regimen may also influence relapse risk. A retrospective real-world study involving 101 patients with AAV demonstrated that an induction strategy combining rituximab and cyclophosphamide was associated with a lower relapse rate compared to rituximab

monotherapy (88). Notably, this association was observed only when both major and minor relapses were considered together and was not confirmed for major relapses alone. Further evidence for the impact of combined induction with rituximab and cyclophosphamide compared to rituximab alone will be provided by the ongoing, randomized controlled ENDURRANCE trial (89).

The underlying mechanisms driving relapse are not fully understood; consequently, our understanding of the relevance of concomitant risk-modifying factors is limited. ENT damage, for example, is associated with a higher relapse risk but a lower risk of kidney disease and better survival rates (87). The high number of relapse risk factors ranging from inherent factors (e.g., ANCA specificity) to single patient "disease behavior" and comorbidities (e.g., previous relapse and infection) suggests a need for advanced modelling techniques that provide accurate estimates of future relapse risk.

6.2 The role of biomarkers to detect imminent relapse

Although ANCA levels, the timing of B-cell return after rituximab treatment, and (in some contexts) complement fluctuations may provide some indication of impending relapse (22, 62, 65, 68), the search for a reliable and reproducible biomarker continues (90). In addition to predicting relapse, biomarkers may provide information on factors that impact overall prognosis (e.g., subclinical disease activity) and help identify patients with an abnormal activation of fibrotic pathways that may contribute to organ damage (91). As our understating of AAV expands and reports emerge of several disease phenotypes (92), it is becoming increasingly likely that a reliable biomarker for patients with one phenotype may not necessarily be appropriate for patients with other characteristics.

6.2.1 Clinical biomarkers

Although increases in ANCA titers are typically associated with increased relapse risk, data from clinical trials and observational studies are often conflicting (8, 46, 49). In patients treated with rituximab, B-cell repopulation after complete peripheral depletion may help inform the risk of relapse and the optimal timing of rituximab administration within a tailored retreatment strategy (63, 66). This hypothesis has been tested in a prospective study, in which B-cell-driven rituximab maintenance therapy was more effective than ANCA-driven rituximab therapy for preventing relapse (78). Therefore, although the peripheral B-cell count monitored for personalized treatment does not necessarily correlate with tissue-resident B-cells, it may be a useful clinical indicator for relapse (93). Of note, characteristics of the B-cell compartment show significant interpatient variability at the time of repopulation and may provide an even more accurate indication of relapse risk (94). Indeed, a greater relapse risk was reported for repopulating B-cell compartments comprising a higher proportion of autoreactive PR3+ B-cells, switched memory B-cells or plasmablasts, and a lower proportion of naïve B-cells (94–96). This suggests that combining ANCA and B-cell monitoring (at least in rituximab-treated patients) may provide useful information on relapse risk in patients with a relative low relapse rate, such as those with MPO-ANCA MPA who exhibit persistent ANCA negativity and B-cell depletion.

Eventually, B-cell repopulation is likely to occur in rituximab-treated patients and further research should focus on determining how to optimize the depletion of the B-cells subsets that drive autoimmunity. It should also be noted that relapses may occur in patients without B-cell repopulation or increasing ANCA titers (48, 63, 66), and that some biomarkers may provide useful information on relapse risk in specific organs.

6.2.2 Exploratory biomarkers

Although exploratory biomarkers are not yet ready for use in clinical practice, they may provide useful insights into disease pathogenesis. Some of these biomarkers have been tested in randomized controlled studies (43).

A retrospective analysis of samples collected during the RAVE trial found high levels of interleukin-6 (IL-6) that positively correlated with ANCA levels in patients with PR3-ANCA but not MPO-ANCA (28).

In addition to IL-6, low levels of autoantibodies targeting C5aR1 show good correlation with both AAV disease activity and relapse risk (22). This suggests a physiologically antagonistic role for endogenous anti-C5aR1 antibodies as regulators of a C5aR1 immune checkpoint and provides support for the use of therapies such as avacopan, which target the complement system in patients with AAV.

Calprotectin is released by neutrophils and monocytes during inflammation and correlates with active AAV (97, 98). Increases in serum calprotectin may predict AAV relapse as a potential indicator of sub-clinical kidney inflammation (99, 100).

The potential role of NETs as biomarkers is supported by their central role in the pathogenesis of AAV (17). Notably, neutrophils expressing type II interferon (IFN) signature genes are increased in patients with MPA and are associated with persistent vasculitis symptoms (101). Furthermore, elevated IFN-γ levels at disease onset, a key cytokine driving the differentiation of mature neutrophils toward a type II IFN signature phenotype, are associated with an increased risk of disease relapse (101). These findings, derived from a Japanese cohort, warrant validation in other ethnic populations to assess their generalizability.

Finally, urinary biomarkers may inform on the status of kidney disease activity. MCP1 and CD163 have been associated with kidney vasculitis relapses (102, 103) and increases in urinary CD4 + T-cell (104, 105). Among the exploratory biomarkers, MCP-1 and CD163 appear to be the most advanced in terms of potential clinical application (40).

6.3 Treatment of relapse

Glucocorticoids are frequently included in treatment strategies for relapse with the dose varying according to relapse severity and

treating physician experience (Figure 2). The risk of glucocorticoid-related toxicity is potentially higher in patients with previous relapses due to prior glucocorticoid exposure. The ideal form of management is therefore prevention and, since relapse frequently occurs after the cessation of maintenance therapy, extending the duration of maintenance treatment for patients with known risk factors (Table 2) could help reduce the likelihood of relapse (52, 66, 106).

There is no "one-size-fits-all" solution, and decisions regarding re-induction treatment should be based on an individual assessment considering ANCA type, disease severity, comorbidities, affected organs, and other patient characteristics such as age (Figure 3). A major relapse requires re-initiation of induction treatment with rituximab or cyclophosphamide, as employed to achieve remission in newly diagnosed cases (14, 33) (Figure 2). In contrast, a minor relapse typically warrants only temporary treatment intensification, such as a short course of low-dose glucocorticoids (Figure 2). It should be noted, however, that minor relapses are often a prelude to a more serious event, especially if there is an accompanying rise in ANCA titer (Figure 2). Among the 44 patients who experienced a minor relapse during follow-up in the RAVE trial, 80% achieved remission with an increase in prednisone dose, but 70% relapsed within 6 months (27). Patients who were least likely to maintain prolonged remission tended to have GPA, be PR3-ANCA positive and have previous relapses. This suggests that adjusting the dose and/or duration of immunosuppression according to patient characteristics might help prevent the need for more intensive treatment in the future. In patients with frequent relapses, alternative strategies beyond a temporary increase in glucocorticoids are recommended (14). This often involves combining a low-dose glucocorticoid with an immunosuppressive agent, most commonly rituximab. However, as previously discussed, emerging evidence suggests that glucocorticoids might not be beneficial for all patients (81).

Although data specifically pertaining to the treatment of relapse are scarce, many studies have included patients with a history of relapse (Table 1). Treatment of relapse typically includes rituximab and/or cyclophosphamide in addition to glucocorticoids (Figure 2). Rituximab has been shown to be as effective as cyclophosphamide in achieving remission and is more effective than azathioprine for maintaining remission (8, 37, 48, 107). A retrospective analysis of data from the RAVE trial found that 88% of patients with a major relapse six to 18 months after initial induction therapy achieved remission following re-induction with rituximab and glucocorticoids (47). Similarly, the RITAZAREM trial found that 90% of patients relapsing with GPA or MPA achieved remission within four months of starting re-induction therapy with rituximab and glucocorticoids (51). However, there is a minority of patients for whom AAV remission is not induced by rituximab (51). Reasons for this are unclear, but a single nucleotide polymorphism of the B-cell activating factor (BAFF) gene and high interpatient variability of serum rituximab levels have been proposed as potential causes (55, 56). Furthermore, data from the RITAZAREM trial confirmed findings from previous retrospective studies, in which higher glucocorticoid doses were associated with an increased risk of developing low IgG levels (48, 74). This supports the use of glucocorticoid-sparing treatment regimens for reducing the risk of infection.

Avacopan effectively enables a reduction in glucocorticoid exposure and glucocorticoid-related toxicity in patients receiving rituximab or cyclophosphamide for relapsing AAV (Table 1). The ADVOCATE trial demonstrated that avacopan was as effective as a prednisone taper as induction therapy in patients with new-onset or relapsing AAV treated with rituximab or cyclophosphamide, with avacopan-based treatment demonstrating a 54% estimated reduction in relapse risk compared to a prednisone taper (40). A supplementary analysis confirmed that avacopan effectively achieved remission in the subgroup of patients with relapsing

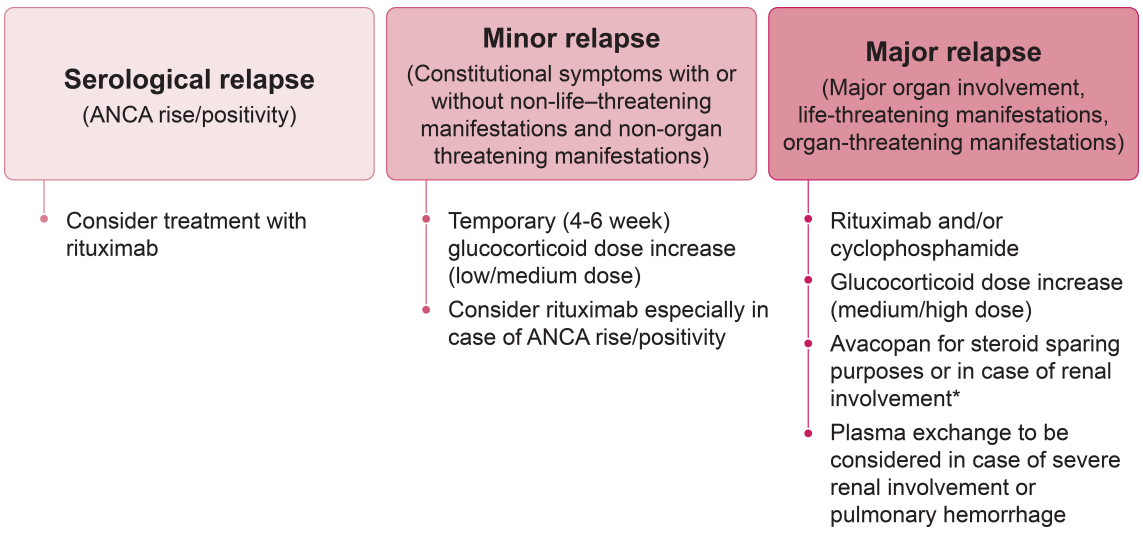


FIGURE 2
Flow-chart outlining the recommended approach for managing AAV relapse. * If avacopan is started, reduce/withdraw glucocorticoids in 4 – 6 weeks. ANCA, antineutrophil cytoplasmic antibody.

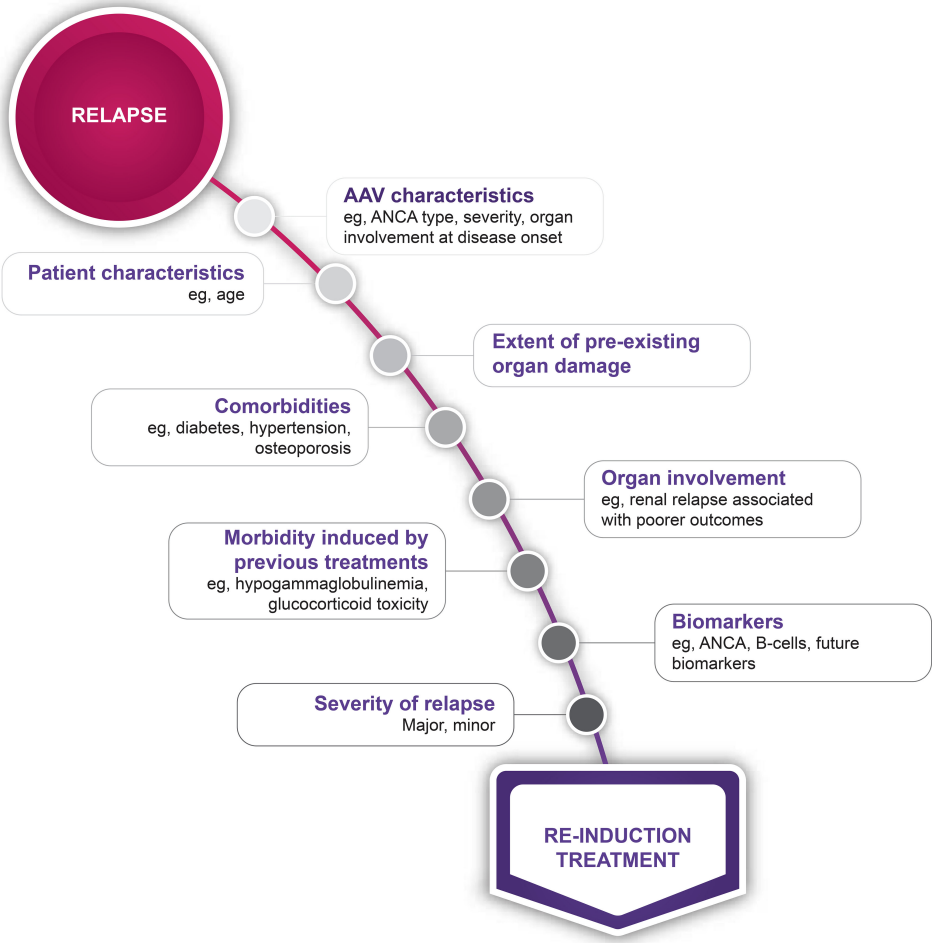


FIGURE 3
Considerations when choosing a re-induction treatment strategy. AAV, antineutrophil cytoplasmic antibody- (ANCA-) associated vasculitis.

disease (40). Importantly, patients who received the avacopan-based regimen received only a third of the cumulative dose of glucocorticoids (equating to a median of 2100 mg less total prednisone-equivalent over a year) compared with the prednisone taper group and experienced statistically significant and clinically meaningful improvements in health-related quality of life (40, 108). Results from the subset of patients who received rituximab echoed the main findings of the ADVOCATE trial, showing a 58% reduction in relapse risk in the avacopan group compared with prednisone (109).

Another benefit for avacopan is that it provides greater kidney function recovery than prednisone taper (40, 110, 111). The least-squares mean improvement in eGFR from baseline for patients with kidney involvement in the ADVOCATE study was significantly greater for those in the avacopan group than for those in the prednisone taper group at 52 weeks (7.3 vs 4.0 mL/min/1.73 m^2; p=0.0259) (40, 112). An even greater improvement from baseline to week 52 (16.1 vs 7.7 mL/min/1.73 m^2; p=0.003) was seen among patients with impaired kidney function at baseline (eGFR <20 mL/min/1.73 m^2) (111). This is particularly relevant for patients requiring re-induction because (as previously discussed) each relapse increases the risk of organ damage due to increased inflammatory disease activity and the use of higher-dose (more toxic) re-induction treatments (31).

Evaluation of avacopan use in clinical practice, including patient categories not eligible for inclusion in the ADVOCATE trial, confirmed the high response rates and steroid-sparing effect of the avacopan regimen (113–115). Furthermore, a small study of Italian clinical practice revealed that avacopan was largely used in relapsing disease and was associated with a high sustained remission rate (116).

Overall, evidence supports the use of rituximab in patients at risk of relapse, and the inclusion of avacopan in the induction regimen, at least in patients who would otherwise be treated with prednisone and in those requiring full re-induction. As the therapeutic armamentarium expands, greater emphasis must be

placed on personalizing treatment to achieve effective disease control while minimizing treatment-related toxicities (Figure 4).

7 Impact of patient perspectives on treatment decisions

Health-related quality of life (HR-QoL) is often lower in patients with AAV compared to the general population, with many patients reporting depression, anxiety, unemployment, fatigue and pain (26, 108, 121). As expected, patient-reported outcomes (PRO) tend to worsen during periods of active disease and improve with remission (121). A *post-hoc* analysis of PRO data from the ADVOCATE trial demonstrated improvements in HR-QoL from baseline to weeks 26 and 52 in patients with AAV treated with rituximab or cyclophosphamide alongside glucocorticoids (108). Improvements in 36-Item Short Form Health Survey (SF-36) summary scores were greater in patients receiving avacopan versus prednisone taper at weeks 26 and 52, while EuroQoL 5-Dimensions 5-Level Questionnaire (EQ-5D-5L) summary scores showed greater improvements for avacopan versus prednisone taper only at week 52 (108). Whether this is directly due to the effects of avacopan, the impact of lower cumulative glucocorticoid exposure, or a combination of both remains to be established in future studies. Either way, results suggest that patient-reported HR-QoL should be taken into account when choosing a treatment regimen.

EULAR guidelines for the treatment of AAV stress the importance of effective communication and shared decision-making between physicians and patients (14). However, results from an online survey completed by 170 healthcare professionals (HCP) and 69 patients suggest that HCPs and patients have different perspectives on treatment aims, with HCPs prioritizing treatment efficacy and clinical outcomes, while patients focus more on long-term outlook, mental health, and functional impact (122). Patient perspectives may also be shaped by individual experiences and disease history. For example, a survey of 470 patients with AAV from 13 countries found that patients with prior exposure to dialysis or plasma exchange were more likely to favor plasma exchange for relapse management than patients without prior dialysis or plasma exchange (123). This highlights the need for a more patient-centered approach to AAV management.

8 The way forward

Future studies are required to evaluate optimal dosing strategies and new combinations of immunosuppressants in patients with AAV. Ongoing studies include the COMBIVAS trial, in which patients with AAV are treated with rituximab in combination with the anti-BAFF agent, belimumab (55, 124, 125). The rationale for this study is that the increased BAFF levels reported in some patients with AAV may hinder the efficacy of rituximab. It is hoped that the distinct mechanisms of action for rituximab and belimumab will enhance B-cell targeting, especially as belimumab appears to mobilize CD27+ memory cells making them available to the cytotoxic effect of rituximab (126). Similarly, since activated CD4 T-cells are involved in the pathogenesis of AAV and are likely central in mediating kidney damage, a therapy that inhibits T-cell activation could help control disease activity (127, 128). However, the ABROGATE trial did not demonstrate reduced relapse rates in patients with GPA treated with abatacept (129). Data from patients with other indications suggest that obinutuzumab may achieve greater tissue B-cell depletion than rituximab (130). The OBIVAS trial is comparing the effects of obinutuzumab and rituximab on B-cell depletion and sustained remission in patients with AAV, with completion expected in late 2025 (131). Over time, the options for re-induction are likely to expand enabling further reductions in glucocorticoid use.

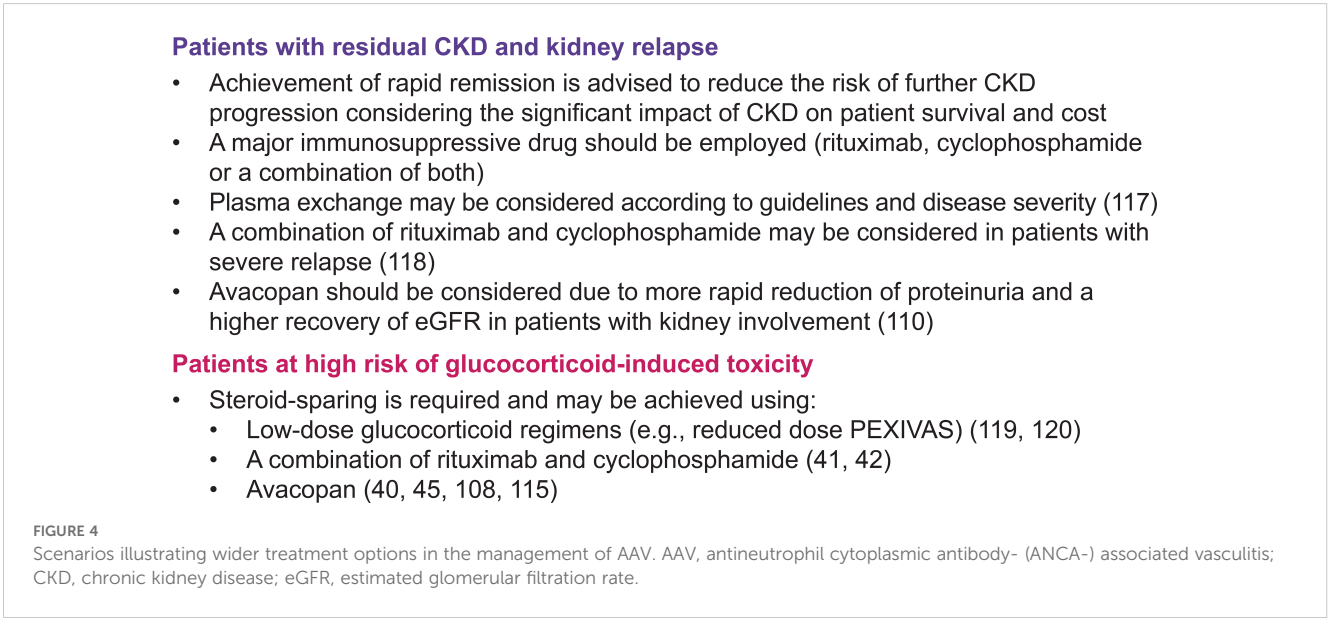


FIGURE 4
Scenarios illustrating wider treatment options in the management of AAV. AAV, antineutrophil cytoplasmic antibody- (ANCA-) associated vasculitis; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

9 Concluding remarks

Effective relapse prevention and/or treatment is critical to minimizing tissue damage and glucocorticoid exposure in patients with AAV. Treatment choices are not straightforward due to interpatient variability in response and the high proportion of patients with significant comorbidities, many of which may be AAV-induced or treatment related. Balancing the benefits of treatment against individual risk factors, treatment toxicities, and organ damage is key to optimizing outcomes.

There is no definitive biomarker for predicting AAV relapse; however, monitoring ANCA titers and (in rituximab-treated patients) B-cell repopulation may help identify patients with a high risk of relapse, thereby guiding preventative dosing. When relapse prevention fails, early treatment re-introduction or intensification will help minimize the effects of active disease on tissue damage and optimize long-term outcomes. Rituximab effectively maintains remission and re-induces remission after relapse. Adjunctive therapy with avacopan can help minimize glucocorticoid exposure while improving kidney function and achieving lower relapse rates than a prednisone-based regimen aimed at corticosteroid withdrawal (40).

Further studies are required to investigate the effects of re-induction treatments specifically in patients with AAV relapse. Although specific data are lacking, it is likely that the pathogenetic mechanisms underlying new-onset AAV and AAV relapse are similar. Importantly, clinical evidence to date supports the comparable efficacy of the same therapeutic approaches in both settings. In both scenarios, reducing the risk of organ damage by minimizing disease activity whilst limiting treatment toxicity remains a top priority.

Author contributions

FA: Conceptualization, Writing – original draft, Writing – review & editing. OF: Conceptualization, Writing – original draft, Writing – review & editing. PL: Conceptualization, Writing – original draft, Writing – review & editing. KL: Conceptualization, Writing – original draft, Writing – review & editing. RP: Conceptualization, Writing – original draft, Writing – review & editing. TP: Conceptualization, Writing – original draft, Writing – review & editing. CS: Conceptualization, Writing – original draft, Writing – review & editing. AM: Conceptualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research and/or publication of this article.

Acknowledgments

We thank Kate Bass and Jackie Read of Bright Red Fox Creative Ltd. for editorial support in the preparation of this manuscript.

Conflict of interest

FA: advisory board, consulting fees, honoraria for presentations or support for attending meetings from Vifor CSL, AstraZeneca, Bayer and Boehringer Lilly. OF: advisory board, consulting fees, honoraria for presentations or support for attending meetings from Vifor CSL, Consulting fees Boehringer Ingelheim. PL: research funding: BMBF, DFG, DGRh, John Grube Foundation, Vifor CSL; consulting fees: AbbVie, Astra Zeneca, GSK, Novartis, UCB, Vifor CSL; lecture fees: Astra Zeneca, Boehringer Ingelheim, GSK, Janssen, Novartis, Rheumaakademie, UCB, Vifor CSL. KL: advisory board and consulting fees: Boehringer Ingelheim, Vigor CSL; honoraria for presentations: Astra Zeneca; support for attending meetings: Novartis. AM: lecture and consultation fees from AMGEN, GSK, Roche Sweden, Vifor CSL, Abbvie and AstraZeneca; lecture fees from Eli Lilly Sweden and Boehringer Ingelheim. RP: consulting, advisory board and educational activities: GSK, CSL Vifor, Sanofi, AstraZeneca; speakers' bureau: GSK, Sanofi, Vifor CSL; Grant and research support: Janssen. TP: employee Vifor CSL. CS: advisory board, consulting fees, honoraria for presentations or support for attending meetings from Vifor CSL.

The authors declare that this study received funding from Vifor Fresenius Medical Care Renal Pharma AG. The funder had the following involvement in the study: Vifor Fresenius Medical Care Renal Pharma AG sponsored the preparation of this paper and were involved in the decision to submit the article for publication.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

References

1. Zheng Y, Zhang Y, Cai M, Lai N, Chen Z, Ding M. Central nervous system involvement in ANCA-associated vasculitis: what neurologists need to know. *Front Neurol*. (2018) 9:1166. doi: 10.3389/fneur.2018.01166

2. Arnold S, Kitching AR, Witko-Sarsat V, Wiech T, Specks U, Klapa S, et al. Myeloperoxidase-specific antineutrophil cytoplasmic antibody-associated vasculitis. *Lancet Rheumatol*. (2024) 6:e300–e13. doi: 10.1016/S2665-9913(24)00025-0

3. Falde SD, Fussner LA, Tazelaar HD, O'Brien EK, Lamprecht P, Konig MF, et al. Proteinase 3-specific antineutrophil cytoplasmic antibody-associated vasculitis. *Lancet Rheumatol*. (2024) 6:e314–e27. doi: 10.1016/S2665-9913(24)00035-3

4. Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, et al. Genetically distinct subsets within ANCA-associated vasculitis. *N Engl J Med*. (2012) 367:214–23. doi: 10.1056/NEJMoa1108735

5. Jennette JC, Nachman PH. ANCA glomerulonephritis and vasculitis. *Clin J Am Soc Nephrol*. (2017) 12:1680–91. doi: 10.2215/CJN.02500317

6. Redondo-Rodriguez R, Mena-Vazquez N, Cabezas-Lucena AM, Manrique-Arija S, Mucientes A, Fernandez-Nebro A. Systematic review and metaanalysis of worldwide incidence and prevalence of antineutrophil cytoplasmic antibody (ANCA) associated vasculitis. *J Clin Med*. (2022) 11:2573. doi: 10.3390/jcm11092573

7. Rhee RL, Hogan SL, Poulton CJ, McGregor JA, Landis JR, Falk RJ, et al. Trends in long-term outcomes among patients with antineutrophil cytoplasmic antibody-associated vasculitis with renal disease. *Arthritis Rheumatol*. (2016) 68:1711–20. doi: 10.1002/art.39614

8. Delestre F, Charles P, Karras A, Pagnoux C, Neel A, Cohen P, et al. Rituximab as maintenance therapy for ANCA-associated vasculitides: pooled analysis and long-term outcome of 277 patients included in the MAINRITSAN trials. *Ann Rheum Dis*. (2024) 83:233–41. doi: 10.1136/ard-2023-224623

9. Heijl C, Mohammad AJ, Westman K, Hoglund P. Long-term patient survival in a Swedish population-based cohort of patients with ANCA-associated vasculitis. *RMD Open*. (2017) 3:e000435. doi: 10.1136/rmdopen-2017-000435

10. Sanchez Alamo B, Moi L, Bajema I, Faurschou M, Flossmann O, Hauser T, et al. Long-term outcomes and prognostic factors for survival of patients with ANCA-associated vasculitis. *Nephrol Dial Transplant*. (2023) 38:1655–65. doi: 10.1093/ndt/gfac320

11. Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. *Nat Rev Rheumatol*. (2022) 18:22–34. doi: 10.1038/s41584-021-00718-8

12. Rathmann J, Segelmark M, Englund M, Mohammad AJ. Stable incidence but increase in prevalence of ANCA-associated vasculitis in southern Sweden: a 23-year study. *RMD Open*. (2023) 9:e002949. doi: 10.1136/rmdopen-2022-002949

13. Alberici F, Tedesco M, Popov T, Balcells-Oliver M, Mescia F. Treatment goals in ANCA-associated vasculitis: defining success in a new era. *Front Immunol*. (2024) 15:1409129. doi: 10.3389/fimmu.2024.1409129

14. Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis*. (2024) 83:30–47. doi: 10.1136/ard-2022-223764

15. Merkel PA, Xie G, Monach PA, Ji X, Ciavatta DJ, Byun J, et al. Identification of functional and expression polymorphisms associated with risk for antineutrophil cytoplasmic autoantibody-associated vasculitis. *Arthritis Rheumatol*. (2017) 69:1054–66. doi: 10.1002/art.40034

16. Thiel J, Schmidt FM, Lorenzetti R, Troilo A, Janowska I, Niessen L, et al. Defects in B-lymphopoiesis and B-cell maturation underlie prolonged B-cell depletion in ANCA-associated vasculitis. *Ann Rheum Dis*. (2024) 83:1536–48. doi: 10.1136/ard-2024-225587

17. Kessenbrock K, Krumbholz M, Schonermarck U, Back W, Gross WL, Werb Z, et al. Netting neutrophils in autoimmune small-vessel vasculitis. *Nat Med*. (2009) 15:623–5. doi: 10.1038/nm.1959

18. Trouw LA, Pickering MC, Blom AM. The complement system as a potential therapeutic target in rheumatic disease. *Nat Rev Rheumatol*. (2017) 13:538–47. doi: 10.1038/nrrheum.2017.125

19. Gou SJ, Yuan J, Wang C, Zhao MH, Chen M. Alternative complement pathway activation products in urine and kidneys of patients with ANCA-associated GN. *Clin J Am Soc Nephrol*. (2013) 8:1884–91. doi: 10.2215/CJN.02790313

20. Wu EY, McInnis EA, Boyer-Suavet S, Mendoza CE, Aybar LT, Kennedy KB, et al. Measuring circulating complement activation products in myeloperoxidase- and proteinase 3-antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol*. (2019) 71:1894–903. doi: 10.1002/art.41011

21. Moiseev S, Lee JM, Zykova A, Bulanov N, Novikov P, Gitel E, et al. The alternative complement pathway in ANCA-associated vasculitis: further evidence and a meta-analysis. *Clin Exp Immunol*. (2020) 202:394–402. doi: 10.1111/cei.13498

22. Klapa S, Muller A, Koch A, Kerstein-Stahle A, Kahler W, Heidecke H, et al. Low concentrations of C5a complement receptor antibodies are linked to disease activity and relapse in antineutrophil cytoplasmic autoantibody-associated vasculitis. *Arthritis Rheumatol*. (2023) 75:760–7. doi: 10.1002/art.42410

23. Hunter RW, Welsh N, Farrah TE, Gallacher PJ, Dhaun N. ANCA associated vasculitis. *BMJ*. (2020) 369:m1070. doi: 10.1136/bmj.m1070

24. Padoan R, Campaniello D, Gatto M, Schiavon F, Doria A. Current clinical and therapeutic approach to tumour-like mass lesions in granulomatosis with polyangiitis. *Autoimmun Rev*. (2022) 21:103018. doi: 10.1016/j.autrev.2021.103018

25. Kronbichler A, Leierer J, Gauckler P, Shin JI. Comorbidities in ANCA-associated vasculitis. *Rheumatol (Oxford)*. (2020) 59:iii79–83. doi: 10.1093/rheumatology/kez617

26. Mercuzot C, Letertre S, Daien CI, Zerkowski L, Guilpain P, Terrier B, et al. Comorbidities and health-related quality of life in Patients with Antineutrophil Cytoplasmic Antibody (ANCA) - associated vasculitis. *Autoimmun Rev*. (2021) 20:102708. doi: 10.1016/j.autrev.2020.102708

27. Miloslavsky EM, Specks U, Merkel PA, Seo P, Spiera R, Langford CA, et al. Outcomes of nonsevere relapses in antineutrophil cytoplasmic antibody-associated vasculitis treated with glucocorticoids. *Arthritis Rheumatol*. (2015) 67:1629–36. doi: 10.1002/art.39104

28. Berti A, Warner R, Johnson K, Cornec D, Schroeder DR, Kabat BF, et al. The association of serum interleukin-6 levels with clinical outcomes in antineutrophil cytoplasmic antibody-associated vasculitis. *J Autoimmun*. (2019) 105:102302. doi: 10.1016/j.jaut.2019.07.001

29. Gamerith G, Mildner F, Merkel PA, Harris K, Cooney L, Lim N, et al. Association of baseline soluble immune checkpoints with the risk of relapse in PR3-ANCA vasculitis following induction of remission. *Ann Rheum Dis*. (2023) 82:253–61. doi: 10.1136/ard-2022-222479

30. McKinney EF, Lee JC, Jayne DR, Lyons PA, Smith KG. T-cell exhaustion, co-stimulation and clinical outcome in autoimmunity and infection. *Nature*. (2015) 523:612–6. doi: 10.1038/nature14468

31. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Hoglund P, et al. Damage in the ANCA-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. *Ann Rheum Dis*. (2015) 74:177–84. doi: 10.1136/annrheumdis-2013-203927

32. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis*. (2011) 70:488–94. doi: 10.1136/ard.2010.137778

33. Floege J, Jayne DRW, Sanders JF, Tesar V, Balk EM, Gordon CE, et al. Executive summary of the KDIGO 2024 clinical practice guideline for the management of ANCA-associated vasculitis. *Kidney Int*. (2024) 105:447–9. doi: 10.1016/j.kint.2023.10.009

34. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med*. (1983) 98:76–85. doi: 10.7326/0003-4819-98-1-76

35. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med*. (2003) 349:36–44. doi: 10.1056/NEJMoa020286

36. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med*. (2009) 150:670–80. doi: 10.7326/0003-4819-150-10-200905190-00004

37. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. (2010) 363:221–32. doi: 10.1056/NEJMoa0909905

38. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. (2010) 363:211–20. doi: 10.1056/NEJMoa0909169

39. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med*. (2014) 371:1771–80. doi: 10.1056/NEJMoa1404231

40. Jayne DRW, Merkel PA, Schall TJ, Bekker P, Group AS. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. (2021) 384:599–609. doi: 10.1056/NEJMoa2023386

41. Cortazar FB, Muhsin SA, Pendergraft WF 3rd, Wallace ZS, Dunbar C, Laliberte K, et al. Combination therapy with rituximab and cyclophosphamide for remission induction in ANCA vasculitis. *Kidney Int Rep*. (2018) 3:394–402. doi: 10.1016/j.ekir.2017.11.004

42. Pepper RJ, McAdoo SP, Moran SM, Kelly D, Scott J, Hamour S, et al. A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody-associated vasculitis. *Rheumatol (Oxford)*. (2019) 58:260–8. doi: 10.1093/rheumatology/key288

43. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol*. (2017) 28:2756–67. doi: 10.1681/ASN.2016111179

44. Merkel PA, Niles J, Jimenez R, Spiera RF, Rovin BH, Bomback A, et al. Adjunctive treatment with avacopan, an oral C5a receptor inhibitor, in patients with antineutrophil cytoplasmic antibody-associated vasculitis. *ACR Open Rheumatol*. (2020) 2:662–71. doi: 10.1002/acr2.11185

45. Merkel PA. Safety of avacopan for the treatment of ANCA-associated vasculitis: combined data from three clinical trials. *ACR Open Rheumatol*. (2025) 7(4):e70001. doi: 10.1002/acr2.70001

46. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med*. (2013) 369:417–27. doi: 10.1056/NEJMoa1213277

47. Miloslavsky EM, Specks U, Merkel PA, Seo P, Spiera R, Langford CA, et al. Rituximab for the treatment of relapses in antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol*. (2014) 66:3151–9. doi: 10.1002/art.38788

48. Terrier B, Pagnoux C, Perrodeau E, Karras A, Khouatra C, Aumaitre O, et al. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. *Ann Rheum Dis*. (2018) 77:1150–6. doi: 10.1136/annrheumdis-2017-212768

49. Charles P, Terrier B, Perrodeau E, Cohen P , Faguer S, Huart A, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). *Ann Rheum Dis*. (2018) 77:1143–9. doi: 10.1136/annrheumdis-2017-212878

50. Charles P, Perrodeau E, Samson M, Bonnotte B, Neel A, Agard C, et al. Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis: A randomized trial. *Ann Intern Med*. (2020) 173:179–87. doi: 10.7326/M19-3827

51. Smith RM, Jones RB, Specks U, Bond S, Nodale M, Aljayyousi R, et al. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. *Ann Rheum Dis*. (2020) 79:1243–9. doi: 10.1136/annrheumdis-2019-216863

52. Smith RM, Jones RB, Specks U, Bond S, Nodale M, Al-Jayyousi R, et al. Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial. *Ann Rheum Dis*. (2023) 82:937–44. doi: 10.1136/ard-2022-223559

53. Treppo E, Binutti M, Agarinis R, De Vita S, Quartuccio L. Rituximab induction and maintenance in ANCA-associated vasculitis: state of the art and future perspectives. *J Clin Med*. (2021) 10:3773. doi: 10.3390/jcm10173773

54. Tieu J, Smith R, Basu N, Brogan P, D'Cruz D, Dhaun N, et al. Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines. *Rheumatol (Oxford)*. (2020) 59:e24–32. doi: 10.1093/rheumatology/kez640

55. Alberici F, Smith RM, Fonseca M, Willcocks LC, Jones RB, Holle JU, et al. Association of a TNFSF13B (BAFF) regulatory region single nucleotide polymorphism with response to rituximab in antineutrophil cytoplasmic antibody-associated vasculitis. *J Allergy Clin Immunol*. (2017) 139:1684–7 e10. doi: 10.1016/j.jaci.2016.08.051

56. Khoudour N, Delestre F, Jabot-Hanin F, Jouinot A, Nectoux J, Letouneur F, et al. Association between plasma rituximab concentration and the risk of major relapse in antineutrophil cytoplasmic antibody-associated vasculitides during rituximab maintenance therapy. *Arthritis Rheumatol*. (2023) 75:2003–13. doi: 10.1002/art.42556

57. Faustini F, Dunn N, Kharlamova N, Ryner M, Bruchfeld A, Malmstrom V, et al. First exposure to rituximab is associated to high rate of anti-drug antibodies in systemic lupus erythematosus but not in ANCA-associated vasculitis. *Arthritis Res Ther*. (2021) 23:211. doi: 10.1186/s13075-021-02589-6

58. Thietart S, Beinse G, Smets P, Karras A, Philipponnet C, Augusto JF, et al. Patients of 75 years and over with ANCA-associated vasculitis have a lower relapse risk than younger patients: A multicentre cohort study. *J Intern Med*. (2022) 291:350–63. doi: 10.1111/joim.13417

59. Hilhorst M, Arndt F, Joseph Kemna M, Wieczorek S, Donner Y, Wilde B, et al. HLA-DPB1 as a risk factor for relapse in antineutrophil cytoplasmic antibody-associated vasculitis: A cohort study. *Arthritis Rheumatol*. (2016) 68:1721–30. doi: 10.1002/art.39620

60. Chen DP, Aiello CP, McCoy D, Stamey T, Yang J, Hogan SL, et al. PRTN3 variant correlates with increased autoantigen levels and relapse risk in PR3-ANCA versus MPO-ANCA disease. *JCI Insight*. (2023) 8:e166107. doi: 10.1172/jci.insight.166107

61. Miloslavsky EM, Specks U, Merkel PA, Seo P, Spiera R, Langford CA, et al. Clinical outcomes of remission induction therapy for severe antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. (2013) 65:2441–9. doi: 10.1002/art.38044

62. Casal Moura M, Specks U, Tehranian S, Sethi S, Zubidat D, Nardelli L, et al. Maintenance of remission and risk of relapse in myeloperoxidase-positive ANCA-associated vasculitis with kidney involvement. *Clin J Am Soc Nephrol*. (2023) 18:47–59. doi: 10.2215/CJN.06460622

63. Mescia F, Salviani C, Tonoli M, Affatato S, Moratto D, Tedesco M, et al. Sustained post-rituximab B-cell depletion is common in ANCA-associated vasculitis and is affected by sex and renal function. *Nephrol Dial Transplant*. (2024) 39:683–93. doi: 10.1093/ndt/gfad197

64. McDermott G, Fu X, Cook C, Ahola C, Doliner B, Hanberg J, et al. The effect of achieving serological remission on subsequent risk of relapse, end-stage renal disease and mortality in ANCA-associated vasculitis: a target trial emulation study. *Ann Rheum Dis*. (2022) 81:1438–44. doi: 10.1136/annrheumdis-2022-222439

65. Schuster DD, Gillis D, Wong RCW, Kodituwakku A, Droney L, Ranganathan D. Anti-neutrophil cytoplasmic antibody monitoring in vasculitis patients to predict relapse. *Int J Rheum Dis*. (2023) 26:1861–5. doi: 10.1111/1756-185X.14728

66. Alberici F, Smith RM, Jones RB, Roberts DM, Willcocks LC, Chaudhry A, et al. Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis. *Rheumatol (Oxford)*. (2015) 54:1153–60. doi: 10.1093/rheumatology/keu452

67. McClure ME, Wason J, Gopaluni S, Tieu J, Smith RM, Jayne DR, et al. Evaluation of PR3-ANCA status after rituximab for ANCA-associated vasculitis. *J Clin Rheumatol*. (2019) 25:217–23. doi: 10.1097/RHU.0000000000001030

68. van Dam LS, Dirikgil E, Bredewold EW, Ray A, Bakker JA, van Kooten C, et al. PR3-ANCAs predict relapses in ANCA-associated vasculitis patients after rituximab. *Nephrol Dial Transplant*. (2021) 36:1408–17. doi: 10.1093/ndt/gfaa066

69. Pope V, Sivashanmugathas V, Moodley D, Gunaratnam L, Barra L. Outcomes in ANCA-associated vasculitis patients with end-stage kidney disease on renal replacement therapy-A meta-analysis. *Semin Arthritis Rheum*. (2023) 60:152189. doi: 10.1016/j.semarthrit.2023.152189

70. Salmela A, Rasmussen N, Tervaert JWC, Jayne DRW, Ekstrand A, European Vasculitis Study G. Chronic nasal Staphylococcus aureus carriage identifies a subset of newly diagnosed granulomatosis with polyangiitis patients with high relapse rate. *Rheumatol (Oxford)*. (2017) 56:965–72. doi: 10.1093/rheumatology/kex001

71. Theofilis P, Vordoni A, Koukoulaki M, Vlachopanos G, Kalaitzidis RG. Overview of infections as an etiologic factor and complication in patients with vasculitides. *Rheumatol Int*. (2022) 42:759–70. doi: 10.1007/s00296-022-05100-9

72. Padoan R, Felicetti M, Gatto M, Polito P, Doria A, Schiavon F. Rituximab-associated hypogammaglobulinaemia in ANCA-associated vasculitis and connective tissue diseases: a longitudinal observational study. *Clin Exp Rheumatol*. (2020) 38 Suppl 124:188–94.

73. Tieu J, Smith RM, Gopaluni S, Kumararatne DS, McClure M, Manson A, et al. Rituximab associated hypogammaglobulinemia in autoimmune disease. *Front Immunol*. (2021) 12:671503. doi: 10.3389/fimmu.2021.671503

74. Podesta MA, Mescia F, Ricchiuto A, Smith R, Tedesco M, Cassia MA, et al. Predictors of hypogammaglobulinemia in ANCA-associated vasculitis after a rituximab-based induction: a multicentre study. *Rheumatol (Oxford)*. (2023) 62:2850–4. doi: 10.1093/rheumatology/keac716

75. Liberatore J, Nguyen Y, Hadjadj J, Cohen P, Mouthon L, Puechal X, et al. Risk factors for hypogammaglobulinemia and association with relapse and severe infections in ANCA-associated vasculitis: A cohort study. *J Autoimmun*. (2024) 142:103130. doi: 10.1016/j.jaut.2023.103130

76. Benavides-Villanueva F, Loricera J, Calvo-Rio V, Corrales-Selaya C, Castaneda S, Blanco R. Intravenous immunoglobulin therapy in antineutrophil cytoplasmic antibody-associated vasculitis. *Eur J Intern Med*. (2023) 117:78–84. doi: 10.1016/j.ejim.2023.06.021

77. Salviani C, Scolari F, Alberici F. Correspondence on 'Immunogenicity and safety of anti-SARS-Cov-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort'. *Ann Rheum Dis*. (2021) 80: e158. doi: 10.1136/annrheumdis-2021-220496

78. Zonozi R, Cortazar FB, Jeyabalan A, Sauvage G, Nithagon P, Huizenga NR, et al. Maintenance of remission of ANCA vasculitis by rituximab based on B cell repopulation versus serological flare: a randomised trial. *Ann Rheum Dis*. (2024) 83:351–9. doi: 10.1136/ard-2023-224489

79. Walsh M, Merkel PA, Mahr A, Jayne D. Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis. *Arthritis Care Res (Hoboken)*. (2010) 62:1166–73. doi: 10.1002/acr.20176

80. Speer C, Altenmuller-Walther C, Splitthoff J, Nusshag C, Kalble F, Reichel P, et al. Glucocorticoid maintenance therapy and severe infectious complications in ANCA-associated vasculitis: a retrospective analysis. *Rheumatol Int*. (2021) 41:431–8. doi: 10.1007/s00296-020-04752-9

81. Merkel P, Pagnoux C, Khalidi N, Specks U, Koenig C, Langford C. A multicenter, randomized, controlled trial to evaluate the effects of low-dose glucocorticoids compared to stopping glucocorticoids to maintain remission of granulomatosis with polyangiitis: the TAPIR trial. *Arthritis Rheumatol*. (2024) 76(Suppl 9).

82. Junek ML, Merkel PA, Vilayur E, Wald R, Khalidi N, Jayne D, et al. Risk of relapse of antineutrophil cytoplasmic antibody-associated vasculitis in a randomized controlled trial of plasma exchange and glucocorticoids. *Arthritis Rheumatol*. (2024) 76:1431–8. doi: 10.1002/art.42843

83. Stone JH, Hoffman GS, Merkel PA, Min YI, Uhlfelder ML, Hellmann DB, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). *Arthritis Rheumatol*. (2021) 44:912–20.

84. Walsh M, Flossmann O, Berden A, Westman K, Hoglund P, Stegeman C, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. (2012) 64:542–8. doi: 10.1002/art.33361

85. Salmela A, Tornroth T, Poussa T, Ekstrand A. Prognostic factors for survival and relapse in ANCA-associated vasculitis with renal involvement: A clinical long-term follow-up study. *Int J Nephrol*. (2018) 2018:6369814. doi: 10.1155/2018/6369814

86. Deshayes S, Martin Silva N, Khoy K, Yameogo S, Mariotte D, Lobbedez T, et al. Clinical impact of subgrouping ANCA-associated vasculitis according to antibody specificity beyond the clinicopathological classification. *Rheumatol (Oxford)*. (2019) 58:1731–9. doi: 10.1093/rheumatology/kez016

87. Felicetti M, Cazzador D, Padoan R, Pendolino AL, Faccioli C, Nardello E, et al. Ear, nose and throat involvement in granulomatosis with polyangiitis: how it presents

and how it determines disease severity and long-term outcomes. *Clin Rheumatol.* (2018) 37:1075–83. doi: 10.1007/s10067-018-4019-0

88. Gialouri CG, Chalkia A, Koutsianas C, Chavatza K, Argyriou E, Panagiotopoulos A, et al. Relapses and serious adverse events during rituximab maintenance therapy in ANCA-associated vasculitis: a multicentre retrospective study. *Rheumatol (Oxford).* (2025) 64:1989–98. doi: 10.1093/rheumatology/keae409

89. Dirikgil E, van Leeuwen JR, Bredewold OW, Ray A, Jonker JT, Soonawala D, et al. ExploriNg DUrable Remission with Rituximab in ANCA-associatEd vasculitis (ENDURRANCE trial): protocol for a randomised controlled trial. *BMJ Open.* (2022) 12:e061339. doi: 10.1136/bmjopen-2022-061339

90. Csernok E, Hellmich B. Usefulness of vasculitis biomarkers in the era of the personalized medicine. *Autoimmun Rev.* (2020) 19:102514. doi: 10.1016/j.autrev.2020.102514

91. Salama AD. Relapse in anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis. *Kidney Int Rep.* (2020) 5:7–12. doi: 10.1016/j.ekir.2019.10.005

92. Gisslander K, White A, Aslett L, Hruskova Z, Lamprecht P, Musial J, et al. Data-driven subclassification of ANCA-associated vasculitis: model-based clustering of a federated international cohort. *Lancet Rheumatol.* (2024) 6:e762–e70. doi: 10.1016/S2665-9913(24)00187-5

93. Ramponi G, Folci M, De Santis M, Damoiseaux J, Selmi C, Brunetta E. The biology, pathogenetic role, clinical implications, and open issues of serum anti-neutrophil cytoplasmic antibodies. *Autoimmun Rev.* (2021) 20:102759. doi: 10.1016/j.autrev.2021.102759

94. Arnold J, Vital EM, Dass S, Aslam A, Rawstron AC, Savic S, et al. A personalized rituximab retreatment approach based on clinical and B-cell biomarkers in ANCA-associated vasculitis. *Front Immunol.* (2021) 12:803175. doi: 10.3389/fimmu.2021.803175

95. Elmer E, Smargianaki S, Pettersson A, Skattum L, Ohlsson S, Hellmark T, et al. Increased frequencies of switched memory B cells and plasmablasts in peripheral blood from patients with ANCA-associated vasculitis. *J Immunol Res.* (2020) 2020:8209737. doi: 10.1155/2020/8209737

96. Berti A, Hillion S, Konig MF, Moura MC, Hummel AM, Carmona E, et al. Autoreactive plasmablasts after B cell depletion with rituximab and relapses in antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol.* (2023) 75:736–47. doi: 10.1002/art.42388

97. Pepper RJ, Draibe JB, Caplin B, Fervenza FC, Hoffman GS, Kallenberg CG, et al. Association of serum calprotectin (S100A8/A9) level with disease relapse in proteinase 3-antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol.* (2017) 69:185–93. doi: 10.1002/art.39814

98. Romand X, Paclet MH, Chuong MV, Gaudin P, Pagnoux C, Guillevin L, et al. Serum calprotectin and renal function decline in ANCA-associated vasculitides: a *post hoc* analysis of MAINRITSAN trial. *RMD Open.* (2023) 9:e003477. doi: 10.1136/rmdopen-2023-003477

99. Anton-Pampols P, Martinez Valenzuela L, Fernandez Lorente L, Quero Ramos M, Gomez Preciado F, Martin Capon I, et al. Combining neutrophil and macrophage biomarkers to detect active disease in ANCA vasculitis: a combinatory model of calprotectin and urine CD163. *Clin Kidney J.* (2023) 16:693–700. doi: 10.1093/ckj/sfac257

100. Wester Trejo MAC, Flossmann O, Westman KW, Hoglund P, Hagen EC, Walsh M, et al. Renal relapse in antineutrophil cytoplasmic autoantibody-associated vasculitis: unpredictable, but predictive of renal outcome. *Rheumatol (Oxford).* (2019) 58:103–9. doi: 10.1093/rheumatology/key260

101. Nishide M, Nishimura K, Matsushita H, Kawada S, Shimagami H, Metsugi S, et al. Neutrophil single-cell analysis identifies a type II interferon-related subset for predicting relapse of autoimmune small vessel vasculitis. *Nat Commun.* (2025) 16:3581. doi: 10.1038/s41467-025-58550-7

102. Moran SM, Scott J, Clarkson MR, Conlon N, Dunne J, Griffin MD, et al. The clinical application of urine soluble CD163 in ANCA-associated vasculitis. *J Am Soc Nephrol.* (2021) 32:2920–32. doi: 10.1681/ASN.2021030382

103. Tam FW, Sanders JS, George A, Hammad T, Miller C, Dougan T, et al. Urinary monocyte chemoattractant protein-1 (MCP - 1) is a marker of active renal vasculitis. *Nephrol Dial Transplant.* (2004) 19:2761–8. doi: 10.1093/ndt/gfh487

104. Prskalo L, Skopnik CM, Goerlich N, Freund P, Wagner L, Grothgar E, et al. Urinary CD4 + T cells predict renal relapse in ANCA-associated vasculitis. *J Am Soc Nephrol.* (2024) 35:483–94. doi: 10.1681/ASN.0000000000000311

105. Sachez-Alamo B, Moi L, Bajema I, Berden A, Flossmann O, Hruskova Z, et al. Long-term outcome of kidney function in patients with ANCA-associated vasculitis. *Nephrol Dial Transplant.* (2024) 39:1483–93. doi: 10.1093/ndt/gfae018

106. Karras A, Pagnoux C, Haubitz M, Groot K, Puechal X, Tervaert JWC, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis.* (2017) 76:1662–8. doi: 10.1136/annrheumdis-2017-211123

107. Geetha D, Specks U, Stone JH, Merkel PA, Seo P, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement. *J Am Soc Nephrol.* (2015) 26:976–85. doi: 10.1681/ASN.2014010046

108. Strand V, Jayne DRW, Horomanski A, Yue H, Bekker P, Merkel PA, et al. The impact of treatment with avacopan on health-related quality of life in antineutrophil cytoplasmic antibody-associated vasculitis: a *post-hoc* analysis of data from the ADVOCATE trial. *Lancet Rheumatol.* (2023) 5:e451–e60. doi: 10.1016/S2665-9913(23)00092-9

109. Geetha D, Dua A, Yue H, Springer J, Salvarani C, Jayne D, et al. Efficacy and safety of avacopan in patients with ANCA-associated vasculitis receiving rituximab in a randomised trial. *Ann Rheum Dis.* (2024) 83:223–32. doi: 10.1136/ard-2023-224816

110. Tanaka R, Toishi T, Masaki R, Aihara H, Sakamoto S, Ikeda M, et al. Effective management of necrotizing crescentic glomerulonephritis using an aggressive combination therapy including avacopan in a patient double-seropositive for anti-GBM antibodies and ANCA: a case report. *CEN Case Rep.* (2024) 14:183–7. doi: 10.1007/s13730-024-00929-4

111. Cortazar FB, Niles JL, Jayne DRW, Merkel PA, Bruchfeld A, Yue H, et al. Renal recovery for patients with ANCA-associated vasculitis and low eGFR in the ADVOCATE trial of avacopan. *Kidney Int Rep.* (2023) 8:860–70. doi: 10.1016/j.ekir.2023.01.039

112. Merkel. P, Jayne D, Yue H, Schall TJ, Kelleher C, Bekker P. A Randomized, double-blind, active-controlled study of avacopan in anti-neutrophil cytoplasmic antibody (ANCA-) associated vasculitis. *Ann Rheumatic Dis.* (2020) 79:8.

113. Gabilan C, Pfirmann P, Ribes D, Rigothier C, Chauveau D, Casemayou A, et al. Avacopan as first-line treatment in antineutrophil cytoplasmic antibody-associated vasculitis: A steroid-sparing option. *Kidney Int Rep.* (2022) 7:1115–8. doi: 10.1016/j.ekir.2022.01.1065

114. Gabilan C, Belliere J, Moranne O, Pfirmann P, Samson M, Delattre V, et al. Avacopan for anti-neutrophil cytoplasm antibodies-associated vasculitis: a multicenter real-world study. *Rheumatol (Oxford).* (2024) 64(4):2214–9. doi: 10.1093/rheumatology/keae359

115. Zonozi R, Aqeel F, Le D, Cortazar FB, Thaker J, Zabala Ramirez MJ, et al. Real-world experience with avacopan in antineutrophil cytoplasmic autoantibody-associated vasculitis. *Kidney Int Rep.* (2024) 9:1783–91. doi: 10.1016/j.ekir.2024.03.022

116. Treppo E, Bello F, Galli E, Padoan R, Monti S, Moroni L, et al. Avacopan in the real-life practice: Evaluation of efficacy, safety, and impact on quality of life in the early stages of treat,ment. *Ann Rheumatic Dis.* (2023) 82:1606. doi: 10.1136/annrheumdis-2023-eular.4738

117. Casal Moura M, Gauckler P, Anders HJ, Bruchfeld A, Fernandez-Juarez GM, Floege J, et al. Management of antineutrophil cytoplasmic antibody-associated vasculitis with glomerulonephritis as proposed by the ACR 2021, EULAR 2022 and KDIGO 2021 guidelines/recommendations. *Nephrol Dial Transplant.* (2023) 38:2637–51. doi: 10.1093/ndt/gfad090

118. Jones RB, Furuta S, Tervaert JW, Hauser T, Luqmani R, Morgan MD, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. *Ann Rheum Dis.* (2015) 74:1178–82. doi: 10.1136/annrheumdis-2014-206404

119. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puechal X, Fujimoto S, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med.* (2020) 382:622–31. doi: 10.1056/NEJMoa1803537

120. De Vriese AS, Fervenza FC. PEXIVAS: the end of plasmapheresis for ANCA-associated vasculitis? *Clin J Am Soc Nephrol.* (2021) 16:307–9. doi: 10.2215//CJN.10550620

121. Tomasson G, Boers M, Walsh M, LaValley M, Cuthbertson D, Carette S, et al. Assessment of health-related quality of life as an outcome measure in granulomatosis with polyangiitis (Wegener's). *Arthritis Care Res (Hoboken).* (2012) 64:273–9. doi: 10.1002/acr.20649

122. Padoan R, Mohammad AJ, Hellmich B, Anastasa Z, Popov T, Balcells M, et al. Care gaps in ANCA-associated vasculitis (AAV): Exploring unmet needs and misalignments between patients and physicians. *Ann Rheumatic Dis.* (2025) 84:1498. doi: 10.1016/j.ard.2025.06.851

123. Collister D, Farrar M, Farrar L, Brown P, Booth M, Firth T, et al. Plasma exchange for ANCA-associated vasculitis: an international survey of patient preferences. *Kidney Med.* (2023) 5:100595. doi: 10.1016/j.xkme.2022.100595

124. McClure ME, Gopaluni S, Wason J, Henderson RB, Van Maurik A, Savage CCO, et al. A randomised study of rituximab and belimumab sequential therapy in PR3 ANCA-associated vasculitis (COMBIVAS): design of the study protocol. *Trials.* (2023) 24:180. doi: 10.1186/s13063-023-07218-y

125. Jayne D, Blockmans D, Luqmani R, Moiseev S, Ji B, Green Y, et al. Efficacy and safety of belimumab and azathioprine for maintenance of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized controlled study. *Arthritis Rheumatol.* (2019) 71:952–63. doi: 10.1002/art.40802

126. Arends EJ, Zlei M, Tipton CM, Cotic J, Osmani Z, de Bie FJ, et al. Disruption of memory B-cell trafficking by belimumab in patients with systemic lupus erythematosus. *Rheumatol (Oxford).* (2024) 63:2387–98. doi: 10.1093/rheumatology/keae286

127. Engesser J, Khatri R, Schaub DP, Zhao Y, Paust HJ, Sultana Z, et al. Immune profiling-based targeting of pathogenic T cells with ustekinumab in ANCA-associated glomerulonephritis. *Nat Commun.* (2024) 15:8220. doi: 10.1038/s41467-024-52525-w

128. Langford C, Khalidi N, Springer J, Friedman M, Hellmich B, Pagnoux C. A Randomized, double-blind, placebo-controlled trial of Abatacept for the treatment of relapsing, non-severe granulomatosis with polyangiitis. *Arthritis Rheumatol.* (2024) 76: Abstract 0823.

129. Hung W, Cusnir I, Habib S, Smylie M, Solez K, Yacyshyn E. Immune checkpoint inhibitor-induced granulomatosis with polyangiitis. *Rheumatol (Oxford).* (2021) 60:e190–e1. doi: 10.1093/rheumatology/keaa818

130. Furie RA, Aroca G, Cascino MD, Garg JP, Rovin BH, Alvarez A, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. (2022) 81:100–7. doi: 10.1136/annrheumdis-2021-220920

131. McGovern DP, McClure ME, Coates M, Bond S, Martinez Del Pero M, Mynard K, et al. Study protocol for a randomised, phase II, double-blind, experimental medicine study of obinutuzumab versus rituximab in ANCA-associated vasculitis: ObiVas. *BMJ Open*. (2024) 14:e083277. doi: 10.1136/bmjopen-2023-083277

frontiers | Frontiers in Immunology

TYPE Case Report
PUBLISHED 21 October 2025
DOI 10.3389/fimmu.2025.1601700

OPEN ACCESS

EDITED BY
Stefania Croci,
IRCCS Local Health Authority of Reggio Emilia, Italy

REVIEWED BY
Santos Castañeda,
Hospital de La Princesa, Spain
Khalid A. Alnaqbi,
Sheikh Tahnoon Medical City, United Arab Emirates

*CORRESPONDENCE
Shifeng Shao
shaosf@tmmu.edu.cn

†These authors have contributed equally to this work

RECEIVED 29 April 2025
ACCEPTED 07 October 2025
PUBLISHED 21 October 2025

CITATION
Zhang X, Wu Z, Li Y and Shao S (2025) Case Report: Severe gastrointestinal complications in adult IgA vasculitis: a fatal case of acute esophageal necrosis. *Front. Immunol.* 16:1601700. doi: 10.3389/fimmu.2025.1601700

Case Report: Severe gastrointestinal complications in adult IgA vasculitis: a fatal case of acute esophageal necrosis

Xun Zhang[1†], Zhengbin Wu[1†], Yuhao Li[2] and Shifeng Shao[1*]

[1]Department of Critical Care Medicine, Daping Hospital, Army Medical University, State Key Laboratory of Trauma, Burns and Combined Injury, Chongqing, China, [2]Department of Dermatology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Henoch–Schönlein purpura (HSP), also known as immunoglobulin A vasculitis (IgAV), is a type of systemic small-vessel inflammatory pathology. Clinical symptoms can range from simple skin purpura to multiorgan damage. IgAV can be divided into cutaneous-limited and multisystem-involved types, with significant individual variability in clinical manifestations. Between 50%–75% of patients experience abdominal symptoms such as abdominal pain and hematochezia; however, the occurrence of IgAV complicated by pancreatitis and esophageal mucosal sloughing is exceedingly rare. We report a case of adult IgAV with widespread purpura as the main clinical manifestation. Abdominal pain emerged during treatment, and pancreatitis was initially diagnosed based on serum amylase findings and CT imaging features. Nevertheless, acute esophageal necrosis was confirmed via gastroscopy, followed by a rapid deterioration in the patient's clinical status within a short period, ultimately leading to death due to massive gastrointestinal (GI) bleeding and disseminated intravascular coagulation (DIC).

KEYWORDS

Henoch-Schönlein purpura, immunoglobulin A, acute esophageal necrosis, pancreatitis, acute abdomen

1 Introduction

Immunoglobulin A vasculitis (IgAV), previously referred to as hypersensitivity purpura, is the most prevalent form of systemic vasculitis in children, with an incidence rate of 70.3 per 100,000 among those aged 4–7 years, compared with an incidence rate in adults that is only one-third to one-half of that in children (1–3). IgAV is a leukocytoclastic vasculitis involving small vessels (4). Pathological examination often reveals deposits of immunoglobulin A and complement component C3 around the walls of small vessels (5). Based on varying clinical manifestations, it can be categorized into localized IgAV, which primarily affects the skin, and systemic IgAV, which involves other organs—commonly the joints, gastrointestinal (GI) tract, and kidneys (6). GI involvement in IgAV may present as

gastritis, duodenitis, GI mucosal ulcers, and purpura, and can lead to severe complications such as intestinal perforation and intussusception (7).

IgAV is mainly characterized by non-thrombocytopenic purpura as the primary clinical manifestation, often accompanied by nephritis, joint pain, and abdominal pain. IgAV is an immune-mediated small-vessel vasculitis that predominantly affects children and is characterized by cutaneous purpura as the core clinical sign. Mild cases are often self-limiting, whereas some patients may experience relapses (8). Infection is a common predisposing factor for IgAV, and COVID-19 may also induce IgAV. However, the patient in this case did not present with any obvious infection-related symptoms (9). Reports of pancreatitis resulting from IgAV have been documented; however, there are no recorded instances of esophageal mucosal exfoliative manifestations associated with IgAV. This article reports a case of IgAV in an adult male in whom, during the gradual disappearance and improvement of systemic purpura, acute esophageal mucosal exfoliation and sudden massive bleeding occurred. This acute abdomen, especially with pancreatitis imaging changes, poses a challenge for clinicians in early diagnosis. By reporting this case, we aim to remind clinicians that when managing patients with IgAV complicated by abdominal pain, they should be alert to rare esophageal lesions. If necessary, early gastrointestinal endoscopy should be performed for evaluation, and early interventional treatment should be implemented to improve the patient's prognosis.

2 Case report

A 35-year-old male developed generalized cutaneous purpura without obvious predisposing factors 20 days prior to admission, predominantly involving the face, back, abdomen, and ankle joints of both lower extremities, with a symmetrical distribution. Concurrently, he experienced diffuse epigastric abdominal pain of a cramping nature. The patient subsequently presented to the First Affiliated Hospital of Chongqing Medical University. Upon detailed inquiry, the physician identified no specific past medical, family, or medication history, and no recent signs of infection were noted. Based on the presentation of cutaneous purpura and diffuse abdominal pain, the patient was diagnosed with immunoglobulin A vasculitis (IgAV). After admission, a skin biopsy was performed, which revealed perivascular inflammatory cell infiltration and vascular endothelial cell swelling (Figure 1). Treatment was initiated with oral prednisone acetate tablets and cetirizine for anti-allergic therapy for 7 days. Following treatment, cutaneous purpura on the trunk resolved, abdominal pain alleviated, and only scattered purpura remained on the extremities. The patient's condition improved, and he was discharged with continued oral anti-allergic medication after discharge.

On October 24, 2023, the patient again developed abdominal pain without obvious predisposing factors, presenting as cramping pain in the upper abdomen. The patient subsequently attended the Emergency Department of Daping Hospital, where physical examination showed stable vital signs. Mild tenderness was noted on palpation of the upper abdomen, without rebound tenderness or muscle rigidity. No abdominal distension, visible intestinal type, or peristaltic wave was observed, and no abdominal mass was palpable. The hepatic dullness boundary was normal. Scattered large patches of purpura were noted on the patient's extremities, with fewer on the trunk (Supplementary Figure 1). No swelling or tenderness was found in large joints such as the knee, ankle, or elbow joints.

Laboratory test results were as follows: white blood cell (WBC) count, 11.55 × 10^9L; C-reactive protein (CRP), < 0.5 mg/L; platelet count, 122 × 10^9L (mildly decreased); hemoglobin, 178 g/L; coagulation function: international normalized ratio (INR), 0.96; activated partial thromboplastin time (APTT), 28.1 s; prothrombin time (PT), 10.6 s; D-dimer, 341.68 μg/L; calcium, 0.96 mmol/L; and amylase, 124 U/L. Tumor marker tests were all negative, including those for carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, and CA 50. These results indicated mild elevations of WBC and amylase (not exceeding three times the normal range). Urinary protein was not elevated, and liver and renal function showed no significant abnormalities. Abdominal CT showed mild swelling of the pancreas, with a small amount of exudation in the pancreatic tail. No segmental intestinal injury was found, and there

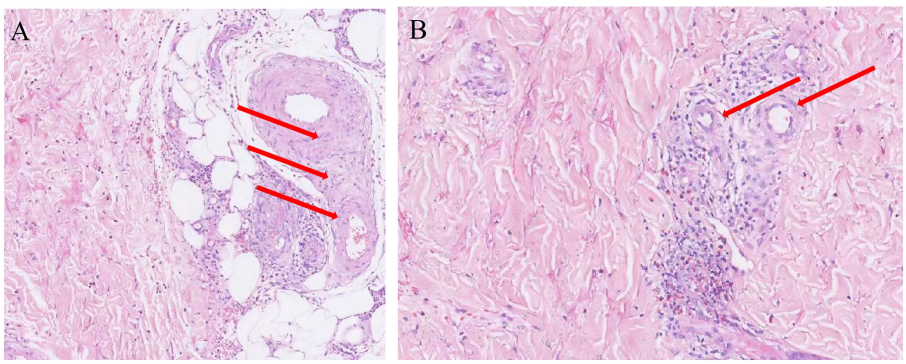


FIGURE 1
(A, B) Skin biopsy pathology. The areas indicated by the arrows show significant swelling of vascular endothelial cells, accompanied by extensive inflammatory cell infiltration.

were no signs of edematous thickening of the involved intestinal wall, free subphrenic air, intestinal stenosis, or other relevant abnormalities (Figure 2). The patient had definite cutaneous purpura accompanied by diffuse abdominal pain, supporting the consideration of abdominal purpura. In addition, the presence of abdominal pain combined with elevated amylase and CT findings suggestive of pancreatitis met the diagnostic criteria for pancreatitis. The patient was admitted to the Department of Gastroenterology for treatment.

The treatment regimen included fasting, inhibition of gastric acid secretion, administration of somatostatin to inhibit pancreatic enzyme secretion, antispasmodic therapy, and anti-allergic treatment with dexamethasone combined with cetirizine.

On the second day after admission, the patient's abdominal pain worsened, and fecal occult blood was positive. Emergency gastroscopy revealed acute peptic esophagitis involving the entire esophagus, local depression and erosion of the gastric antral mucosa, and scattered shallow ulcerative lesions in the duodenal bulb and descending portions (Figure 3). Laboratory tests (Figure 4) showed the following: WBC, 21.98 × 10^9L; platelet count, 28 × 10^9L; hemoglobin, 94 g/L; INR, 1.42; APTT, 38.1 s; PT [missing value—please verify]; and D-dimer, 62,624.8 μg/L. Complement C3, complement C4, immunoglobulins IgG, IgA, and IgM, autoantibody spectrum, T-lymphocyte subset analysis, procalcitonin, liver function, renal function, and urine protein tests all showed no significant abnormalities.

Bacterial and fungal smears and cultures of sputum and urine, routine stool tests, and nucleic acid screening for common viruses were all negative; thus, infections were ruled out. The test results for hepatitis antibodies, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), serum complement levels, serum cryoglobulins, and rheumatoid factor (RF) were all within the normal range.

On the same day, the patient was transferred to the intensive care unit for treatment. Esomeprazole 80 mg was administered via rapid intravenous push, followed by continuous intravenous infusion of esomeprazole at 8 mg/h, along with continuous intravenous infusion of somatostatin for gastrointestinal bleeding control. Concurrently, methylprednisolone 1 mg/kg combined with intravenous immunoglobulin (IVIG) 400 mg/kg was administered intravenously.

On the third day after admission, the patient developed widespread purpura, sudden gastrointestinal bleeding, and hemorrhagic shock. Immediate treatment included blood transfusion, correction of coagulation function, conservative medical hemostasis, antimicrobial therapy, lung-protective mechanical ventilation with tracheal intubation, and fluid resuscitation. However, the patient ultimately died due to ineffective treatment of disseminated intravascular coagulation (DIC).

3 Discussion

The etiology of immunoglobulin A vasculitis (IgAV) remains unclear, but the formation of galactose-deficient IgA1 (Gd-IgA1) and its associated immune complexes is believed to play a significant role in the pathogenesis of systemic vasculitis and tissue damage, thus representing a crucial mechanism in the development of IgAV (10). Skin biopsy often shows leukocytoclastic vasculitis (5). Gastrointestinal (GI) manifestations are mostly ulcerative bleeding and perforation of the stomach and intestines, with severe cases such as intestinal intussusception and intestinal necrosis. The manifestation of acute esophageal mucosal exfoliation is rare (11–13). Acute stripping esophagitis is related to drugs and food, with few reported cases (14, 15). From the current literature search, no cases of IgAV concurrently complicated by acute pancreatitis and acute esophageal mucosal exfoliation have been identified.

The diagnosis of IgAV relies on clinical manifestations and laboratory findings. In this case, the patient presented with distinct cutaneous purpura and extensive peritonitis, satisfying both the 1990 American College of Rheumatology (ACR) criteria and the 2008 final Ankara classification criteria endorsed by EULAR/PRINTO/

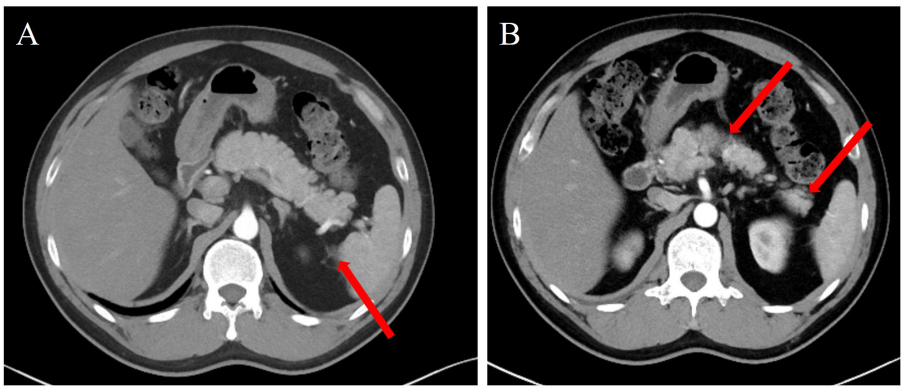


FIGURE 2
(A, B) Computed tomography images show pancreatic edema and surrounding inflammatory exudation. The area indicated by the red arrow demonstrates peripancreatic inflammatory exudate; however, the overall morphology of the pancreas remains intact, indicating mild pancreatitis-related injury.

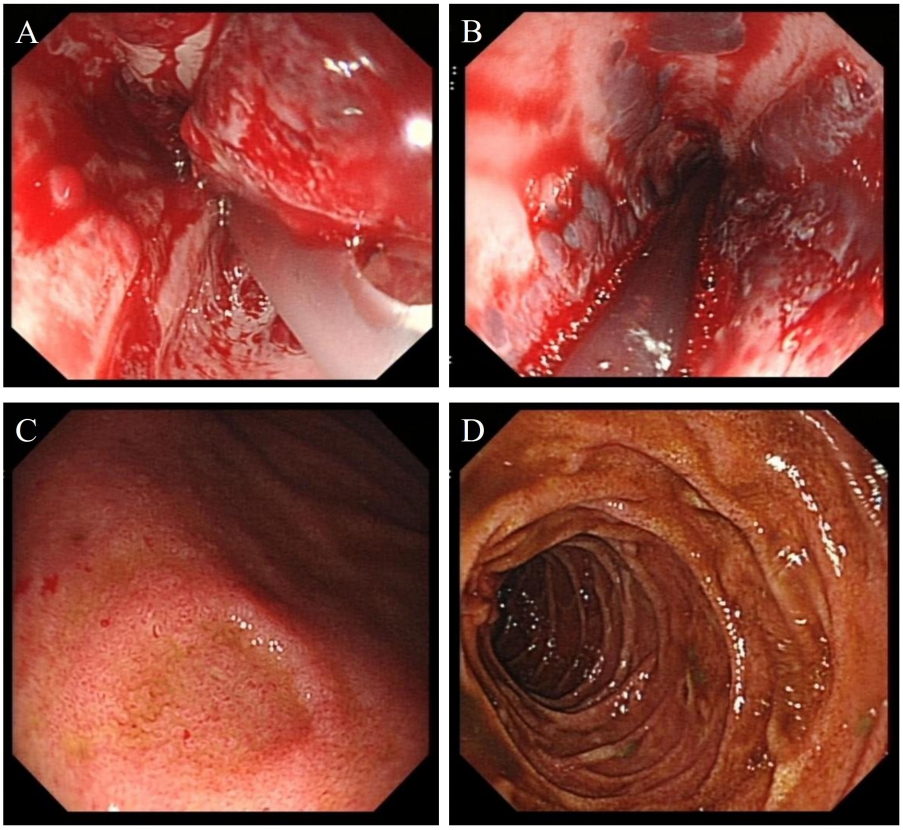


FIGURE 3
(A, B) Endoscopic images show features of peptic esophagitis involving the entire esophagus. **(C)** The gastric antral mucosa appears rough, with localized mucosal depression and erosion. **(D)** Scattered ulcerative lesions are visible in the descending portion of the duodenum.

PReS. Light microscopy of the skin biopsy—a hallmark of IgAV—demonstrated prominent small-vessel vasculitis characterized by vascular wall edema, marked endothelial cell swelling, and extensive perivascular neutrophil aggregation. Admission laboratory investigations showed no thrombocytopenia and normal coagulation profiles (effectively ruling out thrombotic thrombocytopenic purpura and other hemorrhagic rash disorders), while negative antineutrophil cytoplasmic antibody (ANCA) testing excluded ANCA-associated vasculitides.

Symptoms of IgAV in adults are more severe than in children, although treatment approaches are generally similar. In this case, the patient presented with distinct abdominal pain, and CT imaging revealed pancreatic enlargement consistent with edematous pancreatitis, accompanied by elevated amylase levels, aligning with the Atlanta classification criteria for pancreatitis diagnosis (16).

In children diagnosed with IgAV, pancreatitis has been observed in a subset of cases. According to the report by Du et al., only 4 out of 15 pediatric patients exhibited amylase levels exceeding three times the normal range, with a median amylase level of 177 U/L (interquartile range 154–332 U/L; reference range 0–125 U/L). The specificity of amylase in patients with IgAV complicated by pancreatitis is relatively low, and diagnosis primarily relies on clinical manifestations and histopathological findings. Following treatment with glucocorticoids, these patients generally experienced favorable outcomes (17). Frigui summarized cases of adults with IgAV complicated by pancreatitis reported in recent years, noting that treatment with glucocorticoids yielded favorable outcomes (18). The mechanism underlying the occurrence of pancreatitis following IgAV remains unclear but may be associated with factors such as immune dysregulation or vascular occlusion (19). In our case, the onset of the patient's symptoms occurred 7 to 10 days after the appearance of skin purpura. Amylase levels were only mildly elevated, and the pancreatic presentation was consistent with edematous pancreatitis. This suggests that the clinical manifestations of IgAV-associated pancreatitis in adults are similar to those observed in children. The cases we reported indicate that the pancreas mainly exhibits inflammatory edema. However, because the patient's family refused an autopsy, there was no definite pathological evidence of pancreatic inflammation, and the mechanism of its occurrence could not be clearly determined.

The etiology of acute esophageal mucosal exfoliation is complex and commonly includes (1) the oral administration of certain medications, such as dabigatran etexilate and benzodiazepines; (2) ingestion of corrosive liquids; and (3) autoimmune disorders, including systemic lupus erythematosus and pemphigus vulgaris (17, 18). In adults with immunoglobulin A vasculitis (IgAV), gastrointestinal (GI) manifestations are most commonly characterized by abdominal pain, and the condition is prone to

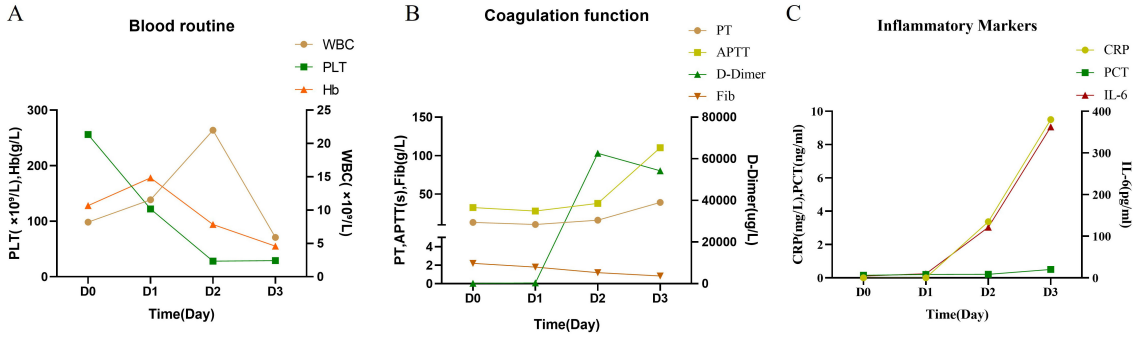


FIGURE 4
Results of laboratory tests at different time points. **(A)** Blood routine. **(B)** Coagulation function. **(C)** Inflammatory markers. WBC, white blood cell; PLT, platelet; Hb, hemoglobin; PT, prothrombin time; APTT, activated partial thromboplastin time; Fib, fibrinogen; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6.

complications such as gastrointestinal bleeding. Among GI sites, the duodenum is the most frequently involved. Computed tomography typically reveals circumferential bowel wall thickening and mesenteric vascular congestion. In severe cases, patients may develop intestinal perforation or even intestinal necrosis. However, there are currently no clear cases of severe esophageal mucosal exfoliation complicated by bleeding caused by IgAV (20). Iorio et al. documented a case of a patient with allergic purpura presenting with concurrent acute esophageal necrosis who also had a history of kidney transplantation, a recognized risk factor for the development of acute esophageal mucosal exfoliation (21). Among patients with IgAV, 50%–75% experience GI involvement, with most lesions occurring in the small intestine (22–24). In our case, the patient's condition deteriorated rapidly during hospitalization. The progression of purpura and the presence of complications such as pancreatitis indicated severe microvascular damage. In addition to the commonly observed injury to the small intestinal mucosa, extensive desquamation of the esophageal mucosa was noted. We hypothesize that the desquamation of the esophageal mucosa may be associated with ischemic necrosis of the mucosal microvasculature due to severe microvascular pathology. Although we cannot definitively establish that IgAV was the direct cause of the esophageal mucosal desquamation, the clinical presentation of the patient—together with the absence of any known risk factors for desquamative esophagitis—strongly suggests a significant correlation between the esophageal desquamation and IgAV in this case.

Glucocorticoids play a crucial role in the management of immunoglobulin A vasculitis (IgAV), particularly in patients with organ involvement, where their use should be more aggressive (25). A review of the patient's diagnostic and therapeutic course reveals that during the early phase, when only skin purpura was present, high-dose corticosteroid pulse therapy was not administered. The patient also did not seek medical attention immediately after the onset of abdominal pain. It was only after the diagnosis of concurrent pancreatitis and esophageal mucosal exfoliation that high-dose corticosteroid pulse therapy combined with immunoglobulin treatment was initiated. Unfortunately, the patient experienced massive gastrointestinal (GI) bleeding and responded poorly to medical management. Ultimately, the patient succumbed to disseminated intravascular coagulation (DIC) secondary to severe bleeding. The patient's condition progressed rapidly. Although glucocorticoids and immunoglobulins were administered, they failed to effectively reverse the uncontrolled immune response. Novel agents—such as the oral targeted-release formulation of budesonide, B cell–directed agents, and complement pathway inhibitors—have demonstrated favorable outcomes in some clinical trials and may offer additional therapeutic options for the management of such patients in the future (26). This case underscores the potential for GI involvement in IgAV to present in a highly insidious manner, highlighting the need for careful diagnostic reflection. Although abdominal CT is the routine first-line examination for acute abdomen, clinicians should remain vigilant for possible GI lesions in patients with IgAV presenting with abdominal pain. This rare, catastrophic case reminds us that early and thorough gastrointestinal endoscopy is essential to identify potential life-threatening complications in the digestive tract.

4 Conclusion

This case highlights a rare and catastrophic complication of immunoglobulin A vasculitis (IgAV) presenting with acute esophageal necrosis and pancreatitis. Clinicians should maintain a high index of suspicion for unusual gastrointestinal (GI) involvement in patients with IgAV presenting with acute abdomen, and early imaging and endoscopic evaluation may be warranted. Prompt initiation of immunosuppressive therapy could potentially alter outcomes; however, further case accumulation is needed to better guide management.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by The Ethics Committee of the PLA Army Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

XZ: Writing – original draft, Supervision, Software, Data curation, Methodology, Formal Analysis, Project administration, Investigation, Conceptualization. ZW: Writing – original draft, Methodology, Software, Investigation, Data curation, Supervision, Formal analysis. YL: Supervision, Project administration, Investigation, Writing – original draft, Conceptualization, Methodology, Software, Data curation. SS: Project administration, Writing – review & editing, Investigation, Supervision, Conceptualization.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. This work was supported by the key specialty of the army's clinical focus.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2025.1601700/full#supplementary-material

References

1. Jennette JC, et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum.* (2013) 65(1):1–1–11.

2. Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *Lancet.* (2002) 360:1197–202.

3. Tan J, Tang Y, Xu Y, Yan S, Xu Y, Tan L, et al. The clinicopathological characteristics of henoch-schönlein purpura nephritis with presentation of nephrotic syndrome. *Kidney Blood Press Res.* (2019) 44:754–64.

4. Yang YH, Tsai IJ, Chang CJ, Chuang YH, Hsu HY, Chiang BL. The interaction between circulating complement proteins and cutaneous microvascular endothelial cells in the development of childhood Henoch-Schönlein Purpura. *PloS One.* (2015) 10: e0120411.

5. Hastings MC, Rizk DV, Kiryluk K, Nelson R, Zahr RS, Novak J, et al. IgA vasculitis with nephritis: update of pathogenesis with clinical implications. *Pediatr Nephrol.* (2022) 37:719–33.

6. Sunderkötter CH, Zelger B, Chen KR, Requena L, Piette W, Carlson JA, et al. Nomenclature of cutaneous vasculitis: dermatologic addendum to the 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheumatol.* (2018) 70:171–84.

7. Ebert EC. Gastrointestinal manifestations of henoch-schonlein purpura. *Dig Dis Sci.* (2008) 53:2011–9.

8. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. *Part II: Final Classific Criter Ann Rheum Dis.* (2010) 69:798–806.

9. Alnaqbi KA, Abunamous N, Saleem T. A rare twist: COVID-19 infection masquerading as IgA vasculitis in a hemophilia a patient. *Clin Rheumatol.* (2024) 43:1393–9.

10. Xu L, Li Y, Wu X. IgA vasculitis update: Epidemiology, pathogenesis, and biomarkers. *Front Immunol.* (2022) 13:921864.

11. Hetland LE, Susrud KS, Lindahl KH, Bygum A. Henoch-schönlein purpura: A literature review. *Acta Derm Venereol.* (2017) 97:1160–6. doi: 10.2340/00015555-2733

12. Hammad H, Krausz J, Barcan M, Fisher S, Edison N, Ziv M. Adult henoch-schönlein purpura: comprehensive assessment of demographic, clinical, and histopathological features as predictors for systemic involvement. *Dermatology.* (2023) 239:609–15. doi: 10.1159/000530820

13. Shang XP, Wu JG, Cheng Y, Hu HB. Epidemiology and clinical characteristics of henoch-schönlein purpura associated with mycoplasma pneumoniae infection in 131 children in hubei province, China. *Mediterr J Hematol Infect Dis.* (2021) 13:e2021037. doi: 10.4084/MJHID.2021.037

14. Nagata K, Akazawa Y. Exfoliative esophagitis induced by sunitinib. *Mayo Clin Proc.* (2019) 94:557–8. doi: 10.1016/j.mayocp.2018.12.005

15. Schertl F, Lewerenz B, Schepp W. Exfoliative esophagitis caused by habitual ingestion of very hot coffee. *Clin Gastroenterol Hepatol.* (2018) 16:e119. doi: 10.1016/j.cgh.2017.10.033

16. Lerch MM. Classifying an unpredictable disease: the revised Atlanta classification of acute pancreatitis. *Gut.* (2013) 62:2–3.

17. Du L, Liu C, Wang X, Mu J, Yang Y. Acute pancreatitis associated with immunoglobulin A vasculitis: report of fifteen cases. *Clin Rheumatol.* (2023) 42:839–47.

18. Frigui M, Lehiani D, Koubaa M, Bouaziz Z, Abid B, Beyrouti I, et al. Acute pancreatitis as initial manifestation of adult Henoch-Schönlein purpura: report of a case and review of literature. *Eur J Gastroenterol Hepatol*. (2011) 23:189–92.

19. Rawla P, Bandaru SS, Vellipuram AR. Review of infectious etiology of acute pancreatitis. *Gastroenterol Res*. (2017) 10:153–8.

20. Castañeda S, Vicente-Rabaneda EF, Blanco R, González-Gay MA. Gastrointestinal involvement in adult IGA vasculitis. *Rheumatol (Oxford)*. (2020) 59(10):2659–60.

21. Iorio N, Bernstein GR, Malik Z, Schey R. Acute esophageal necrosis presenting with henoch-schönlein purpura. *ACG Case Rep J*. (2015) 3:17–9.

22. Saulsbury FT. Clinical update: Henoch-Schönlein purpura. *Lancet*. (2007) 369:976–8. doi: 10.1016/S0140-6736(07)60474-7

23. Han DG, Huang C, Liu W. Duodenal and jejunal involvement by IgA vasculitis. *Am J Med Sci*. (2024) 367:e69–70. doi: 10.1016/j.amjms.2024.01.021

24. Han DG, Liu X, Liu W. Immunoglobulin A vasculitis involving the duodenum and jejunum. *Dig Liver Dis*. (2024) 56:522–4. doi: 10.1016/j.dld.2023.11.036

25. Ozen S, Marks SD, Brogan P, Groot N, de Graeff N, Avcin T, et al. European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis-the SHARE initiative. *Rheumatol (Oxford)*. (2019) 58:1607–16. doi: 10.1093/rheumatology/kez041

26. Castañeda S, Quiroga-Colina P, Floranes P, Uriarte-Ecenarro M, Valero-Martínez C, Vicente-Rabaneda EF, et al. IgA vasculitis (Henoch-schönlein purpura): an update on treatment. *J Clin Med*. (2024) 13:6621. doi: 10.3390/jcm13216621

frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 03 November 2025
DOI 10.3389/fimmu.2025.1675251

OPEN ACCESS

EDITED BY
Maria Giovanna Danieli,
Università Politecnica delle Marche, Italy

REVIEWED BY
Davide Firinu,
University of Cagliari, Italy
Antonio Giovanni Solimando,
University of Bari Aldo Moro, Italy
Mario Andrea Piga,
Università Politecnica delle Marche, Italy

*CORRESPONDENCE
Elean S. V. Tay
elean.tay@monash.edu

RECEIVED 29 July 2025
ACCEPTED 20 October 2025
PUBLISHED 03 November 2025

CITATION
Tay ESV, Ting YT, Gan P-Y and Ooi JD (2025) Regulatory T cell therapy for myeloperoxidase-specific anti-neutrophil cytoplasmic antibody associated vasculitis. *Front. Immunol.* 16:1675251. doi: 10.3389/fimmu.2025.1675251

Regulatory T cell therapy for myeloperoxidase-specific anti-neutrophil cytoplasmic antibody associated vasculitis

Elean S. V. Tay*, Yi T. Ting, Poh-Yi Gan and Joshua D. Ooi

Center for Inflammatory Diseases, School of Clinical Sciences at Monash Health, Monash University, Melbourne, VIC, Australia

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a rare autoimmune disease characterized by the inflammation of small vessels. It is most commonly caused by ANCA targeting proteinase 3 (PR3) and myeloperoxidase (MPO) which are found in neutrophil lysosomes. The most common affected organs are respiratory tracts and kidneys, though other organs can be involved too. Although the cause of disease between PR3-AAV and MPO-AAV is similar, they vary in pathogenesis. Epigenetic and genetic factors may play a role in the disease development as certain population such as Chinese with HLA-DRB1*04:05 are more prevalent in MPO-AAV patient population. The prognosis for them is usually poor, often resulting in end-stage renal failure even with existing treatment. Current treatment for AAV relies heavily on corticosteroids which are toxic for long-term usage. Hence, there is a strong need to develop new, less toxic and targeted therapy for this disease. Regulatory T cell (Treg) therapy is a new type of therapy with the potential to specifically re-establish tolerance to the target autoantigen (MPO or PR3). This review will delve into the pathogeneses of AAV and discuss the potential of using genetically engineered Tregs to treat the cause of disease.

KEYWORDS

MPO-AAV, HLA, preclinical model, TCR-T and CAR-T therapy, ANCA

Anti-neutrophil cytoplasmic antibodies-associated vasculitis

AAV is a rare autoimmune disease that causes inflammation and subsequently damage to the small vessels (1–3). The main characteristic of the disease is the pauci-immune state of deposition of immunoglobulin within the small vessels of the glomeruli, which stands out as a subgroup of the small vessel vasculitides (1–3). The common affected organs include the respiratory tract, lungs and kidney. The underlying causes are autoantibodies to the neutrophil proteins; particularly proteinase 3 (PR3) and myeloperoxidase (MPO),

however, other neutrophil proteins including lysosome-associated membrane protein 2 (LAMP-2) and elastase are involved to a lesser extent.

Classification and clinical presentation

AAV can be subclassified into granulomatosis with polyangiitis (GPA) (previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA) (previously known as Churg-Strauss syndrome) according to the 2012 Revised Chapel Hill Consensus Conference (4). GPA is presented with necrotizing vasculitis with extravascular granulomatosis that usually involves respiratory tract and kidney whereas MPA is like GPA, but in the absence of granulomatosis. EGPA is characterized with necrotizing granulomatous vasculitis in the presence of eosinophilia, and it usually involves the respiratory tract with an association with asthma. A famous disease manifestation is the detection of little or no deposition of immune complexes in the affected tissue area. This results in an interesting disease presentation of pauci-immune necrotizing crescentic glomerulonephritis (NCGN). The absence of the immune complexes is due to the release of elastase from the dead neutrophils, digesting the immunoglobulin (5).

Furthermore, PR3-ANCA is usually associated with GPA (around 85% of patients) whereas MPO-ANCA is more frequently associated with MPA (around 60% of patients) (6). The titres of ANCA do not correlate with the severity of the disease as ANCA can be found in asymptomatic or healthy individuals (1, 7). The pathogenic T cell epitopes of MPO-AAV have been delineated in experimental models of disease (8).

Epigenetic and genetic factors of MPO-AAV

The prevalence of AAV has increased in recent years from 48–184 cases to 300–421 cases per million individuals, indicating improved survival of patients (6). Efforts have been put into genome wide association studies (GWAS) to investigate genetic variants and subsets occurring in patients that might be the key towards disease pathogenesis. PR3 is mostly found in Caucasian population whereas Asians such as Chinese and Japanese dominates MPA, indicating the role of different genetic subsets. Studies have supported an association of the disease with non-major histocompatibility complex (MHC) and MHC, though MPO-AAV is mostly associated with MHC II alleles (9). Japanese patients with MPO-AAV are skewed towards DRB1*09:01 being the risk allele (10) whereas Chinese patients are frequently carrying DQA1*03:02, DQB1*03:03 and DRB1*04:05 (11, 12). In particular, MPO-AAV patients carrying DRB1*04:05 exhibit the worst prognosis, with ~50% of patients progressing to end-stage renal failure (ESRF) within 1 year of diagnosis (11).

Other factors including infections, drugs and silica exposure have been associated with disease progression. Patients who are carriers of *S. aureus* are more susceptible to relapse as *S. aureus* infection triggers the disease onset for PR3-AAV. This is because *S. aureus* demonstrates a molecular mimicry to the complementary peptide of $PR3_{105\text{-}201}$, and the B cells responds by producing antibodies against this $cPR3_{105–201}$ peptide (13). However, the resulting antibodies were also found to be reactive towards the $PR3_{105\text{-}201}$, contributing towards the autoimmunity in patients. Whereas in MPO-AAV, Ooi et al. demonstrated that certain *S. aureus* strain carries a plasmid-encoded 6-phosphogluconate dehydrogenase amino acid sequence ($6PGD_{391\text{-}410}$) can trigger anti-MPO immunity due to molecular mimicry (14). Certain drugs such as propylthiouracil (PTU), an antithyroid drug is commonly associated with MPO-AAV even though its exact mechanism is unknown, further contributing towards the risk of certain population to develop AAV (6). Intensity of silica exposure impacts on the development of AAV as well, though its exact mechanism is unknown (15).

Previous studies have identified the immunodominant region of MPO, which tends to be in a 'hotspot' region in the heavy chain of MPO. Patients' sera were used to map these immunogenic epitopes, with identification of shared epitopes between T and B cells further emphasize the importance of the hotspot region through their persistence presence in remission patients. The human chimera to the identified immunogenic MPO epitope in a mouse study by Ooi et. al., $MPO_{435–453}$ lies within the hotspot region (8), whereas clinical studies had identified $MPO_{393\text{-}402}$, $MPO_{437\text{-}446}$, $MPO_{447\text{-}461}$, $MPO_{479\text{-}488}$, $MPO_{717–726}$ to be immunogenic (7, 16, 17).

Diagnosis

Currently, patients are diagnosed based on clinical symptoms; pathology tests (urine and blood) and tissue biopsy (6). However, it must be noted that having a positive ANCA does not necessarily mean the patient has AAV, rather it could be other autoimmune diseases such as lupus nephritis (LN), inflammatory bowel disease (IBD), ulcerative colitis (UC) and autoimmune hepatitis (AIH). Birmingham Vasculitis Activity Score (BVAS) is a well-developed tool that is used by clinicians to quantify the disease activity in patients (18–20). Histologic examination of tissue biopsy remains to be the gold standard in diagnosing AAV. It is crucial to differentiate them with immune complex small vessel vasculitis because it determines the type of treatment and prognosis of patients (6).

Pathogenesis of MPO-AAV

Innate immune response

The pathogenesis of AAV is not completely elucidated and the suggested pathways are based on patient and experimental observations (Figure 1). The autoantigen, MPO is a sequestered antigen, found in the lysosomes of neutrophils. Hence, a stimulus is required to activate neutrophils to cause an upregulation of membrane bound MPO in neutrophils. Proinflammatory

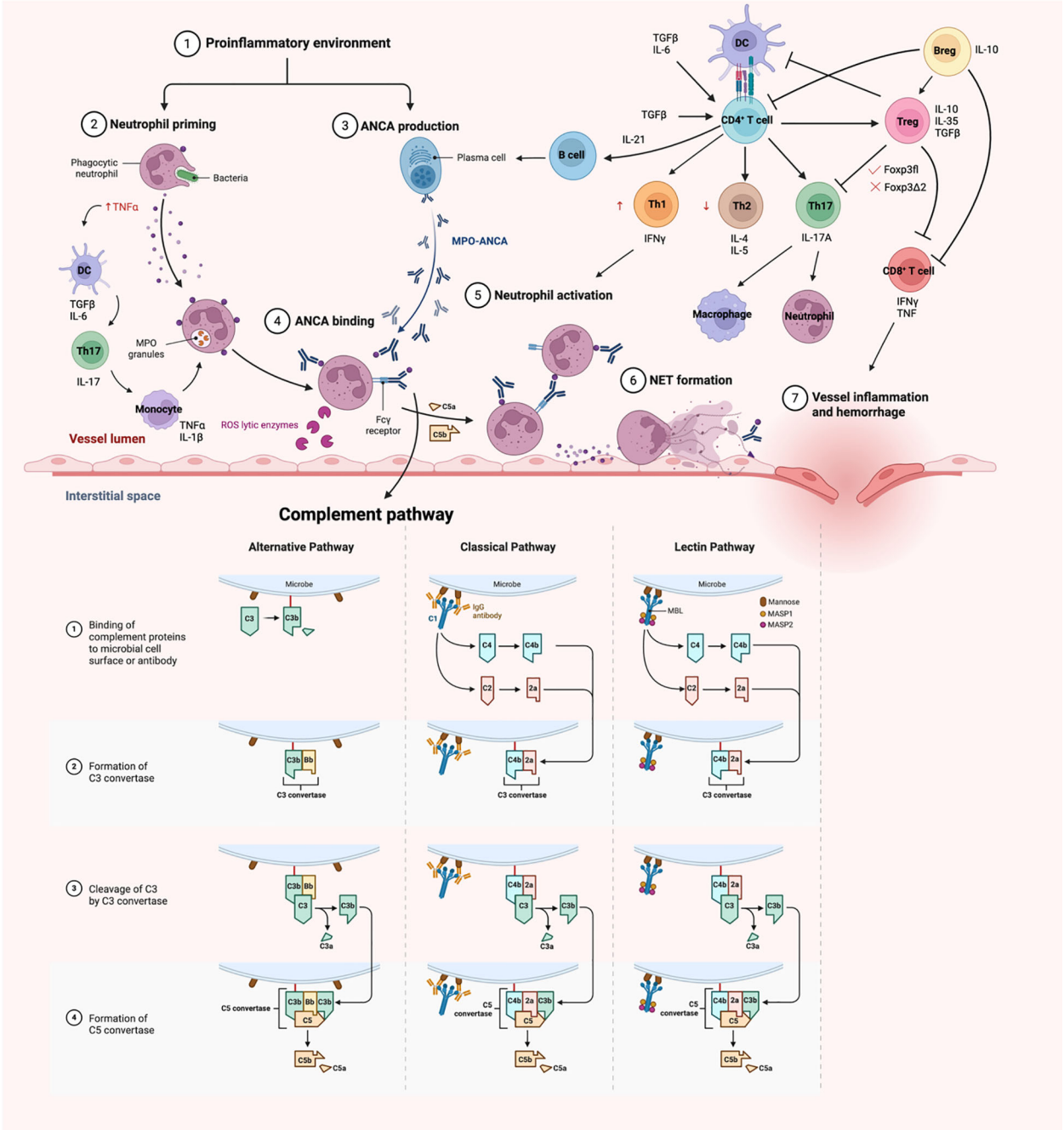


FIGURE 1
A schematic overview of pathogenesis of MPO-AAV. Neutrophils are primed with TNFα in a proinflammatory environment, resulting in an upregulation of membrane MPO. These neutrophils are targeted by ANCA, hence destroying them in the process, resulting in damage of endothelium lining. The adaptive immune system comes in later and act in a delayed-type hypersensitivity (DTH) fashion, enhancing the disease activity. *Diagrams created with Biorender.com.*

cytokines such as tumour necrosis factor alpha (TNF-α) are usually the trigger for disease onset, which commonly happens in infection. The presence of infectious agent stimulates the release of transforming growth factor beta (TGFβ) and interleukin 6 (IL-6) by dendritic cells (21, 22). ANCAs produced by B cells bind to membrane bound MPO on activated neutrophils. This in turn triggers the naïve T cells to differentiate into T helper 17 (Th17) cells and produce IL-17. IL-17 is a potent proinflammatory cytokine that stimulates the immune system, including the monocytes and macrophages to release TNFα and IL-1β, which further prime the neutrophils during the acute phase of the disease (21, 22). Renal neutrophils are found to be capable of producing proinflammatory cytokines TNFα and IL-17 as well, contributing to the differentiation of Th17 cells. The innate γδ T cells migrate to the site of inflammation and produce IL-17 that contributes to disease development (23).

Studies have shown that TNF-α primed neutrophils upregulates membrane expression of MPO, allowing the interaction between MPO and MPO-ANCA, in which the MPO-ANCA acts as a bridge between the Fcγ receptors and MPO. The FcγR of the adjacent neutrophils can then recognize the Fc portion of these ANCAs, resulting in neutrophil activation, hence releasing reactive oxygen species (ROS) that kills the 'victim' neutrophils. This causes the neutrophils to undergo respiratory burst, degranulation, releasing neutrophil extracellular traps (NETosis), apoptosis and necrosis (3).

Furthermore, the FcγR becomes the target of complement, activating the classical and alternate complement pathways, encouraging the destruction of neutrophils. In particular, C5a is the central complement in both pathways and studies had shown an increase in circulating levels of C5a in patients (24). The ablation of the C5a receptor on neutrophils also attenuate the disease phenotype, indicating a probable therapeutic target (25, 26). Despite the importance of FcγR being stated, FcγRIIB plays a role as the only inhibitory Fc receptor that regulates and maintains peripheral tolerance (27). An *in vivo* mouse model showed that the FcγRIIB deficient mice developed more severe glomerular injury. The whole process releases proinflammatory cytokines which attract more neutrophils to the site by adhering to the vessel wall and undergo diapedesis (1–3, 6). Spillage of plasma then happens, and the presence of the coagulation factor encourages the formation of fibrinoid necrosis, ultimately damaging the fragile monolayer endothelium.

Involvement of the adaptive immune response

B cells

B cells are responsible for generating autoantibodies, and some studies suggests that this arises from a deficiency or dysfunction of regulatory T cells (Treg), leading to a loss of immune tolerance. Neutrophils also contribute by releasing B-cell activating factors (BAFF)/B lymphocyte stimulator (BLyS) (28) which stimulate B cell differentiation, proliferation and immunoglobulins (Igs) production. Regulatory B cells (Breg) that express CD5 and is important for IL-10 production, are downregulated in disease. These Bregs play a key role in suppressing activated T cells and supporting Treg differentiation (29, 30). Research has shown that $CD5^+CD24^{hi}CD38^+$ B cells are reduced during active disease but return to levels comparable levels to healthy controls (HC) during remission (31). Additionally, $CD4^+$ T cells contribute to B cells stimulation through the production of IL-21 (30).

T cells

T cells play a critical, non-redundant role in disease pathogenesis (6, 32. 1, 33). They mediate delayed-type hypersensitivity (DTH) responses, perpetuating inflammation and ultimately leading to tissue destruction (Figure 1).

$CD4^+$ T helper (Th) cells are central to adaptive immunity, activating B cells, recruiting macrophages and promoting cytotoxic T cell responses, all of which drive autoimmune response. Gan et al. demonstrated that the depletion of MPO-specific $CD4^+$ T cells ameliorates GN, highlighting their importance in disease activity (33). Specifically, Th1 cell contributes to the nephritogenic immune responses, where IL-12p40 guides Th1 cells in inducing crescentic GN (34). The balance between Th1 and Th2 cells is critical for maintaining self-immune tolerance (21). Th1 cells drive the severity and progression of autoimmune disease through IFNγ production, while Th2 cells act in opposition (35). Th17 cell is another subset linked to autoimmunity due to its pro-inflammatory nature. Retinoic acid receptor-related orphan nuclear receptor γt (RORγt) is an important transcription factor essential for Th17 cells differentiation, and its absence attenuates GN (36). Both TGFβ and IL-6 encourages the Th17 lineage differentiation, but TGFβ alone supports Treg differentiation (37). Th17 cells produce IL-17 which significantly contributes to disease manifestation, with elevated IL-17 levels exacerbating crescentic GN formation (38). IL-17A not only activates Th17 cells but also enhances neutrophils and macrophages recruitment (39).

In experimental anti-MPO GN mouse models, depletion of MPO-specific $CD8^+$ T cells ameliorate kidney injury, as evidenced by reduction in albuminuria, blood urea nitrogen (BUN) and proteinuria (40). Notably, $CD8^+$ T cells can mediate glomerular injury in an MPO^+ environment even in the absence of $CD4^+$ T cells, highlighting their independent pathogenic potential (40). These $CD8^+$ T cells are major sources of proinflammatory cytokines such as interferon gamma (IFNγ) and TNF. Furthermore, IL7R (CD127) signalling is critical for Teff function, as demonstrated by increased expression in a transcriptome analysis (41).

Besides, toll-like receptors (TLRs) which function to recognize pathogen associated molecular patterns are found to engage in disease pathogenesis. The activation of TLR2 stimulates IL-17A production, promoting Th17 cells activity, while TLR9 enhances anti-MPO driven autoimmunity through Th1 committed lineage pathway (42). In addition, TLR4 is constitutively expressed in glomeruli and its expression is upregulated during GN (43), drive the production of chemokines, CXCL1 and CXCL2 where they serve as the major chemoattractant for neutrophils (43). An experimental murine anti-MPO model further showed that lipopolysaccharide (LPS) can synergize with anti-MPO autoimmunity, exacerbating the NCGN disease phenotype (44). Collectively, these findings suggest that infection and innate immune activation can amplify the anti-MPO driven autoimmunity.

Regulatory T cells

A subset of T cells, known as the regulatory T cells (Tregs) are key mediators of self-tolerance and immune homeostasis. The critical role of Tregs was first elucidated in the 1990s by Sakaguchi et. al, where adoptive transfer of $CD4^+CD25^+$ but not $CD4^+CD25^-$ T cells could prevent autoimmune disease in athymic mice (45). The scurfy phenotype observed in mice is linked to mutations in the Forkhead box protein p3 (Foxp3) gene, which is also implicated in the human immunodysregulation polyendocrinopathy enteropathy X-linked

(IPEX) syndrome. This syndrome arises from recessive mutations in Foxp3 and results in severe autoimmune manifestations, underscoring the essential role of Foxp3 in Treg function (45).

Foxp3 is a transcription factor uniquely expressed in Treg, but its precise regulatory mechanisms remain incompletely understood. At the genomic level, Foxp3 controls the expression of genes critical for T cell function, including nuclear factor of activated T cells (NFAT) and AML1/RunX1, which are required for effector T cells (Teff) differentiation (46). Foxp3 also interacts with RORγt, inhibiting the differentiation of naïve T cells into Th17, further clarifying its role in MPO-AAV disease mechanism. Notably, only the full length Foxp3 isoform (Foxp3fl) can interact with RORγt, while the exon 2-spliced variant (Foxp3Δ2) cannot (32).

Given their potent immunosuppressive capacity, Tregs are a great therapeutic tool to treat autoimmune diseases. In patients with MPO-AAV, Treg numbers are often elevated, but their suppressive function is frequently imparied (47, 48), potentially due to a reduction in activated Treg (aTreg) characterized by $CD45RA^{-}Foxp3^{high}$[51]. This impairment may also relate to increased expression of the Foxp3Δ2 isoform, which is associated with reduced suppressive function and a higher proportion of resistant $CD4^{+}$ Teff cells within the patient population (47). A recent discovery demonstrated that co-expression of Foxp3fl and Foxp3Δ2 are essential for optimal Treg suppressive capacity (49).

Autoimmune regulator (Aire) is a transcription factor found in lymphoid organs, particularly in medullary thymic epithelial cells (mTECs) of the thymus, where it plays an inevitable role in immune regulation and the establishment of central tolerance. Aire enables mTECs to express a broad array of tissue-specific antigens, facilitating the presentation of self-peptides on major histocompatibility complex (pMHC) molecules to developing T cells. This process ensures that T cells with high affinity TCRs for self-antigens are either deleted or diverted to differentiate into Treg, resulting in a Treg population with a diverse and high affinity T-cell receptor (TCR) repertoire. The importance of Aire is further highlighted through an experimental anti-MPO murine model where Aire deficient mice exhibit more severe disease phenotype due to the escape of autoreactive anti-MPO T cells (50).

Tregs naturally develop in the thymus (nTreg), but they can also be peripherally induced (pTreg) from naïve T cells. While pTreg can be induced transiently in the presence of anti-inflammatory cytokines such as TGFβ and IL-10, they may revert to Teff cells under proinflammatory conditions. TGFβ is crucial for pTreg induction, as it phosphorylates the Smad transcription factors, Smad2 and Smad3, which interact with conserved non-coding sequence (CNS) 1 region in the Foxp3 gene locus, driving Foxp3 expression and thus Treg differentiation. Stable Treg identity is maintained through epigenetic mechanisms. In nTreg, the CpG island in the CNS2 region of the Foxp3 gene which is known as the Treg-specific demethylated region (TSDR) remains hypomethylated, supporting sustained Foxp3 expression and Treg lineage stability even in inflammatory environments. which constitutes towards the promoter (51). The TSDR methylation status distinguishes nTreg from pTreg and is crucial for long-term suppressive function, as TSDR demethylation enables the binding of key transcription factors and preserves cell memory. TSDR comprises of a few functionally crucial genes for Treg differentiation and function, including Foxp3, Ctla4, Il2ra, Ikzf4 and Tnfrs18 (51). On top of the suggested phenotype, CD127 is found to be inversely correlated with $Foxp3^{+}$ cells, and the isolated Treg population is highly purified if included with this marker (52). Therefore, the current best phenotype of Treg is $CD4^{+}CD25^{high}CD127^{low}Foxp3^{+}$[55].

Previous pioneer work revealed how Treg functions although its exact working mechanism is still unknown. A primary mode of suppression is the secretion of inhibitory cytokines IL-10, IL-35 and TGFβ, which collectively act to inhibit the activity of effector immune cells (32, 53). IL-35 is a heterodimer formed through the pairing of Epstein-Barr virus-induced gene 3 (Ebi3) and interleukin-12 alpha (Il12a), which is proficient in suppressing T cell proliferation (53, 54). Treg also mediate cytotoxicity through the production of granzymes A and B, which are involved in the direct killing of target cells. The high expression of CD25 on Treg enable them to mop up IL-2, a cytokine essential for T cells survival, thereby depriving Teffs of this growth factor, although IL-2 depletion alone does not fully account for Treg-mediated suppression (53). Another key mechanism involves the generation of pericellular adenosine via the CD73/CD39 ectonucleotidase pathway on Treg (55). This adenosine acts on the adenosine 2A (A2A) receptor on activated T cells, potently inhibiting their activity. Activation of A2A receptor also supresses IL-6 production by Teff while promoting TGFβ generation (56), further shifting the immune response towards regulation rather than inflammation. Furthermore, Tregs interact with dendritic cells (DC) via lymphocyte activation gene (LAG) 3 and cytotoxic T lymphocyte-associated Ag (CTLA)-4 (32, 53). These interactions promote the development of tolerogenic DC, which can produce immunoregulatory enzymes like indoleamine 2, 3-dioxygenase (IDO) that suppresses T cell responses. Odobasic et al. have demonstrated the importance of these tolerogenic DCs in an experimental murine anti-MPO GN model (57).

Current animal model

Animal models are essential for studying diseases like MPO-AAV because they allow researchers to identify therapeutic targets and evaluate potential treatments *in vivo*. However, most current MPO-AAV models primarily replicate the acute phase of disease rather than full remission, highlighting the need for improved models that better capture the complexity of human disease. To summarize, there are currently 4 ways to induce MPO-AAV in mice (refer to Figure 2).

Passive transfer of IgG, splenocytes, MPO-specific T cells into mice

The foundational anti-MPO GN mouse model was developed by Xiao et al. and has been instrumental in understanding MPO-

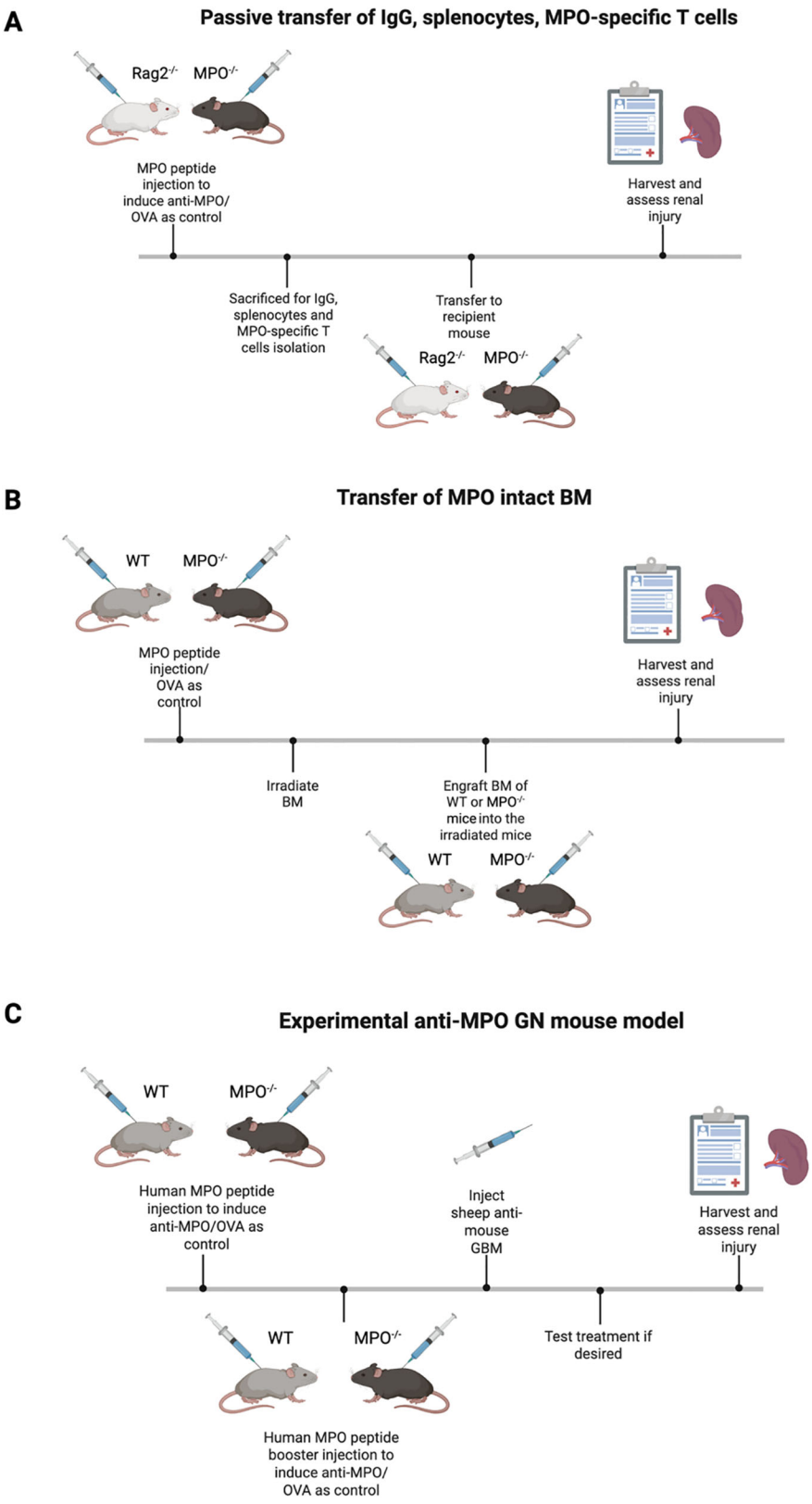


FIGURE 2
An overview of the current most used mouse models. **(A)** Passive transfer mouse model that showed MPO-ANCA initiates the hallmark of renal injury. **(B)** BM engraftment model further digs into the role of adaptive immune system where MPO-specific T cells enhance renal injury. **(C)** Experimental anti-MPO GN model allows the investigation of MPO-AAV pathogenesis and testing new therapies. *Diagrams created with Biorender.com*.

AAV pathogenesis (58, 59). In this model, MPO knockout ($MPO^{-/-}$) and recombinase-activating gene-2-deficient ($Rag2^{-/-}$) mice, where the $Rag2^{-/-}$ mice lack both T and B cells are first immunized with MPO to induce anti-MPO immune responses. IgG is then isolated from these immunized mice and injected into wildtype (WT) or $Rag2^{-/-}$ mice. This transfer reliably induces focal necrotizing GN, providing direct evidence that anti-MPO IgG alone can cause renal injury. Disease severity increases when splenocytes of the MPO-immunized $MPO^{-/-}$ mice are transferred into WT and $Rag2^{-/-}$ mice (58). These recipient mice develop severe NCGN, with marked elevation of BUN and serum creatinine, indicating significant kidney dysfunction. The disease can be further exacerbated by introducing proinflammatory stimuli such as LPS, resulting in even more severe pathology. Despite the utility of this model in establishing the pathogenicity of anti-MPO antibodies and immune cell, they have limitations. Notably, glomerular immune complex deposition is commonly observed, which differs from the pauci-immune pattern in human cases of MPO-AAV. Therefore, while these models are invaluable for dissecting disease mechanisms and testing therapies, further refinement is necessary to more accurately reflect human disease.

Transfer of MPO intact bone marrow

Another strategy involves first immunizing $MPO^{-/-}$ and WT mice with MPO, followed by irradiation (59, 60). Bone marrow from naïve WT or $MPO^{-/-}$ mice is then transplanted into these immunized recipients to repopulate their immune cells. Only mice receiving WT bone marrow but not those receiving $MPO^{-/-}$ bone marrow develop NCGN after transfer. This finding underscores the necessity of MPO+ neutrophils in peripheral blood of recipient mice for disease development post engraftment. These results suggest that immune cells, particularly neutrophils are the pathogenic targets for anti-MPO IgG (60).

Active immunization of MPO inducing experimental GN

The experimental anti-MPO GN murine model is particularly valuable as it enables the study of loss of tolerance and the development of active autoimmunity. This model also facilitates the identification of potential therapeutic targets by allowing reestablishment of immune tolerance, which is not possible in the passive transfer model. In this approach, WT and $MPO^{-/-}$ mice are sensitized with human MPO to induce anti-MPO antibodies (59, 61). These mice are then injected with sheep anti-mouse glomerular basement membrane (GBM) ten days later to activate neutrophils and deposit MPO in the glomeruli, thereby inducing experimental MPO-ANCA. The use of a minimal dose of sheep anti-mouse GBM is important as it triggers neutrophils influx into the glomeruli without causing significant anti-GBM disease, which would confound the results. Importantly, only MPO-sensitized mice develop diseases, confirming the requirement for both anti-MPO immunity and MPO deposition in disease pathogenesis. Ovalbumin (OVA) was also included as control as an irrelevant antigen confirm the specificity of the model (61). This model advances our knowledge in characterizing the role of $CD4^+$ and $CD8^+$ T cells as well as B cells in disease pathogenesis.

Although the above-mentioned animal models are well-established for the study of MPO-AAV, exploring options beyond them is necessary to facilitate with the understanding of later phase of disease. Humanized mouse model and organoids are promising next steps for the advancement of preclinical models (62, 63). Harnessing immunodeficient mice to allow engraftment of human cells creates a 3D environment for the study of cells and tissues interactions, however, it is usually expensive and is met with the common limitations of cross-species difference. On the other hand, the cost-effective organoids-based approaches is attractive as it aligns with the reduction usage of animals but retaining the capability for inter-species translation. Kidney is a complex organ and the development of 3D organoids is still on-going with efforts being put into mimicking the kidney environment with reproducible conditions (64). Nevertheless, more research is still required for the development of appropriate preclinical models to assist with the study of chronic disease pathogenesis and treatment targets.

Treatment

Current therapy

Treatment for AAV is segregated into two phases, that are induction of remission and maintenance therapy. The current standard treatment for severe AAV is the combination of glucocorticoids; either prednisone with cyclophosphamide (CYC) or with rituximab (RTX) (65, 66). Oral CYC is associated with greater toxicity due to prolonged drug exposure, thus pulse intravenous (i.v.) CYC is preferred, despite a higher relapse risk. This preference is supported by evidence showing that patients receiving i.v. CYC experience less renal impairment and fewer cases of leucopaenia (67, 68). CYC toxicity arises from its broad immunosuppressive effects, often lead to opportunistic infections such as *Pneumocystis jiroveci* pneumonia, haemorrhagic cystitis, malignancy, and gonadal failure resulting in infertility (68). Meanwhile, RTX is an anti-CD20 monoclonal antibody drug that depletes B cells, thereby preventing ANCA production. RTX is preferred if CYC overdose is a concern, or in patients prone to relapse. Additionally, RTX had been shown to enhance Treg immunomodulatory capacity by inducing B cell apoptosis, though B cell depletion can result in hypogammaglobulinaemia that leads to immune suppression (69).

To minimize cumulative CYC exposure, alternate therapies such as methotrexate (MTX) are considered in early disease, although longer treatment is required and relapse rates are higher compared to CYC (70, 71). Maintenance therapy may involve MTX

or azathioprine (AZA), both of which are noninferior to CYC and associated with lesser adverse events (66, 72). Leflunomide and mycophenolate mofetil (MMF) are less commonly used as leflunomide is associated with higher frequency of adverse events (73, 74), whereas in the case of MMF, showed lower efficacy than AZA except in MPO-AAV patients experience less severe renal disease (75, 76).

Given the toxicity of long-term immunosuppressive therapy, biologic agents are being explored. TNFα blocker like etanercept is tested in GPA patients though not proven to be effective in MPO-AAV patients (66, 77). On the contrary, plasma exchange is considered adjunctive for severe cases with pulmonary and renal involvement (78, 79), though recent study shows no superiority over standard treatment (80). Long-term outcome on these patients, however, have shown promising results as they require lower steroid dosage for maintenance therapy, reducing toxicity. Avacopan (CCX168), a C5a inhibitor, has shown promise in replacing glucocorticoids for maintenance therapy (81, 82), potentially reducing morbidity and mortality in AAV patients (83). Patients are spared from higher dose of steroids and safer for renal recovery. Low dose IL-2 is another emerging option, selectively stimulating Treg cells to modulate immune response (84). A recent study employing spatial transcriptomics and digital pharmacology had identified ustekinumab, a human monoclonal antibody which target IL-12 and IL-23 to be effective in disease remission (85). It potently inhibits the dominated Th1/Tc1 and Th17/Tc17 cells in inflamed kidneys as seen in patients, suggesting the use of personalized therapy through combination of current available drug with rapid immune profiling.

TABLE 1 Summary of current available therapy associated with their clinical trials studies.

Biologics	Disease phase	Clinical trial no.	Clinical trial phase
Oral vs IV CYC	Induction of remission	NCT01697267	RITUXVAS
Pulse vs continuous CYC	Induction of remission	NCT00430105	CYCLOPS
MMF vs CYC	Induction of remission	NCT00301652	MYCYC
MMF	Induction of remission for relapse	NCT00103792	Phase 3
Rituximab	Induction of remission	NCT00104299	RAVE Phase 2 Phase 3
Plasma exchange	Induction of remission	NCT00987389	PEXIVAS Phase 3
CCX168	Induction of remission	NCT02994927	ADVOCATE Phase 3
Belimumab	Maintenance	NCT01663623	BREVAS Phase 3
Rituximab	Maintenance	NCT02433522	MAINRITSAN Phase 1-3

Future therapy

While current standard treatment is well-defined with mature clinical trials results supporting in place (Table 1), retaining kidney function is the top priority and with several events of relapse, patients eventually develop end-stage renal failure. Therefore, exploring alternative therapeutic options is important, and recent success in emerging cell-based therapies that offer personalized treatment with fewer side effects through direct target of disease mechanism.

Adoptive cell transfer

Previous attempts on harnessing the potent immunosuppressive capacity of Treg have led to various studies evaluating their efficacy in treating autoimmune diseases and preventing graft rejection. *Ex vivo* expanded polyclonal Treg have been tested in multiple clinical settings and have shown promise in inducing immune tolerance. This process involves isolating Tregs from patients' peripheral blood mononuclear cells (PBMCs), expanding them *in vitro*, and then reinfusing them into the patients.

Multiple studies have demonstrated that adoptive transfer of Tregs attenuates symptoms of immune-mediated conditions, such as asthma (86), graft versus host disease (GvHD) (87) and several autoimmune diseases including type 1 diabetes (T1D) (88), multiple sclerosis (MS) (89) and autoimmune hepatitis (AIH) (90). For example, a phase 1 clinical trial evaluated the polyclonal Treg therapy in paediatric T1D patients, with results indicating therapeutic effectiveness following the infusion of two doses of polyclonal Tregs (91). However, similar benefit was not observed in adult trials, where no significant efficacy was detected (88). This discrepancy may be due to differences in immune system maturity between children and adults, leading to varied responses to therapy.

Another possible explanation is that polyclonal Treg may function differently in inducing peripheral immune tolerance. One study suggested that polyclonal Treg might inhibit the migration of Teff cells to specific tissue sites, whereas antigen-specific iTreg can act directly at the target site, potentially providing more precise immune regulation (92). This distinction highlights the potential advantages of using antigen-specific Tregs, especially since autoimmune diseases are often diagnosed only after tissue damage has occurred. In such cases, Teff cells may already have infiltrated the target site, making site-specific intervention by engineered Tregs a more effective therapeutic approach.

CAR-T cell therapy

Chimeric antigen receptor (CAR)-T cell therapy is an FDA-approved treatment that specifically targets CD19, a B cell antigen, and has demonstrated significant efficacy in the management of B cell leukaemias and lymphomas (93, 94). However, the application of CAR-T cell therapy to solid tumours has met with limited success, primarily due to the unique challenges posed by the tumour microenvironment and tumour biology (95, 96).

The engineering of CAR-T cells involves the introduction of a synthetic receptor, the chimeric antigen receptor, which is composed of several key domains. The extracellular portion

consists of a single-chain variable fragment (scFv), derived from the variable region of antibody heavy and light chains (refer to Figure 3), which confers antigen specificity (97, 98). A flexible spacer region links the scFv to a transmembrane domain, allowing for optimal antigen binding. The transmembrane domain anchors the receptor within the T cell membrane and connects to intracellular signalling domains. The first-generation CARs utilized only the CD3ζ signalling domain, resulting in weak T cell activation and limited therapeutic persistence. Subsequent generations incorporated additional costimulatory molecules, such as CD28 or 4-1BB (CD137), which markedly enhance CAR-T cell activation, persistence, and overall therapeutic efficacy.

Despite these advances, several barriers hinder the effectiveness of CAR-T cell therapy in solid tumours. A major challenge is the limited infiltration of CAR-T cells into the tumour site, which is influenced by the tumour's structural complexity and the surrounding extracellular matrix. Additionally, the tumour microenvironment is often immunosuppressive, characterized by low oxygen levels, high acidity, and nutrient scarcity, all of which impair CAR-T cell function and survival. Tumour heterogeneity, whereby cancer cells exhibit diverse antigen expression profiles, further complicates the targeting of all malignant cells by CAR-T therapy.

The success of CAR-T cell therapy in haematologic malignancies has spurred interest in extending its application to other disease areas (98). For example, preclinical and early clinical studies are exploring the use of CAR-T cells for the treatment of autoimmune diseases, such as systemic lupus erythematosus (SLE) (NCT03030976) and carcinoembryonic antigen (CEA)-specific CAR-Treg to treat ulcerative colitis (UC) (99). Additionally, CAR-T cell approaches are being investigated to induce immune tolerance in patients with haemophilia A, with the aim of enabling sustained recombinant Factor VIII therapy without the risk of inhibitor formation. Other autoimmune diseases including myelin-oligodendrocyte glycoprotein (MOG)-specific CAR-Treg to treat MS (100) and Dsg-3 chimeric autoantibody receptor (CAAR)-T to treat pemphigus vulgaris (PV) (101). This review will only cover the aspects of autoimmune diseases for the sake of comparison between treatments in MPO-AAV. CAR-Treg is easier to produce and convenient to use as it is independent of MHC antigen recognition, hence it does not select patient population for a specific HLA to use (Table 2).

TCR-Treg therapy

Since the manifestation of MPO-AAV also involves the autoantigen recognition of immune cells presenting processed MPO on MHC II (refer to Figure 3), TCR-Treg is suited to use to target these autoreactive cells. The approach involves directing Treg to recognize MHC II-bound MPO, which can be achieved through gene transfer of T cell receptor (TCR) specific to the epitope of interest.

Although further studies are required to confirm the efficacy of TCR-Treg, several *in vitro* studies provide foundational insights. T1D, a highly prevalent autoimmune disease, serves as a notable reference point for such research. An *in vitro* study on T1D had employed TCR-Treg specific for islet antigen 2 (IA2) and insulin, with influenza-specific TCR-Tregs included as controls to assess specificty (102). The suppressive potency of these TCR-Tregs was evaluated by co-culturing them with either wild-type or antigen-presenting cells loaded with their respective peptides. Results demonstrated that the generated TCR-Tregs are highly immunosuppressive in the presence, but not absence of their cognate peptides (102). Conversely, patients with Haemophilia A require constant intake of recombinant FVIII (rFVIII) as they lack the critical coagulation factor FVIII, however, rFVIII is not native to patients' immune systems, thus causing gradual destruction of rFVIII (103, 104). To address this, studies have introduced FVIII-specific TCR-Treg into patients, showing successful suppression of immune responses against FVIII-specific Teff cells (103). Additionally, another study had explored the use of myelin-basic protein (MBP)-specific TCR-Treg to investigate the efficacy in treating MS (105). Despite the need for further validation, these findings collectively highlight the therapeutic potential of antigen-specific TCR-Treg in a range of autoimmune conditions.

Previous studies have successfully determined the immunodominant epitope of MPO that triggers autoimmune activation, with disease severity and prevalence are HLA-linked. The importance of HLA-DRB1*04:05 and HLA-DQA1*03:02, DQB1*03:03 in Chinese patients whereas HLA-DRB1*09:01 in Japanese patients were well elucidated. This attracts molecular studies to be performed on these disease-linked HLAs, which could possibly open the doors to enhance the development of better cell-based therapy. HLA-DRB1*04:05 is the most severe related HLA class II molecule found in patients that usually progress into ESRF within six months even with existing treatment. Thus, initiating the alternative cell-based therapy with HLA-DRB1*04:05 would be a major step towards the development of next-generation personalized therapy (Table 2).

TABLE 2 Comparison between the cell-based therapies.

Cell-based therapy	Advantages	Disadvantages
CAR-Treg	• Not HLA specific, can be used for any population with the specified disease • Bispecific targets of CAR-T cells was developed and proved to be potent	• Requires higher antigenic dose for T cell activation • CAR molecule is not endogenous to human, might trigger immunity against CAR, destroying the cells. • Cells are less stable; longevity of cells is a problem
TCR-Treg	• Requires only small antigenic dose to activate the T cells • TCR is endogenous to human, unlikely to trigger immunity against the cells • TCR-T cells are more stable	• HLA and antigen specific

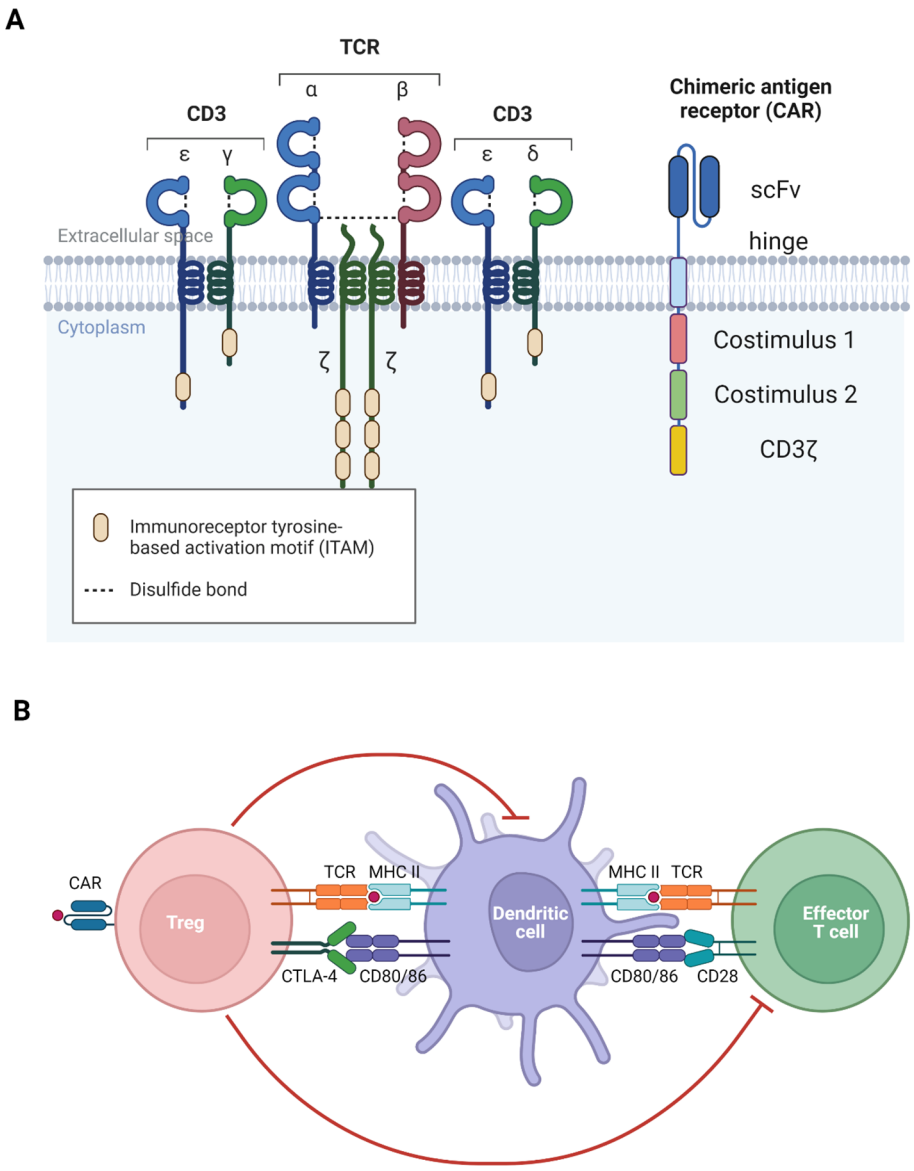


FIGURE 3
Visualization of TCR and CAR. **(A)** The main difference between TCR and CAR is that TCR recognizes MHC-bound peptide but CAR recognizes free antigen. **(B)** Both TCR and CAR function to activate the generated antigen-specific Treg to recognize self-antigen to induce immune tolerance. *Diagrams created with Biorender.com.*

Challenges in TCR-Treg production

Cell-based therapy represents a promising frontier in individualized immunotherapy, yet the high production cost remains a significant barrier to widespread clinical adoption. The process is resource-intensive, requiring the collection of blood, isolation of Treg, transduction and expansion of these cells, and ultimately their infusion into patients. To address scalability and cost, one proposed solution is the use of platforms such as Lonza, which can be adopted by laboratories that mimic clean room environments, thereby commercializing production while maintaining the Good Manufacturing Practice (GMP) standards. A major safety concern in TCR-Treg therapy is the potential for the introduced transgenic TCR to mispair with the endogenous TCR, leading to the formation of hybrid receptors that may trigger harmful autoimmune responses. To mitigate this risk, clustered regularly interspaced short palindromic repeats (CRISPR)-based knockout of the endogenous TCR prior to gene transfer has been explored. Studies have shown that this approach enhances the expression of the transduced TCR, resulting in improved function of engineered T cells (106). By also knocking out endogenous HLA presenting on the Tregs, the product could be possibly made off-shelf, significantly improving the feasibility of the therapy. Although autologous T cell therapy is more favourable due to unlikely event of graft-versus-host disease (GvHD) in patients, it is less available to rural area and is often required to be operated at a more centred venue for product production, storage and delivery. This makes off-shelf product to be more convenient as it does not

require patients' cells and with proper management, they can be delivered to more rural areas for infusion. Knocking in the TCR of interest using the same method can therefore create super-Tregs. These super-Tregs can be further produced through induction from peripheral T cells to iTreg; and through CRISPR-based demethylation of the TSDR region of T cells (107, 108), can create a more stable Treg phenotype, overcoming the limit on the Tregs number since they occur in small amount naturally. The pipeline for Treg cell therapy production includes isolation, expansion, storage, transport, infusion into the patients. The toughest part is the scalability and cost as the naturally existing Tregs occur in small numbers in human body. But with the above-mentioned gene editing method, $CD4^+$ T cells can be isolated in larger numbers and expanded. The study of Tregs stability is crucial as Tregs can still convert to Teffs under pro-inflammatory environment, hence, *in vivo* humanized model is required for not only to study the functionality of the engineered Tregs, but also to determine their longevity and stability.

There are several current Treg manufacturing protocols, and no method is proven to be superior to one another. A standardized protocol is yet to be developed as little is known about how the different manufacturing options can cause different patients' outcome, though they are not supposed to differ significantly to each other. Briefly, the enriched Treg population can be expanded in presence of rapamycin to maintain Treg phenotype and prevent Teff expansion. Other methods including bead-based enrichment and flow cytometry-based selection to expand then isolate is considered as well. A recent GMP certified protocol approved by the Spanish authority can be considered as well (109), and using this as a foundation to further modify the product can help with the establishment of Treg product. As the study only used natural Treg as the source for amplification and subsequent product development, the iTreg product is yet to be investigated.

There are several challenges regarding cell-based therapies, especially the optimal treatment regimen for patients. Given the nature of complexity of autoimmune diseases, current landscape involves infusing the engineered Tregs into patients for induction of remission. However, the longevity of these infused cells remains unknown, as a recent CAR-T study in an autoimmune disease, idiopathic inflammatory myositis indicate patients may relapse within a year (110). It is still unknown whether the cell-based therapies can be given for maintenance therapy. Options for therapy include one-time induction until disease recurrence or utilizing a higher initial dose followed by lower, regular doses for maintenance. Patient outcomes are still measured using standards like the BVAS score, which provides clear criteria for diagnosis and disease activity. A key advance would be the elimination of steroids as part of therapy, greatly improving quality of life and disease manageability. Autoimmune diseases are challenging and long-term, therefore, robust and comprehensive studies including long-term clinical trials spanning 5–10 years are necessary to fully understand patient outcomes and refine future treatment strategies.

Future directions

MPO-AAV with HLA-DRB1*04:05 garners particular interest because, despite its rarity, it is associated with the poorest 5-year survival among MPO-AAV. Cell-based therapies using engineered Treg are attractive for MPO-AAV as they may circumvent the broad immunosuppression and associated side effects observed with conventional treatments such as CYC or RTX combined with glucocorticoids. Two main strategies are under investigation, which are CAR-Treg and TCR-Treg therapies. Of these, TCR-Treg which recognize antigen-MHC complexes, may offer superior efficacy in MPO-AAV due to their MHC-dependence in ensuring the specificity of the developed therapy to minimize possible side effects. Although clinical trials using CAR-Treg and TCR-Treg therapies in MPO-AAV have not yet commenced, both *in vitro* and *in vivo* studies in other autoimmune diseases support their feasibility and therapeutic potential. This is further underscored by promising results in related models, such as MOG-specific CAR-Treg and MBP-specific TCR-Treg for MS as well as the FVIII-specific CAR-Treg and FVIII-specific TCR-Treg to tolerate rFVIII in Haemophilia A patients. In summary, while TCR-Treg therapy holds great promise for the treatment in refractory autoimmune diseases, its clinical translation will require overcoming challenges related to manufacturing scalability, cost, and safety. Advances in gene editing technologies and optimized manufacturing protocols are critical next steps for bridging these therapies into routine clinical practice.

This also allows exploration of other similar diseases of vasculitis in the broader terms for the application of the Treg-based therapy. Since other vasculitis involving big and medium vessels like giant cell arthritis involves a more systemic disease rather than organ-specific, a potent alternate therapy to the corticosteroid's regimen is required for the patients' quality of lives and prognosis (111). The involvement of adaptive immune system points to the vital role of Tregs to be developed as a possible next-generation personalized therapy.

Literature searches and article selection

Clinicaltrials.gov (Pubmed) was used for clinical trial searches on current treatment in ANCA-AAV using the keyword ANCA associated vasculitis. The search was further filtered to include only interventional, completed and active, but not recruiting participant studies. 73 studies were filtered out and only studies covering MPA were selected. The Google search engine was used to select top 30 articles with keywords including pathogenesis of MPO-AAV, Treg function, therapy for MPO-AAV in separate occasions. Related references within the selected articles were further studied and included as part of review writing.

Author contributions

ET: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization. YT: Supervision, Writing – review & editing, Conceptualization, Data curation, Project administration. PG: Conceptualization, Supervision, Writing – review & editing, Data curation, Methodology. JO: Conceptualization, Funding acquisition, Supervision, Writing – review & editing, Data curation, Methodology, Project administration, Resources.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

References

1. Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. *Nat Rev Rheumatol*. (2014) 10:463–73. doi: 10.1038/nrrheum.2014.103

2. Jennette JC, Falk RJ, Gasim AH. Pathogenesis of ANCA vasculitis. *Curr Opin Nephrol Hyperten*. (2011) 20:263–70. doi: 10.1097/MNH.0b013e3283456731

3. Jennette JC, Xiao H, Falk RJ. Pathogenesis of vascular inflammation by anti-neutrophil cytoplasmic antibodies. *J Am Soc Nephrol*. (2006) 17:1235–42. doi: 10.1681/ASN.2005101048

4. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Arthritis Rheum*. (2013) 65:1–11. doi: 10.1002/art.37715

5. Futamata E, Masuda S, Nishibata Y, Tanaka S, Tomaru U, Ishizu A. Vanishing immunoglobulins: the formation of pauci-immune lesions in myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis. *Nephron*. (2018) 138:328–30. doi: 10.1159/000485902

6. Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis. *Nat Rev Dis Primers*. (2020) 6:71. doi: 10.1038/s41572-020-0204-y

7. Roth AJ, Ooi JD, Hess JJ, van Timmeren MM, Berg EA, Poulton CE, et al. Epitope specificity determines pathogenicity and detectability in ANCA-associated vasculitis. *J Clin Invest*. (2013) 123:1773–83. doi: 10.1172/JCI65292

8. Ooi JD, Chang J, Hickey MJ, Borza DB, Fugger L, Holdsworth SR, et al. The immunodominant myeloperoxidase T-cell epitope induces local cell-mediated injury in antimyeloperoxidase glomerulonephritis. *Proc Natl Acad Sci United States America*. (2012) 109:E2615–2624. doi: 10.1073/pnas.1210147109

9. Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DRW, et al. Genetically distinct subsets within ANCA-Associated vasculitis. *New Engl J Med*. (2012) 367:214–23. doi: 10.1056/NEJMoa1108735

10. Hiwa R, Ohmura K, Arase N, Jin H, Hirayasu K, Kohyama M, et al. Myeloperoxidase/HLA class II complexes recognized by autoantibodies in microscopic polyangiitis. *Arthritis Rheumatol*. (2017) 69:2069–80. doi: 10.1002/art.40170

11. Chang DY, Luo H, Zhou XJ, Chen M, Zhao MH. Association of HLA genes with clinical outcomes of ANCA-associated vasculitis. *Clin J Am Soc Nephrol*. (2012) 7:1293–9. doi: 10.2215/CJN.13071211

12. Wang HY, Cui Z, Pei ZY, Fang SB, Chen SF, Zhu L, et al. Risk HLA class II alleles and amino acid residues in myeloperoxidase-ANCA-associated vasculitis. *Kidney Int*. (2019) 96:1010–9. doi: 10.1016/j.kint.2019.06.015

13. Pendergraft WF 3rd, Preston GA, Shah RR, Tropsha A, Carter CW Jr, Jennette JC, et al. Autoimmunity is triggered by cPR-3(105-201), a protein complementary to human autoantigen proteinase-3. *Nat Med*. (2004) 10:72–9. doi: 10.1038/nm968

14. Ooi JD, Jiang JH, Eggenhuizen PJ, Chua LL, van Timmeren M, Loh KL, et al. A plasmid-encoded peptide from Staphylococcus aureus induces anti-myeloperoxidase nephritogenic autoimmunity. *Nat Commun*. (2019) 10:3392. doi: 10.1038/s41467-019-11255-0

15. Hogan SL, Cooper GS, Savitz DA, Nylander-French LA, Parks CG, Chin H, et al. Association of silica exposure with anti-neutrophil cytoplasmic autoantibody small-vessel vasculitis: a population-based, case-control study. *Clin J Am Soc Nephrol*. (2007) 2:290–9. doi: 10.2215/CJN.03501006

16. Bruner BF, Vista ES, Wynn DM, James JA. Epitope specificity of myeloperoxidase antibodies: identification of candidate human immunodominant epitopes. *Clin Exp Immunol*. (2011) 164:330–6. doi: 10.1111/j.1365-2249.2011.04372.x

17. Free ME, Stember KG, Hess JJ, McInnis EA, Lardinois O, Hogan SL, et al. Restricted myeloperoxidase epitopes drive the adaptive immune response in MPO-ANCA vasculitis. *J Autoimmun*. (2020) 106:102306. doi: 10.1016/j.jaut.2019.102306

18. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *QJM Int J Med*. (1994) 87:671–8. doi: 10.1093/qjmed/87.11.671

19. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the birmingham vasculitis activity score (version 3). *Ann Rheum Dis*. (2009) 68:1827–32. doi: 10.1136/ard.2008.101279

20. Suppiah R, Mukhtyar C, Flossmann O, Alberici F, Baslund B, Batra R, et al. A cross-sectional study of the Birmingham Vasculitis Activity Score version 3 in systemic vasculitis. *Rheumatology*. (2011) 50:899–905. doi: 10.1093/rheumatology/keq400

21. Kronbichler A, et al. . doi: 10.3390/ijms21197319

22. Nakazawa D, Masuda S, Tomaru U, Ishizu A. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. *Nat Rev Rheumatol*. (2019) 15:91–101. doi: 10.1038/s41584-018-0145-y

23. Gan PY, Fujita T, Ooi JD, Alikhan MA, Dick J, Shim R, et al. Pathogenic role for γδ T Cells in autoimmune anti-myeloperoxidase glomerulonephritis. *J Immunol*. (2017) 199:3042–50. doi: 10.4049/jimmunol.1602025

24. Yuan J, Gou SJ, Huang J, Hao J, Chen M, Zhao MH. C5a and its receptors in human anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Arthritis Res Ther*. (2012) 14:R140. doi: 10.1186/ar3873

25. Schreiber A, Xiao H, Jennette JC, Schneider W, Luft FC, Kettritz R. C5a receptor mediates neutrophil activation and ANCA-induced glomerulonephritis. *J Am Soc Nephrol*. (2009) 20:289–98. doi: 10.1681/ASN.2008050497

26. Dick J, Gan PY, Ford SL, Odobasic D, Alikhan MA, Loosen SH, et al. C5a receptor 1 promotes autoimmunity, neutrophil dysfunction and injury in experimental anti-myeloperoxidase glomerulonephritis. *Kidney Int*. (2018) 93:615–25. doi: 10.1016/j.kint.2017.09.018

27. Ooi JD, Gan PY, Chen T, Eggenhuizen PJ, Chang J, Alikhan MA, et al. FcγRIIB regulates T-cell autoreactivity, ANCA production, and neutrophil activation to suppress anti-myeloperoxidase glomerulonephritis. *Kidney Int*. (2014) 86:1140–9. doi: 10.1038/ki.2014.189

28. Scapini P, Bazzoni F, Cassatella MA. Regulation of B-cell-activating factor (BAFF)/B lymphocyte stimulator (BLyS) expression in human neutrophils. *Immunol Lett*. (2008) 116:1–6. doi: 10.1016/j.imlet.2007.11.009

29. Bunch DO, McGregor JG, Khandoobhai NB, Aybar LT, Burkart ME, Hu Y, et al. Decreased CD5(+) B cells in active ANCA vasculitis and relapse after rituximab. *Clin J Am Soc Nephrol*. (2013) 8:382–91. doi: 10.2215/CJN.03950412

30. Dumoitier N, Terrier B, London J, Lofek S, Mouthon L. Implication of B lymphocytes in the pathogenesis of ANCA-associated vasculitides. *Autoimmun Rev*. (2015) 14:996–1004. doi: 10.1016/j.autrev.2015.06.008

31. Aybar LT, McGregor JG, Hogan SL, Hu Y, Mendoza CE, Brant EJ, et al. Reduced CD5(+) CD24(hi) CD38(hi) and interleukin-10(+) regulatory B cells in active anti-neutrophil cytoplasmic autoantibody-associated vasculitis permit increased circulating autoantibodies. *Clin Exp Immunol*. (2015) 180:178–88. doi: 10.1111/cei.12483

32. von Borstel A, Sanders JS, Rutgers A, Stegeman CA, Heeringa P, Abdulahad WH. Cellular immune regulation in the pathogenesis of ANCA-associated vasculitides. *Autoimmun Rev*. (2018) 17:413–21. doi: 10.1016/j.autrev.2017.12.002

33. Gan PY, Holdsworth SR, Kitching AR, Ooi JD. Myeloperoxidase (MPO)-specific CD4+ T cells contribute to MPO-antineutrophil cytoplasmic antibody (ANCA) associated glomerulonephritis. *Cell Immunol*. (2013) 282:21–7. doi: 10.1016/j.cellimm.2013.04.007

34. Kitching AR, Turner AL, Wilson GR, Semple T, Odobasic D, Timoshanko JR, et al. IL-12p40 and IL-18 in crescentic glomerulonephritis: IL-12p40 is the key Th1-defining cytokine chain, whereas IL-18 promotes local inflammation and leukocyte recruitment. *J Am Soc Nephrol*. (2005) 16:2023–33. doi: 10.1681/ASN.2004121075

35. Nicholson LB, Kuchroo VK. Manipulation of the Th1/Th2 balance in autoimmune disease. *Curr Opin Immunol*. (1996) 8:837–42. doi: 10.1016/s0952-7915(96)80013-6

36. Steinmetz OM, Summers SA, Gan PY, Semple T, Holdsworth SR, Kitching AR. The Th17-defining transcription factor RORgammat promotes glomerulonephritis. *J Am Soc Nephrol*. (2011) 22:472–83. doi: 10.1681/ASN.2010040435

37. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature*. (2006) 441:235–8. doi: 10.1038/nature04753

38. Nogueira E, Hamour S, Sawant D, Henderson S, Mansfield N, Chavele KM, et al. Serum IL-17 and IL-23 levels and autoantigen-specific Th17 cells are elevated in patients with ANCA-associated vasculitis. *Nephrol Dial Transplant*. (2010) 25:2209–17. doi: 10.1093/ndt/gfp783

39. Gan PY, Steinmetz OM, Tan DS, O'Sullivan KM, Ooi JD, Iwakura Y, et al. Th17 cells promote autoimmune anti-myeloperoxidase glomerulonephritis. *J Am Soc Nephrol*. (2010) 21:925–31. doi: 10.1681/ASN.2009070763

40. Chang J, Eggenhuizen P, O'Sullivan KM, Alikhan MA, Holdsworth SR, Ooi JD, et al. CD8+ T Cells effect glomerular injury in experimental anti-myeloperoxidase GN. *J Am Soc Nephrol*. (2017) 28:47–55. doi: 10.1681/ASN.2015121356

41. McKinney EF, Lyons PA, Carr EJ, Hollis JL, Jayne DR, Willcocks LC, et al. A CD8+ T cell transcription signature predicts prognosis in autoimmune disease. *Nat Med*. (2010) 16:586–91. doi: 10.1038/nm.2130

42. Summers SA, Steinmetz OM, Gan PY, Ooi JD, Odobasic D, Kitching AR, et al. Toll-like receptor 2 induces Th17 myeloperoxidase autoimmunity while Toll-like receptor 9 drives Th1 autoimmunity in murine vasculitis. *Arthritis Rheumatol*. (2011) 63:1124–35. doi: 10.1002/art.30208

43. Summers SA, van der Veen BS, O'Sullivan KM, Gan P-Y, Ooi JD, Heeringa P, et al Intrinsic renal cell and leukocyte-derived TLR4 aggravate experimental anti-MPO glomerulonephritis. *Kidney Int*. (2010) 78:1263–74. doi: 10.1038/ki.2010.327

44. Huugen D, Xiao H, van Esch A, Falk RJ, Peutz-Kootstra CJ, Buurman WA, et al. Aggravation of anti-myeloperoxidase antibody-induced glomerulonephritis by bacterial lipopolysaccharide: role of tumour necrosis factor-alpha. *Am J Pathol*. (2005) 167:47–58. doi: 10.1016/s0002-9440(10)62952-5

45. Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J Immunol*. (1995) 155:1151–64. doi: 10.4049/jimmunol.155.3.1151

46. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. *Cell*. (2008) 133:775–87. doi: 10.1016/j.cell.2008.05.009

47. Free ME, Bunch DO, McGregor JA, Jones BE, Berg EA, Hogan SL, et al. ANCA-associated vasculitis patients have defective Treg function exacerbated by presence of a suppression-resistant effector population. *Arthritis Rheum*. (2013) 65:1922–33. doi: 10.1002/art.37959

48. Wang Y, Zhang S, Zhang N, Feng M, Liang Z, Zhao X, et al, et al. Reduced activated regulatory T cells and imbalance of Th17/activated Treg cells marks renal involvement in ANCA-associated vasculitis. *Mol Immunol*. (2020) 118:19–29. doi: 10.1016/j.molimm.2019.11.010

49. Sato Y, Liu J, Lee E, Perriman R, Roncarolo MG, Bacchetta R. Co-expression of FOXP3FL and FOXP3Delta2 isoforms is required for optimal treg-like cell phenotypes and suppressive function. *Front Immunol*. (2021) 12:752394. doi: 10.3389/fimmu.2021.752394

50. Tan DS, Gan PS, O'Sullivan KM, Hammett MV, Summers SA, Ooi JD, et al. Thymic deletion and regulatory T cells prevent antimyeloperoxidase GN. *J Am Soc Nephrol*. (2013) 24:573–85. doi: 10.1681/ASN.2012090898

51. Kanamori M, Nakatsukasa H, Okada M, Lu Q, Yoshimura A. Induced regulatory T cells: their development, stability, and applications. *Trends Immunol*. (2016) 37:803–11. doi: 10.1016/j.it.2016.08.012

52. Liu W, Putnam AL, Xu-Yu Z, Szot GL, Lee MR, Zhu S, et al. CD127 expression inversely correlates with FoxP3 and suppressive function of human CD4+ T reg cells. *J Exp Med*. (2006) 203:1701–11. doi: 10.1084/jem.20060772

53. Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. *Nat Rev Immunol*. (2008) 8:523–32. doi: 10.1038/nri2343

54. Collison LW, Workman CJ, Kuo TT, Boyd K, Wang Y, Vignali KM, et al. The inhibitory cytokine IL-35 contributes to regulatory T-cell function. *Nature*. (2007) 450:566–9. doi: 10.1038/nature06306

55. Deaglio S, Dwyer KM, Gao W, Friedman D, Usheva A, Erat A, et al. Adenosine generation catalysed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. *J Exp Med*. (2007) 204:1257–65. doi: 10.1084/jem.20062512

56. Zarek PE, Huang C-T, Lutz ER, Kowalski J, Horton MR, Linden J, et al. A2A receptor signalling promotes peripheral tolerance by inducing T-cell anergy and the generation of adaptive regulatory T cells. *Blood*. (2008) 111:251–9. doi: 10.1182/blood-2007-03-081646

57. Odobasic D, Oudin V, Ito K, Gan P-Y, Kitching AR, Holdsworth S. Tolerogenic dendritic cells attenuate experimental autoimmune antimyeloperoxidase glomerulonephritis. *J Am Soc Nephrol*. (2019) 30:2140–57. doi: 10.1681/ASN.2019030236

58. Xiao H, Heeringa P, Hu P, Liu Z, Zhao M, Aratani Y, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest*. (2002) 110:955–63. doi: 10.1172/JCI15918

59. Salama AD, Little MA. Animal models of antineutrophil cytoplasm antibody-associated vasculitis. *Curr Opin Rheumatol*. (2012) 24:1–7. doi: 10.1097/BOR.0b013e32834d2d52

60. Schreiber A, Xiao H, Falk RJ, Jennette JC. Bone marrow-derived cells are sufficient and necessary targets to mediate glomerulonephritis and vasculitis induced by anti-myeloperoxidase antibodies. *J Am Soc Nephrol*. (2006) 17:3355–64. doi: 10.1681/ASN.2006070718

61. Ruth AJ, Kitching AR, Kwan RYQ, Odobasic D, Ooi JDK, Timoshanko JR. Anti-neutrophil cytoplasmic antibodies and effector CD4+ cells play nonredundant roles in anti-myeloperoxidase crescentic glomerulonephritis. *J Am Soc Nephrol*. (2006) 17:1940–9. doi: 10.1681/ASN.2006020108

62. Chen J, Liao S, Xiao Z, Pan Q, Wang X, Shen K, et al. The development and improvement of immunodeficient mice and humanized immune system mouse models. *Front Immunol*. (2022) 13:1007579. doi: 10.3389/fimmu.2022.1007579

63. Park G, Rim YA, Sohn Y, Nam Y, Ju JH. Replacing animal testing with stem cell-organoids: advantages and limitations. *Stem Cell Rev Rep*. (2024) 20:1375–86. doi: 10.1007/s12015-024-10723-5

64. Liu Q, Yue L, Deng J, Tan Y, Wu C. Progress and breakthroughs in human kidney organoid research. *Biochem Biophys Rep*. (2024) 39:101736. doi: 10.1016/j.bbrep.2024.101736

65. Byng-Maddick R, Ehrenstein MR. The impact of biological therapy on regulatory T cells in rheumatoid arthritis. *Rheumatology*. (2015) 54:768–75. doi: 10.1093/rheumatology/keu487

66. Lally L, Spiera R. Current therapies for ANCA-associated vasculitis. *Annu Rev Med*. (2015) 66:227–40. doi: 10.1146/annurev-med-011514-023051

67. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med*. (2009) 150:670–80. doi: 10.7326/0003-4819-150-10-200905190-00004

68. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis*. (2012) 71:955–60. doi: 10.1136/annrheumdis-2011-200477

69. Gan PY, Dick J, O'Sullivan KM, Oudin V, Cao Le A, Koo Yuk Cheong D, et al. Anti-CD20 mAb-induced B cell apoptosis generates T cell regulation of experimental myeloperoxidase ANCA-associated vasculitis. *J Am Soc Nephrol*. (2021) 32:1071–83. doi: 10.1681/ASN.2020060834

70. De Groot K, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. (2005) 52:2461–9. doi: 10.1002/art.21142

71. Faurschou M, Westman K, Rasmussen N, de Groot K, Flossmann O, Hoglund P, et al. Brief report: long-term outcome of a randomized clinical trial comparing

methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. (2012) 64:3472–7. doi: 10.1002/art.34547

72. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med*. (2008) 359:2790–803. doi: 10.1056/NEJMoa0802311

73. Bremer JP, Ullrich S, Laudien M, Gross WL, Lamprecht P. Methotrexate plus leflunomide for the treatment of relapsing Wegener's granulomatosis. A retrospective uncontrolled study. *Clin Exp Rheumatol*. (2010) 28:67–71. doi: 10.1002/art.21142

74. Metzler C, Miehle N, Manger K, Iking-Konert C, de Groot K, Hellmich B, et al. Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. *Rheumatol (Oxford)*. (2007) 46:1087–91. doi: 10.1093/rheumatology/kem029

75. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA*. (2010) 304:2381–8. doi: 10.1001/jama.2010.1658

76. Silva F, Specks U, Kalra S, Hogan MC, Leung N, Sethi S, et al. Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement–a prospective, open-label pilot trial. *Clin J Am Soc Nephrol*. (2010) 5:445–53. doi: 10.2215/CJN.06010809

77. Wegener's Granulomatosis Etanercept Trial Research G. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med*. (2005) 352:351–61. doi: 10.1056/NEJMoa041884

78. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol*. (2007) 18:2180–8. doi: 10.1681/ASN.2007010090

79. Walsh M, Catapano F, Szpirt W, Peh CA, Thorlund K, Bruchfeld A, et al. Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis. *Am J Kidney Dis*. (2011) 57:566–74. doi: 10.1053/j.ajkd.2010.10.049

80. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puechal X, Fujimoto S, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med*. (2020) 382:622–31. doi: 10.1056/NEJMoa1803537

81. Jayne DRW, Merkel PA, Schall TJ, Bekker P, Group AS. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. (2021) 384:599–609. doi: 10.1056/NEJMoa2023386

82. Merkel PA, Jayne DR, Wang C, Hillson J, Bekker P. Evaluation of the safety and efficacy of avacopan, a C5a receptor inhibitor, in patients with antineutrophil cytoplasmic antibody-associated vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine: protocol for a randomized, double-blind, active-controlled, phase 3 trial. *JMIR Res Protoc*. (2020) 9:e16664. doi: 10.2196/16664

83. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol*. (2017) 28:2756–67. doi: 10.1681/ASN.2016111179

84. Wu R, Su R, Ding T, Xue H, An J, Jiang L, et al. Low-dose IL-2 restores Treg-mediated immune tolerance in patients with ANCA-associated vasculitis. *Ann Rheum Dis 79*. (2020) 384. doi: 10.1136/annrheumdis-2020-eular.4346

85. Engesser J, Khatri R, Schaub DP, Zhao Y, Paust HJ, Sultana Z, et al. Immune profiling-based targeting of pathogenic T cells with ustekinumab in ANCA-associated glomerulonephritis. *Nat Commun*. (2024) 15:8220. doi: 10.1038/s41467-024-52525-w

86. Xu W, Lan Q, Chen M, Chen H, Zhu N, Zhou X, et al. Adoptive transfer of induced-Treg cells effectively attenuates murine airway allergic inflammation. *PloS One*. (2012) 7: e40314. doi: 10.1371/journal.pone.0040314

87. Chandran S, Tang Q, Sarwal M, Laszik ZG, Putnam AL, Lee K, et al. Polyclonal Regulatory T cell therapy for control of inflammation in kidney transplants. *Am J Transplant*. (2017) 17:2945–54. doi: 10.1111/ajt.14415

88. Bluestone JA, Buckner JH, Fitch M, Gitelman SE, Gupta S, Hellerstein MK, et al. Type 1 diabetes immunotherapy using polyclonal regulatory T cells. *Sci Trans Med*. (2015) 7:315ra189. doi: 10.1126/scitranslmed.aad4134

89. Duffy SS, Keating BA, Moalem-Taylor G. Adoptive transfer of regulatory T Cells as a promising immunotherapy for the treatment of multiple sclerosis. *Front Neurosci*. (2019) 13:1107. doi: 10.3389/fnins.2019.01107

90. Lapierre P, Beland K, Yang R, Alvarez F. Adoptive transfer of ex vivo expanded regulatory T cells in an autoimmune hepatitis murine model restores peripheral tolerance. *Hepatology*. (2013) 57:217–27. doi: 10.1002/hep.26023

91. Marek-Trzonkowska N, Myśliwiec M, Iwaszkiewicz-Grześ D, Gliwiński M, Derkowska I, Żalińska M, et al. Factors affecting long-term efficacy of T regulatory cell-based therapy in type 1 diabetes. *J Transl Med*. (2016) 14:332. doi: 10.1186/s12967-016-1090-7

92. Shevach EM, Thornton AM. tTregs, pTregs, and iTregs: similarities and differences. *Immunol Rev*. (2014) 259:88–102. doi: 10.1111/imr.12160

93. June CH, Sadelain M. Chimeric antigen receptor therapy. *New Engl J Med*. (2018) 379:64–73. doi: 10.1056/NEJMra1706169

94. Park JH, Geyer MB, Brentjens RJ. CD19-targeted CAR T-cell therapeutics for hematologic Malignancies: interpreting clinical outcomes to date. *Blood*. (2016) 127:3312–20. doi: 10.1182/blood-2016-02-629063

95. Zhang H, Ye ZL, Yuan ZG, Luo ZQ, Jin HJ, Qian QJ. New strategies for the treatment of solid tumours with CAR-T cells. *Int J Biol Sci*. (2016) 12:718–29. doi: 10.7150/ijbs.14405

96. Beavis PA, et al. Reprogramming the tumour microenvironment to enhance adoptive cellular therapy. *Semin Immunol*. (2016) 28:64–72. doi: 10.1016/j.smim.2015.11.003

97. Sadeqi Nezhad M, Seifalian A, Bagheri N, Yaghoubi S, Karimi MH, Adbollahpour-Alitappeh M. Chimeric antigen receptor based therapy as a potential approach in autoimmune diseases: how close are we to the treatment? *Front Immunol*. (2020) 11:603237. doi: 10.3389/fimmu.2020.603237

98. Zhang Q, Lu W, Liang CL, Chen Y, Liu H, Qiu F, et al. Chimeric antigen receptor (CAR) Treg: a promising approach to inducing immunological tolerance. *Front Immunol*. (2018) 9:2359. doi: 10.3389/fimmu.2018.02359

99. Blat D, Zigmond E, Alteber Z, Waks T, Eshhar Z. Suppression of murine colitis and its associated cancer by carcinoembryonic antigen-specific regulatory T Cells. *Mol Ther*. (2014) 22:1018–28. doi: 10.1038/mt.2014.41

100. Fransson M, Piras E, Burman J, Nilsson B, Essand M, Lu B, et al. CAR/FoxP3-engineered T regulatory cells target the CNS and suppress EAE upon intranasal delivery. *J Neuroinflamm*. (2012) 9:1–12. doi: 10.1186/1742-2094-9-112

101. Ellebrecht CT, Bhoj VG, Nace A, Choi EJ, Mao X, Cho MJ, et al. Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease. *Science*. (2016) 353:179–84. doi: 10.1126/science.aaf6756

102. Hull CM, Nickolay LE, Estorninho M, Richardson MW, Riley JL, Peakman M, et al. Generation of human islet-specific regulatory T cells by TCR gene transfer. *J Autoimmun*. (2017) 79:63–73. doi: 10.1016/j.jaut.2017.01.001

103. Kim YC, Zhang A-H, Su Y, Rieder SA, Rossi RJ, Ettinger RA, et al. Engineered antigen-specific human regulatory T cells: immunosuppression of FVIII-specific T- and B-cell responses. *Blood*. (2015) 125:1107–15. doi: 10.1182/blood-2014-04-566786

104. Yoon J, Schmidt A, Zhang AH, Konigs C, Kim YC, Scott DW, et al. FVIII-specific human chimeric antigen receptor T-regulatory cells suppress T- and B-cell responses to FVIII. *Blood*. (2017) 129:238–45. doi: 10.1182/blood-2016-07-727834

105. Kim YC, Zhang A-H, Yoon J, Culp WE, Lees JR, Wucherpfennig KW, et al. Engineered MBP-specific human Tregs ameliorate MOG-induced EAE through IL-2-triggered inhibition of effector T cells. *J Autoimmun*. (2018) 92:77–86. doi: 10.1016/j.jaut.2018.05.003

106. Legut M, Dolton G, Mian AA, Ottmann OG, Sewell AK. CRISPR-mediated TCR replacement generates superior anticancer transgenic T cells. *Blood*. (2018) 131:311–22. doi: 10.1182/blood-2017-05-787598

107. Amini L, Greig J, Schmueck-Henneresse M, Volk HD, Bezie S, Reinke P, et al. Super-treg: toward a new era of adoptive treg therapy enabled by genetic modifications. *Front Immunol*. (2020) 11:611638. doi: 10.3389/fimmu.2020.611638

108. Stoops J, Morton T, Powell J, Pace AL, Bluestone JA. Treg cell therapy manufacturability: current state of the art, challenges and new opportunities. *Front Immunol*. (2025) 16:1604483. doi: 10.3389/fimmu.2025.1604483

109. Bernaldo-de-Quirós E, Cózar B, López-Esteban R, Clemente M, Gil-Jaurena JM, Pardo C, et al. A novel GMP protocol to produce high-quality treg cells from the paediatric thymic tissue to be employed as cellular therapy. *Front Immunol*. (2022) 13:893576. doi: 10.3389/fimmu.2022.893576

110. Muller F, Wirsching A, Hagen M, Völkl S, Tur C, Raimondo MG, et al. BCMA CAR T cells in a patient with relapsing idiopathic inflammatory myositis after initial and repeat therapy with CD19 CAR T cells. *Nat Med*. (2025) 31:1793–7. doi: 10.1038/s41591-025-03718-3

111. Solimando AG, Vacca A, Dammacco F. Highlights in clinical medicine-Giant cell arteritis, polymyalgia rheumatica and Takayasu's arteritis: pathogenic links and therapeutic implications. *Clin Exp Med*. (2022) 22:509–18. doi: 10.1007/s10238-021-00770-4

frontiers | Frontiers in Immunology

TYPE Original Research
PUBLISHED 17 November 2025
DOI 10.3389/fimmu.2025.1655917

OPEN ACCESS

EDITED BY
Sebastian Dolff,
University Duisburg-Essen, Germany

REVIEWED BY
Emanuele Bizzi,
Vita-Salute San Raffaele University, Italy
Yannick van Sleen,
University Medical Center Groningen, Netherlands

*CORRESPONDENCE
Alexandre Wagner Silva de Souza
alexandre_wagner@uol.com.br

RECEIVED 28 June 2025
ACCEPTED 27 October 2025
PUBLISHED 17 November 2025

CITATION
Biegelmeyer E, de Freitas Aguiar M, Dias Cardoso Ribeiro P, Machado KLLL, Paiva França Telles CM, Euzébio Ribeiro SL, Sarzi Sartori N, Poubel Vieira de Rezende R, Guedes de Melo AK, Alves Cruz V, Rodrigues de Abreu Vieira RM, Kakehasi AM, Dias Corrêa MC, Azevedo VF, Martins-Filho OA, Matos Melo Campos Peixoto FM, de Oliveira Magalhães V, Gomes Gouveia MdP, Karnopp TE, Lino Baptista K, Santos Melo T, Rêgo J, Rodrigues Vieira AS, Faria Moreira Gomes Tavares AC, Dornelas Paz Carvalho V, Peruhype-Magalhães V, Dias LH, Lima de Lima R, da Silva Gonçalves KR, Rodrigues Querido Fortes N, Marques Veghini D, Amorim JA, Tuão RC, Lallemand Tapia KR, Kayser C, Castro CHdM, Barbosa Beloni Lirio M, Bühring J, Xavier RM, Teixeira-Carvalho A, Angelina de Souza V, Monticielo OA, Ferreira GA, Pinheiro MdM, Torres dos Reis Neto E, Sato EI, Valim V, Pileggi GS and de Souza AWS (2025) Immunogenicity and safety to SARS-Cov-2 vaccination in patients with systemic vasculitis.
Front. Immunol. 16:1655917.
doi: 10.3389/fimmu.2025.1655917

Immunogenicity and safety to SARS-Cov-2 vaccination in patients with systemic vasculitis

Erika Biegelmeyer[1], Mariana de Freitas Aguiar[1], Priscila Dias Cardoso Ribeiro[1], Ketty Lysie Libardi Lira Machado[2], Camila Maria Paiva França Telles[3], Sandra Lúcia Euzébio Ribeiro[3], Natália Sarzi Sartori[4], Rodrigo Poubel Vieira de Rezende[5], Ana Karla Guedes de Melo[6], Vitor Alves Cruz[7], Rejane Maria Rodrigues de Abreu Vieira[8], Adriana Maria Kakehasi[9], Maria Cecília Dias Corrêa[10], Valderilio Feijó Azevedo[11], Olindo Assis Martins-Filho[12], Flávia Maria Matos Melo Campos Peixoto[1], Vanessa de Oliveira Magalhães[1], Maria da Penha Gomes Gouveia[2], Thaís Evelyn Karnopp[4], Katia Lino Baptista[5], Tâmara Santos Melo[6], Jozelia Rêgo[7], Adah Sophia Rodrigues Vieira[8], Anna Carolina Faria Moreira Gomes Tavares[9], Victória Dornelas Paz Carvalho[10], Vanessa Peruhype-Magalhães[12], Laiza Hombre Dias[2], Raquel Lima de Lima[3], Kimberly Rossana da Silva Gonçalves[4], Natália Rodrigues Querido Fortes[5], Débora Marques Veghini[2], Jônatas Almeida Amorim[3], Raiza Casian Tuão[2], Karina Rosemarie Lallemand Tapia[2], Cristiane Kayser[1], Charlles Heldan de Moura Castro[1], Maressa Barbosa Beloni Lirio[2], Juliana Bühring[3], Ricardo Machado Xavier[4], Andréa Teixeira-Carvalho[12], Viviane Angelina de Souza[10], Odirlei André Monticielo[4], Gilda Aparecida Ferreira[9], Marcelo de Medeiros Pinheiro[1], Edgard Torres dos Reis Neto[1], Emilia Inoue Sato[1], Valeria Valim[2], Gecilmara Salviato Pileggi[1] and Alexandre Wagner Silva de Souza[1*]

[1]Rheumatology Division, Escola Paulista de Medicina da Universidade Federal de São Paulo (EPM-UNIFESP), São Paulo, SP, Brazil, [2]Rheumatology Division, Hospital Universitário Cassiano Antônio Moraes da Universidade Federal do Espírito Santo (HUCAM-UFES), Vitória, ES, Brazil, [3]Rheumatology Division, Faculdade de Medicina, Universidade Federal do Amazonas (FM- UFAM), Manaus, AM, Brazil, [4]Rheumatology Division, Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil, [5]Rheumatology Division, Universidade Federal Fluminense, Niterói, RJ, Brazil, [6]Rheumatology Division, Hospital Universitário Lauro Wanderley, Universidade Federal da Paraíba (UFPB), João Pessoa, PB, Brazil, [7]Rheumatology Division, Universidade Federal de Goiás, Goiânia, GO, Brazil, [8]Rheumatology Division, Hospital Geral de Fortaleza (HGF), Universidade de Fortaleza (UNIFOR), Fortaleza, CE, Brazil, [9]Rheumatology Division,

Hospital das Clínicas - Empresa Brasileira de Serviços Hospitalares (HC-EBSERH), Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil, [10]Rheumatology Division, Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil, [11]Edumed - Educação em Saúde S/S Ltda, Research Institute, Curitiba, PR, Brazil, [12]Instituto Renè Rachou, Fundação Oswaldo Cruz (FIOCRUZ-Minas), Belo Horizonte, MG, Brazil

Background/objectives: Patients with systemic vasculitis faced the risk of severe COVID-19 and high mortality during the pandemic. Although SARS-CoV-2 vaccination mitigates these outcomes, vaccine hesitancy persists, and data on immunogenicity and safety in vasculitis is still limited. This study aims to assess response to primary and booster doses of SARS-CoV-2 vaccination in systemic vasculitis.

Methods: This multicenter cohort study including systemic vasculitis included patients from SAFER study (Safety and Efficacy of COVID-19 Vaccines in Rheumatic Diseases). We evaluated serum IgG levels against the SARS-CoV-2 spike protein receptor-binding domain (IgG anti-RBD) at baseline and 28 days post-vaccination, disease activity scores, new cases of COVID-19 infections, and adverse events.

Results: Seventy-three patients with systemic vasculitis were included. Behçet's disease (n=39), Takayasu arteritis (n=15), and antineutrophil cytoplasmic antibody-associated vasculitis (n=14) were the most common vasculitis forms. The majority of the patients had no comorbidities and were in remission. Seventy patients received one, 65 two, and 60 three vaccine doses. ChAdOx1 nCoV-19 (AstraZeneca/Oxford) (n=36) and CoronaVac (Sinovac) (n=25) were primarily the most common vaccines, while BNT162b2 (Pfizer–BioNTech) was usually the booster vaccine. ChAdOx1 nCoV-19 induced higher IgG anti-RBD than CoronaVac after two doses (p=0.002), but this difference disappeared after the booster dose. No differences in vaccine response were noted between heterologous and homologous regimens or vasculitis types. The new cases of COVID-19 (16.9%), hospitalization (1.5%), and mortality (1.5%) rates were relatively low following vaccination. Disease activity remained stable, and adverse events were mostly mild. Only one severe adverse event was observed.

Conclusion: Different SARS-CoV-2 vaccines demonstrated immunogenicity and clinical effectiveness in systemic vasculitis. The three-dose schedule was safe without increasing relapse risk.

KEYWORDS

vasculitis, vaccination, COVID-19, Behçet's disease, ANCA-associated vasculitis, Takayasu arteritis, SARS-CoV-2 vaccination

1 Introduction

The COVID-19 pandemic led to elevated morbidity and mortality rates in vulnerable populations, particularly immunosuppressed patients with immune-mediated rheumatic diseases (IMRDs) (1, 2). Factors such as disease activity, comorbidities, and specific medications (e.g., rituximab, cyclophosphamide, and high-dose glucocorticoids) were associated with worsening prognosis (2–7). The risk of severe COVID-19 differed among IMRDs, with worse outcomes seen in those with rheumatoid arthritis (RA), systemic sclerosis (SSc), idiopathic inflammatory myopathies, and systemic vasculitis (3, 8–11).

Systemic vasculitis is a heterogeneous group of rare, systemic autoimmune diseases characterized by inflammation and/or necrosis of blood vessel walls of varying sizes (12). The prevalence and phenotypic expression of specific forms of systemic vasculitis may vary based on ethnic and geographic factors (13–16). When compared to other IMRDs, systemic vasculitis frequently requires intensive immunosuppression due to its severity (17, 18). Furthermore, factors such as the subacute onset and protean manifestations of systemic vasculitis, delayed

diagnosis, and the potentially aggressive nature of systemic vasculitis can often lead to permanent damage to target organs (17, 18). These features contribute to the increased risk of severe COVID-19 in this group of diseases (11).

Vaccination against SARS-CoV-2 is the main strategy to reduce adverse outcomes associated with COVID-19 (19–23) as evidenced by a reduction in overall population mortality following its introduction Nevertheless, vaccine hesitancy persists, usually driven by safety concerns (24–28). Although, several isolated case reports describe new-onset vasculitis following COVID-19 vaccination (29–31), large pharmacovigilance and epidemiological studies have not demonstrated a causal association, suggesting that such events may be a result of coincidental temporal clustering (32–34). In addition, we still see apprehension towards possible disease flares in patients with established systemic vasculitis after vaccination (20–34).

Numerous studies have investigated the immune response to SARS-CoV-2 vaccines in IMRDs, and most data focus on the more prevalent IMRD (35–44). Nevertheless, due to the rarity of systemic vasculitides, fewer studies have assessed immunization in this specific group of diseases (45–48). Most published studies on vasculitis immunization usually examine a single subtype of vasculitis, with relatively small sample sizes, focusing mainly on safety or immunogenicity following two or three doses of homologous vaccines (45–51). Furthermore, some IMRD cohort studies have reported lower immunogenicity in patients with vasculitis, which is usually attributed to those with AAV (52).

Studies evaluating SARS-CoV-2 vaccination in Behçet's disease (BD) stand out for having the largest sample sizes among vasculitis patients, but all of them were conducted in Turkey, an endemic area for BD (53–55). They focused mainly on immune responses after two vaccine doses, comparing CoronaVac and BNT162b2, with additional doses assessed only for safety (53–55). Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is the most studied group regarding immunogenicity for SARS-CoV-2 vaccination (45–51), but most studies evaluate the vaccine response in patients under rituximab (RTX) therapy after two or three homologous doses. There is less evidence for those not receiving B-cell–depleting therapy or for those receiving heterologous schemes (45–51). In patients with giant cell arteritis (GCA), immunogenicity and safety were evaluated only up to the booster dose (56–59).

SARS-CoV-2 vaccination was less investigated in Takayasu arteritis (TAK) compared to other systemic vasculitides. Two online surveys explored the frequency of vaccination and disease relapse (28, 60). They observed higher vaccination adherence in Turkey (91%) (60), whereas coverage was lower in China (i.e., 42% received at least 2 doses) (28). Across different cohorts, vaccination was consistently well tolerated and not associated with disease flare. However, a critical knowledge gap remains. No study to date has evaluated the immunogenicity of vaccines or antibody responses in longitudinal cohorts, leaving the efficacy of SARS-CoV-2 vaccination in TAK still uncertain.SARS-CoV-2 vaccination in other forms of vasculitis, such as cryoglobulinemic vasculitis and IgA vasculitis (IgAV) in adults, were evaluated in some studies assessing immunogenicity and safety after the primary series (61–63).

Regarding safety, previous studies have shown a low frequency of relapses after two doses of vaccine in IgAV patients (63), as well as after three homologous doses in AAV and GCA (45, 64, 65). Conversely, an increased relapse rate has been reported in cryoglobulinemic and in BD after SARS-CoV-2 vaccination (54, 55, 61, 62). Although in BD most relapses were mild and predominantly mucocutaneous, severe manifestations still occurred in a few patients (55). Overall, variability across vasculitis subtypes underscores the need for more comprehensive data.

In summary, despite the growing body of evidence, key uncertainties remain. BD data are still limited to an endemic population, and most AAV studies focus on patients undergoing rituximab therapy. Furthermore, immunogenicity has not been assessed in longitudinal TAK cohorts, and the safety of additional doses of heterologous vaccine platforms remains limited for certain vasculitis subtypes. Moreover, concerns about vaccine-related relapses in clinical practice reinforce the need for studies that address both immunogenicity and safety across systemic vasculitides. Hence, this study aims to analyze the vaccine response to three doses of SARS-CoV-2 vaccines (ChAdOx1nCoV-19/Oxford–AstraZeneca, CoronaVac, and BNT162b2/Pfizer–BioNTech) in a multicenter real-life cohort of Brazilian patients with systemic vasculitis. We assessed immunogenicity, clinical effectiveness, adverse event profiles, and relapse rates. We also compared immunogenicity across vasculitis subtypes and examined the influence of csDMARDs and bDMARDs.

2 Materials and methods

2.1 Patients

This observational, multicenter, real-life, and prospective cohort study involved patients with systemic vasculitis who underwent SARS-CoV-2 vaccination between May 2021 and March 2024, across ten sites in Brazil. The study is a subset analysis of the Brazilian SAFER project (Study of Safety, Effectiveness, and Duration of Immunity after Vaccination against SARS-CoV-2 in Patients with Immune-mediated Chronic Inflammatory Diseases) (40–43). The SAFER project is supported by the Brazilian Society of Rheumatology and the Department of Science and Technology of the Ministry of Health of Brazil. Patients were eligible if they were 18 years or older, met diagnostic or classification criteria for specific forms of vasculitis (66–74) (Supplementary Table S1), were SARS-CoV-2 vaccination-naïve at enrollment, and had a minimum follow-up time of 4 weeks after receiving at least one dose of the SARS-CoV-2 vaccine. The following forms of systemic vasculitis were included in the study: BD, TAK, polyarteritis nodosa (PAN), IgAV, cryoglobulinemic vasculitis, primary angiitis of the central nervous system (PACNS), thromboangiitis obliterans, and AAV including

granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Exclusion criteria included pregnancy, history of severe adverse reactions to any previously administered vaccines, and secondary causes of immunosuppression such as living with HIV (i.e., $CD4^+$ T cell count <200 cells/mm3), organ transplant, primary immunodeficiency, cancer, or history of disorders of the thymus (e.g., myasthenia gravis, thymoma, absence of the thymus or surgical removal).SARS-CoV-2 vaccination was postponed for patients who had received rituximab within the last six months, intravenous (IV) cyclophosphamide pulse therapy within the last three months, IV glucocorticoid (GC) pulse therapy, IV immunoglobulins, or underwent plasmapheresis within the previous 30 days, as well as those who received any blood product transfusions within 30 days before study inclusion. Additionally, vaccination was postponed for at least four weeks after suspicion or confirmed diagnosis of SARS-CoV-2 (i.e., via RT-PCR or rapid test), or two weeks after receiving another type of vaccine.

This study was performed according to Helsinki's declaration and its updates. The institutional review board approved the study protocol at each site and all study participants gave written informed consent (CAAE 43479221.0.1001.5505).

2.2 Vaccines

The following SARS-CoV-2 vaccines were included in the analysis: the inactivated SARS-CoV-2 virus vaccine (CoronaVac/Sinovac/Butantan), the mRNA-based vaccine BNT162b2 (Pfizer-BioNTech), the adenoviral vector vaccines ChAdOx1 nCoV-19 (AstraZeneca/Oxford), and Ad26COV2-S (Janssen/Johnson&Johnson). This study was conducted in accordance with the protocols outlined by Brazil's National Immunization Program, and vaccines were made available by the Brazilian public health system (75, 76). CoronaVac was administered in two doses 28 days apart; BNT162b2 in two doses 21 days apart; ChAdOx1 in two doses 12 weeks apart; and Ad26.COV2-S as a single-dose scheme. Booster doses were recommended at least four months after completion of the primary series or two months for Ad26.COV2-S.

2.3 Follow-up assessments

The study visit schedule included a baseline visit (T0) before vaccination, and three follow-up visits (i.e., T1, T2, and T3), carried out at least 28 days after the administration of each vaccine dose, totaling three doses. The T1 visit occurred after the first dose, T2 after the completion of the full vaccination schedule, and T3 after the booster dose. During each visit, we collected blood samples and assessed patients for signs and symptoms related to vasculitis using specific disease activity tools for each form of vasculitis, as well as therapeutic interventions. A diary of symptoms was provided for patients to complete for 28 days after vaccination, and active monitoring of severe adverse events was conducted at each subsequent visit. The data were recorded using the Research Electronic Data Capture (REDCap) tool.

2.4 SARS-CoV-2 serologic assays

Immunogenicity was assessed by measuring IgG antibodies against the SARS-CoV-2 spike receptor-binding domain (IgG-RBD) using a chemiluminescent microparticle immunoassay (CMIA) for qualitative and semi-quantitative detection (SARS-CoV-2 IgG-II Quant assay, Abbott Laboratories, Green Oaks, IL, USA) (77). The titers of IgG-RBD antibodies were expressed as geometric mean (GMT) and described in binding antibody units (BAU/mL). Seropositivity was defined as IgG-RBD antibody titers of 7.1 BAU/mL or higher. The increase in IgG-RBD GMT titers after each vaccine dose was compared between different doses during the follow-up and among different vaccine types. The rate of IgG-RBD titer increase after each dose was calculated.

2.5 Diagnostic confirmation of COVID-19 infection and suspected cases

Confirmed cases of COVID-19 were defined as patients testing positive for SARS-CoV-2 via reverse transcription-polymerase chain reaction (RT-PCR) or validated antigen tests. Due to limited testing accessibility in our population, suspected cases were also included to minimize data loss. Suspected cases were classified according to Brazilian Ministry of Health definition, as patients presenting characteristic COVID-19 symptoms, including fever, dry cough, and respiratory distress, in conjunction with a loss of smell or taste or a history of close contact with a confirmed COVID-19 case within the preceding two weeks.

2.6 Tools to assess disease activity

Disease activity was assessed using specific tools for each type of vasculitis. The Birmingham Vasculitis Activity Score (BVAS) v3 was used to evaluate AAV, PAN, cryoglobulinemic vasculitis, and IgAV patients. Active disease was defined as BVAS v3 $\geq$ 1 (78). The short form of the Brazilian version of Behçet's Disease Current Activity Form (BR-BDCAF) was used to evaluate disease activity in BD, and a score $\geq$ 2 was regarded as an active disease (79). In TAK patients, disease activity was defined according to Kerr's criteria (80).

2.7 Study endpoints

The primary endpoint of this study was the immunogenicity of SARS-CoV-2 vaccination after the booster dose, evaluated as IgG-RBD GMT titers and seropositivity four weeks following the booster dose. Secondary endpoints included seropositivity after each dose, and the comparison of vaccine responses among different SARS-

CoV-2 vaccines, as well as between homologous and heterologous vaccination schemes, and among different types of vasculitis. Additionally, the influence of current therapy on the immunogenicity of SARS-CoV-2 vaccination was assessed, as well as the clinical effectiveness of SARS-CoV-2 vaccines and vaccination schemes during the follow-up period. Safety outcomes included the number of disease relapses, changes in disease activity scores after each dose, and the adverse events profile after the SARS-CoV-2 vaccination.

2.8 Statistics

The proportions between groups were compared using the chi-square test or Fisher's exact test for categorical variables. For continuous variables, the mean and standard deviation (SD), as well as the median and interquartile range (IQR), were calculated according to the normality of the data. The interquartile range was expressed as Q1–Q3. Continuous variables were compared using the Student's t-test or the Mann-Whitney test, respectively. For comparisons among three or more groups, one-way analysis of variance (ANOVA) or the Kruskal-Wallis test was used.

For the longitudinal analysis of IgG titers, data were normalized using base 10 logarithms, and the median increase in titers was calculated after each dose. The variation in normalized IgG titers over time was assessed using repeated measures (ANOVA). The rate of increase between doses was expressed as medians and compared using the non-parametric Wilcoxon/Mann-Whitney test, with Bonferroni correction.

To identify predictors of higher or lower anti-RBD IgG titer responses after the booster dose, univariate linear regression was used to select variables for the multivariate analysis. A p-value < 0.2 was the criterion for the inclusion of an independent variable in the backward stepwise multivariate model. If this criterion was not met, a biological model was constructed for multivariate linear regression analysis, including the main factors known to influence vaccine responses. All statistical analyses were carried out using the Stata statistical package (v.17) and R (v.4.2.0).

3 Results

3.1 Profile of the whole cohort

Seventy-three patients with systemic vasculitis were assessed at baseline, 70 patients received the first SARS-CoV-2 vaccine dose, 65 completed the primary vaccination series, and 60 patients received the booster dose (Figure 1).

At baseline, the majority of patients were female, Whites and Mestizos represented the largest group. Table 1 depicts demographic parameters, and the frequency of each vasculitis form and its therapy. The three main vasculitis forms included in the study were BD, TAK, and AAV. About half of the cohort had comorbidities, with hypertension and obesity being the most common. In terms of therapy, over half of the patients were taking csDMARDs, and more than one-third were on bDMARDs, primarily TNFi or tocilizumab. Only a few were under rituximab therapy. Glucocorticoids were used by about one-third of the patients, typically in low daily doses. Approximately half of the patients had at least one comorbidity, including hypertension (31.5%), obesity (12.3%), diabetes (8.2%), heart disease (4.1%), and lung disease (1.4%). None of the patients had end-stage kidney disease. Around two-thirds of participants underwent heterologous vaccination regimens combining ChAdOx1 nCoV-19, CoronaVac, and BNT162b2, whereas homologous regimens were mainly based on ChAdOx1 nCoV-19 (Figure 2).

3.2 Comparison of baseline features of study participants

Vasculitis patients originally immunized by CoronaVac had a higher frequency of previous COVID-19 infection compared to those vaccinated with ChAdOx1 nCoV-19. Additionally, AAV patients were more frequently vaccinated with a heterologous regimen than with a homologous one. These differences, along with the frequency of bDMARD use (e.g., TNFi/tocilizumab in BD and TAK; rituximab in a few AAV patients), are summarized in Table 1 and Supplementary Table S1. No other significant differences regarding demographic data, comorbidities, diagnosis of vasculitis, or therapy at the baseline visit were found between the different SARS-CoV-2 vaccination schemes.

3.3 Immunogenicity to SARS-CoV-2 vaccines

At the baseline visit before SARS-CoV-2 vaccination, the CoronaVac group had higher mean levels of IgG-RBD titers (Supplementary Table S2, Figure 3A) and a higher seropositivity rate (47.8% vs. 13.9%; p=0.004) compared to the ChAdOx1 nCoV-19 group (Figure 4A, Supplementary Table S3). These findings are consistent with a higher COVID-19 pre-exposure rate in the CoronaVac group. After the primary SARS-CoV-2 vaccination series (i.e., T2 visit), the ChAdOx1 nCoV-19 group achieved significantly higher levels of immunogenicity compared to the CoronaVac group (Supplementary Table S2, Figure 3A), even though there was no significant difference regarding the seropositivity rate between the groups (94.1% vs. 90.9% respectively; p=0.13) (Figure 4A). After the booster dose (i.e., T3 visit), both groups achieved similar IgG-RBD titers, regardless of the vaccine scheme used (Supplementary Table S2).

When comparing heterologous and homologous SARS-CoV-2 vaccination schemes, no significant differences were observed in the mean IgG anti-RBD titers between both schemes (p=0.580). However, the heterologous group had only a tendency for higher mean IgG anti-RBD titers (p=0.073) at the T3 visit (Supplementary Table S2, Figure 3B). The seropositivity rates were also similar between patients who underwent a homologous and heterologous

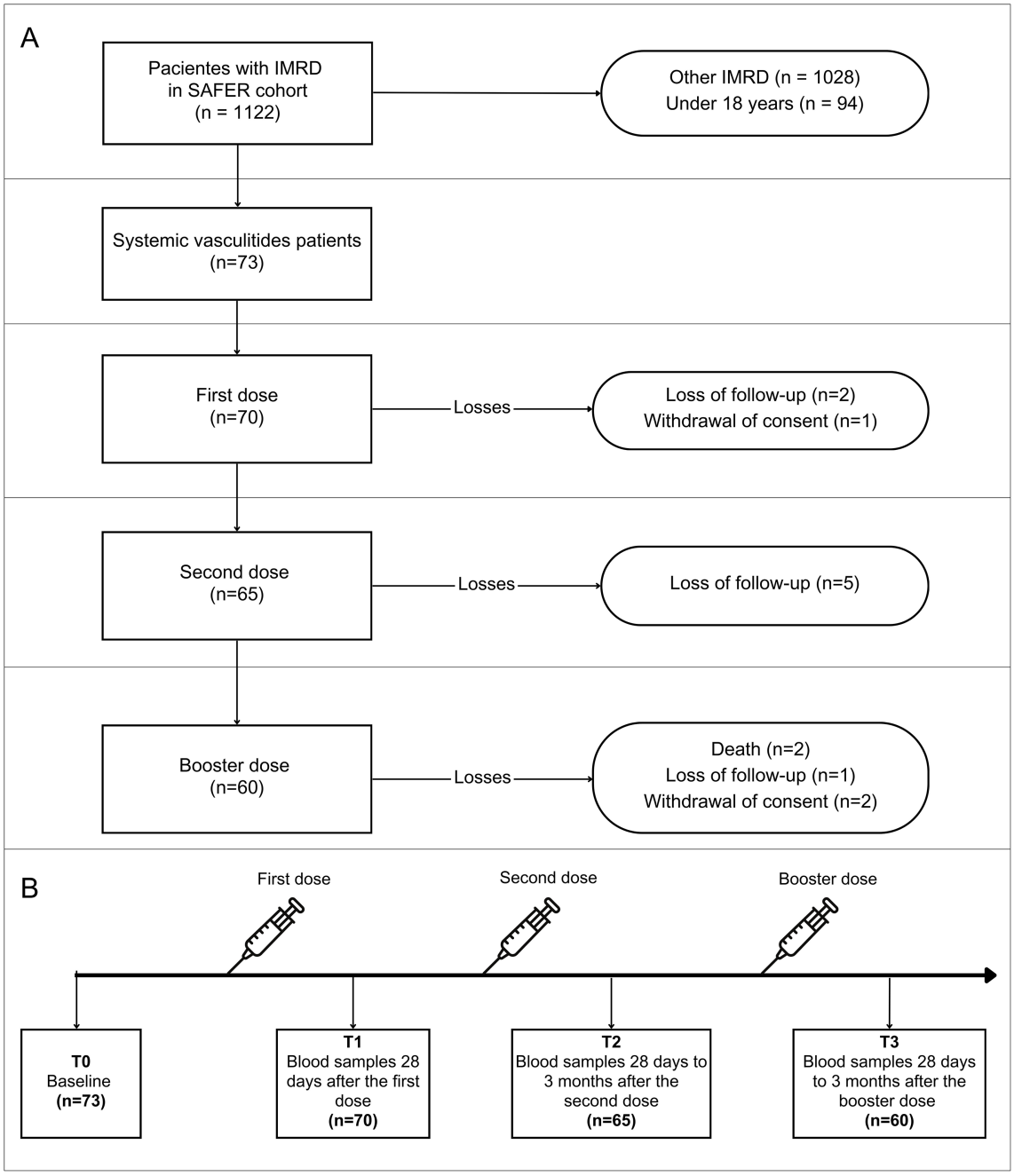


FIGURE 1
Flow chart and follow-up reporting the number of patients investigated for Sars-Cov-2 immunogenicity at different time points in the study. **(A)** shows the patient inclusion flowchart; **(B)** illustrates the study follow-up schedule of visit intervals concerning vaccine doses. IMRD, Immune-mediated rheumatic diseases; SAFER, Study on Safety, Effectiveness, and Duration of Immunity after SARS-CoV-2 Vaccination in Patients with Chronic Immune-Mediated Inflammatory Diseases.

SARS-CoV-2 vaccination scheme at baseline and during the follow-up ($p > 0.05$) (Figure 4B, Supplementary Table S3).

When patients with BD, TAK, and AAV were compared regarding levels of immunogenicity to SARS-CoV-2 vaccination, no significant differences were found in mean levels of IgG-RBD antibodies during the follow-up period (p=0.809) (Supplementary Table S2, Figures 3C, 4C, Supplementary Table S4). A significant rise in IgG-RBD antibody titers was observed within each group over time (p<0.0001).

For all groups, the IgG-RBD GMT increment rate was higher after the first dose of the SARS-CoV-2 vaccine, but this IgG-RBD GMT rise gradually declined with subsequent vaccine doses (Table 2). An exception for this was observed in the group initially allocated to vaccination with CoronaVac, as this group

TABLE 1 Baseline features of vasculitis patients undergoing different SARS-CoV-2 vaccination schemes in the cohort.

Variables	CoronaVac (n = 25)	ChAdOx1 nCoV-19 (n = 36)	*p*	Heterologous scheme (n = 40)	Homologous scheme (n 19)	*p*
Females, n (%)	19 (76.0)	23 (63.9)	0.32	31 (77.5)	10 (52.6)	0.053
Age, years	34.4 ±10.7	39.9 ±11.5	0.067	38.9 ±11.0	38.1 ±11.5	0.79
Race,						
Whites, n (%)	12 (48.0)	18 (50.0)		22 (55.0)	12 (63.2)	
Blacks, n (%)	4 (16.0)	4 (11.1)	0.87	3 (7.5)	2 (10.5)	0.69
Mestizos, n (%)	9 (36.0)	14 (38.9)		15 (37.50)	5 (26.3)	
BMI, kg/m2,	27.6 ± 6.3	26.5 ± 4.7	0.46	27.5 ± 5.0	26.5 ± 7.7	0.56
No comorbidities, n (%)	11 (44.0)	19 (52.8)	0.50	19 (47.5)	10 (52.6)	0.71
Pre-exposed to COVID-19, n (%)	5 (20.0)	1 (2.8)	0.038*	4 (10.0)	1 (5.3)	1.000
Systemic vasculitis						
AVV, n (%)	6/14 (42.8)	8/14 (57.2)	0.87	11/12 (91.6)	1/12 (83.4)	0.04*
BD, n (%)	9/24 (37.5)	15/24 (62.5)	0.65	16/26 (61.5)	10/26 (38.5)	0.36
TAK, n (%)	5/11 (45.4)	7/11 (63.6)	0.95	8/11 (72.7)	3/11 (27.3)	0.69
Oral GCs, n (%)	11 (44.0)	12 (33.3)	0.43	15 (37.5)	6 (31.6)	0.77
Up to 5mg/day	8/23 (34.8)	5/12 (41.7)	NA	6/15 (40.0)	1/6 (16.7)	NA
≥6 a 10 mg/day, n (%)	5/23 (21.7)	4/12 (33.3)	NA	2/15 (13.3)	4/6 (66.7)	NA
≥11 a 20 mg/day, n (%)	6/23 (26.1)	2/12 (16.7)	NA	4/15 (26.7)	0/6 (0.0)	NA
>20 mg/day, n (%)	4/23 (17.4)	1/12 (8.3)	NA	3/15 (20.0)	1/6 (16.7)	NA
csDMARD, %	12 (48.0)	22 (61.1)	0.31	23 (57.5)	9 (47.4)	0.46
Methotrexate ≤20mg/week, n (%)	0/2 (0.0)	5/6 (83.3)	NA	3/6 (50.0)	2/2 (100.0)	NA
Methotrexate >20mg/week, n (%)	2/2 (100.0)	1/6 (16.7)	NA	3/6 (50.0)	0/2 (0.0)	NA
Mycophenolate mofetil, n (%)	2/25 (8.0)	6/36 (16.7)	0.45	7/40 (17.5)	1/19 (5.3)	0.42
Hydroxychloroquine, n (%)	0/25 (0.0)	1/36 (2.8)	1.00	0/40 (0.0)	1/19 (5.3)	0.32
bDMARD						
TNFi or tocilizumab, n (%)	4/25 (16.0)	13/36 (36.1)	0.15	11 (27.5)	9 (47.4)	0.15
Rituximab, n (%)	2/25 (8.0)	2/36 (5.6)	1.00	4/40 (10.0)	0/19 (0.0)	0.29

AAV, ANCA associated Vasculitis; BD, Behçet's disease; bDMARD, Biological disease modifying antirheumatic drugs; BMI, Body mass index; csDMARD, Conventional synthetic disease modifying antirheumatic drugs; GC, Glucocorticoid; n, Number of patients; NA, Not applicable; TAK, Takayasu arteritis; TNFi, Tumor necrosis factor inhibitors; * - Flags significant results.

exhibited the lowest IgG-RBD GMT increment after the first and particularly after the second dose. Interestingly, this group showed higher GMT increments after the booster dose, typically administered with BNT162b2, catching up with IgG-RBD GMT levels comparable to levels achieved by other vaccines.

3.4 Clinical effectiveness SARS-CoV-2 vaccination in vasculitis

After the first two doses of SARS-CoV-2 vaccination, three patients (4.9%) developed either suspected or confirmed COVID-19, all of whom were in the CoronaVac group (Supplementary Table S5). Following the booster dose, ten patients (16.9%) developed COVID-19, but no significant differences were found between the different vaccine groups (Supplementary Table S6).

Only one case of severe COVID-19 that resulted in death was observed in the study. The patient was a 63-year-old and had IgAV with renal involvement characterized by nephrotic-range proteinuria, with chronic kidney disease (CKD) as a permanent damage. The patient had been treated with RTX one year prior to vaccination and had been maintained on long-term prednisone therapy between 6–10 mg/day for approximately ten years. Despite remission, disease recurred upon discontinuation of low-dose

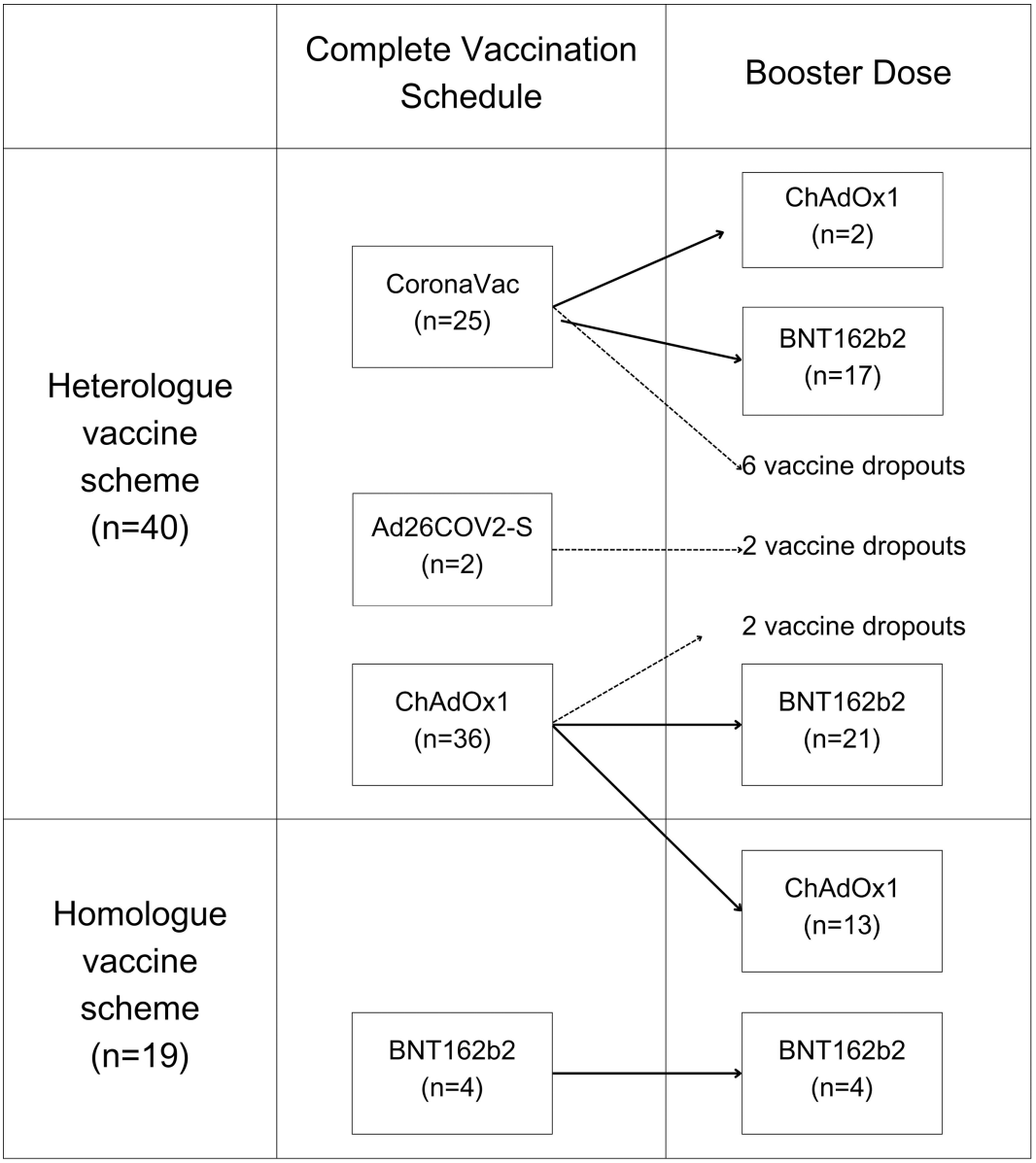


FIGURE 2
Vaccination distribution between homologous and heterologous vaccination schedules.

prednisone. After vaccination, the patient did not show any humoral response following the initial two doses of ChAdOx1 nCoV-19. The first reactive serology (IgG anti-RBD: 2.2 log10 BAU/mL) was detected only after the booster dose. Severe COVID-19 symptoms emerged two months after the booster, leading to ICU admission due to respiratory failure, and ultimately resulting in death. The adverse outcome was attributed to multifactorial risks, including CKD, advanced age, and vaccine anergy related to prior RTX and chronic GC therapy. Importantly, no IgAV disease activity was detected during this adverse event. In this cohort, no other severe cases of COVID-19 were reported. Thus, hospitalization and mortality rates were 1.5% each among 65 patients who received three vaccine doses.

3.5 Predictors of IgG anti-RBD antibody titers after vaccination

The univariate linear regression was first used as a screening tool to explore potential predictors of anti-RBD IgG titers after the third SARS-CoV-2 vaccine dose. Although only one variable met the conventional p-value threshold of <0.2, we decided to build a

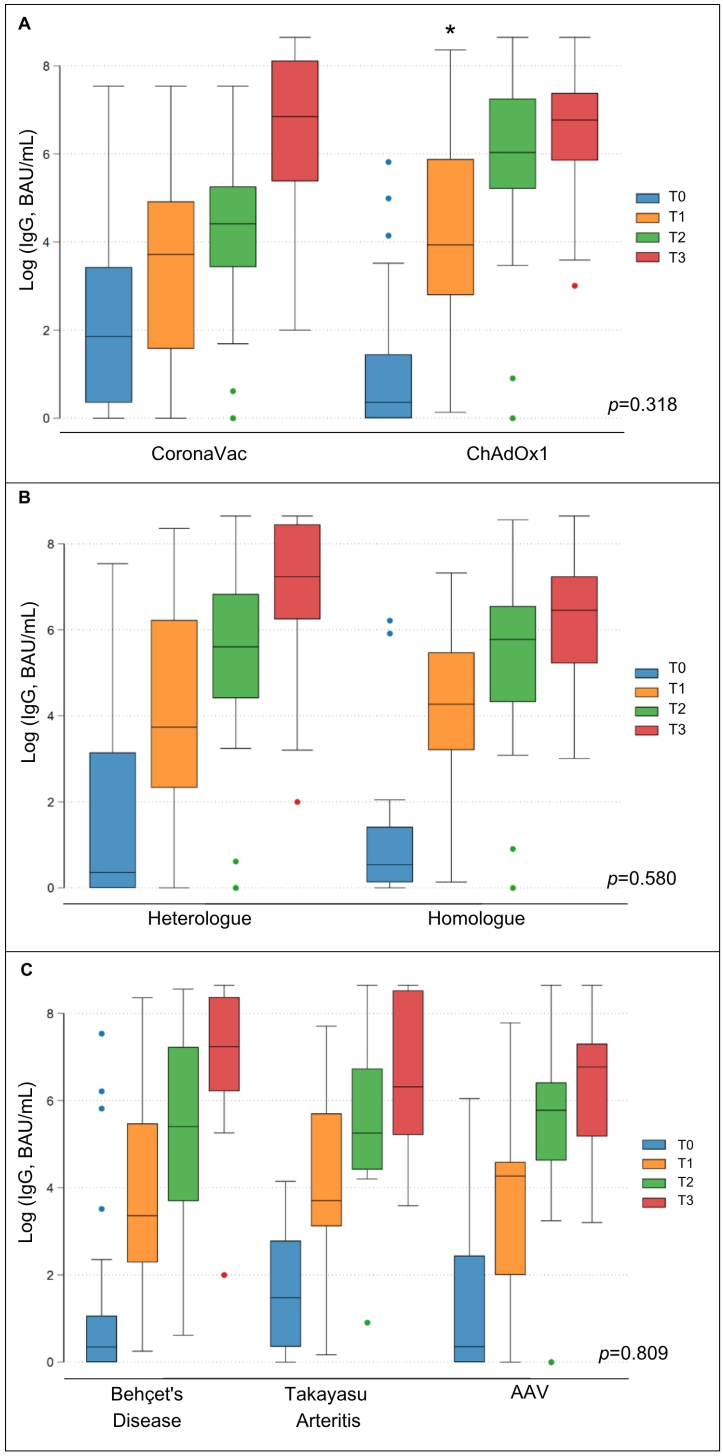


FIGURE 3
Immunogenicity of SARS-CoV-2 vaccination in subgroups of vasculitis patients. Boxplot graphs describe the comparison of the geometric means of IgG anti-RBD antibodies between vasculitis patients vaccinated with Coronavac or ChAdOx1 nCoV-19 **(A)**, between those immunized with heterologous or homologous vaccine schemes **(B)** and between different forms of vasculitis **(C)**. T0, baseline visit; T1, 28 days after first dose; T2, 28 days after second dose; T3, 28 days after third dose of SARS-CoV-2 vaccine; *Flags significant results.

multivariate model including key variables of clinical relevance (i.e., rituximab, immunosuppressants, type of vasculitis, and vaccination scheme), regardless of their univariate statistical significance. This approach aimed to account for potential confounders while minimizing model overfitting. The analysis showed that the immune response was not significantly affected by medication use, vaccination schedule, or type of vasculitis in this study (Table 3).

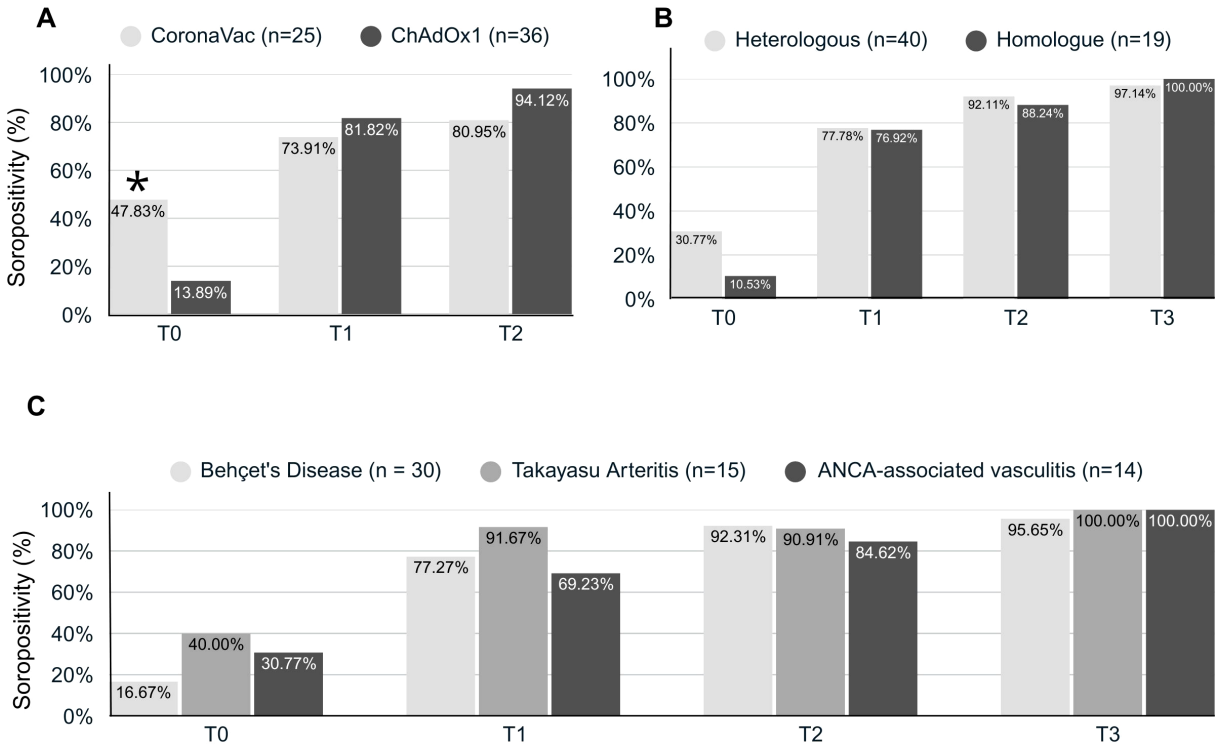


FIGURE 4
Seropositivity against SARS-CoV-2 in vasculitis patients. Bar charts graphs describe the comparison of the seropositivity (responder) of IgG anti-RBD antibodies between vasculitis patients vaccinated with Coronavac or ChAdOx1 nCoV-19 **(A)**, between those immunized with heterologous or homologous vaccine schemes **(B)** and between different forms of vasculitis **(C)**. T0, baseline visit; T1, 28 days after first dose; T2, 28 days after second dose; T3, 28 days after third dose of SARS-CoV-2 vaccine; *Flags significant results.

3.6 Safety of SARS-CoV-2 vaccination in vasculitis patients

The frequency of patients presenting active disease was similar at inclusion and during follow-up with successive vaccine doses (Table 4). The BVAS v3 and BR-BDCAFs scores did not change significantly before or after SARS-CoV-2 vaccination, as the frequency of patients in remission and those remaining at very low disease activity remained stable throughout the study (Table 4). No thromboembolic events were reported in BD patients after SARS-CoV-2 vaccination. However, we observed one severe adverse event related to a life-threatening disease relapse in an 80-year-old female patient with EGPA. Before receiving the booster dose, the patient had signs of mild active disease, and approximately five days after the BNT162b2 booster, the disease activity flared up with the development of myocarditis, fleeting pulmonary infiltrates, and eosinophilia. The possibility of myocarditis associated with the BNT162b2 vaccine was ruled out, as the patient did not fit the typical profile of individuals who develop this vaccine-related complication and had other features consistent with active EGPA. The patient was hospitalized and treated with intravenous methylprednisolone and cyclophosphamide pulse therapy, as well as with high-dose glucocorticoids, showing a good response to therapy. In the investigator's opinion, immunization was likely to contribute to the vasculitis flare-up of an underlying disease activity.

Most adverse events (AEs) related to SARS-CoV-2 vaccination were mild. Injection-site pain and skin rashes were more frequent in vasculitis patients undergoing the first ChAdOx1 nCoV-19 dose compared to CoronaVac. There were no other significant differences regarding AEs between vaccination groups, neither in the complete schedule (Table 5) nor in the booster dose scheme (Supplementary Table S7).

A total of four SAEs (serious adverse events) were reported, two of which were described above (i.e., severe COVID-19 in a patient with IgAV and myocarditis due to EGPA). In addition to these events, there was one death following severe dengue infection in a patient with BD, unrelated to SARS-CoV-2 vaccination, and one case of intracranial hemorrhage due to the rupture of an intracranial aneurysm in a patient with BD on TNFi therapy, who was in remission. This severe event occurred several months after the booster dose and is unlikely to be related to SARS-CoV-2 vaccination. Only one of the severe adverse events observed in this study was directly related to the SARS-CoV-2 vaccine, that is, myocarditis due to EGPA in a patient who received the vaccination while presenting with mild active disease.

TABLE 2 Median of the log increment rates of anti-RBD IgG levels after each vaccine dose.

Interval between timepoints	CoronaVac (n=25)	ChAdOx1 nCoV-19 (n=36)	*p*	Heterologous (n=40)	Homologous (n=10)	*p*
T0 - T1	54.84 (12.40-158.05)	222.76 (116.57-831.40)	0.007*	145.51 (35.53-426.04)	257.97 (116.57-768.74)	0.62
T1 - T2	1.46 (-4.06-50.93)	46.61 (5.82-97.15)	0.099*	33.97 (-1.51-91.30)	28.49 (0.22-72.04)	0.89
T2 - T3	30.52 (-1.03-90.67)	3.20 (-8.58-35.48)	0.14	15.21 (-1.22-50.57)	4.08 (-1.19-51.88)	0.96
p	0.079	<0.001*		<0.001*	0.023*	

T0, Baseline; T1, 28 days after the 1st dose; T2, 28 days after the 2nd dose; T3, 28 days or more after the 3rd dose; *significant results. Continuous variables are presented as medians (Q1-Q3).

4 Discussion

In this prospective cohort study of planned vaccination, we evaluated the immune vaccine response, clinical effectiveness, and safety of SARS-CoV-2 vaccination in patients with systemic vasculitis. All vaccine schedules evaluated in this study demonstrated an increase in anti-RBD IgG titers, with the ChAdOx1 nCoV-19 vaccine showing greater immunogenicity than the CoronaVac vaccine after the complete schedule. However, this initial difference in vaccine response between ChAdOx1 nCoV-19 and CoronaVac disappeared after the booster dose, usually done with the BNT162b2 vaccine. Additionally, there were no differences in the immune response between homologous and heterologous vaccine schedules. The rate of suspected or confirmed COVID-19 cases after the booster dose was as low as 16.9%, accompanied by a low COVID-19 mortality (i.e., 1.5%). The use of immunosuppressive medications was not shown to affect the immunogenicity of SARS-CoV-2 vaccination in this population. However, we acknowledge that this study may not have sufficient statistical power to detect associations. In terms of safety, all SARS-CoV-2 vaccines demonstrated a favorable safety profile as no increase in disease relapses was observed throughout the study, and most reported adverse events were mild in intensity. However, there was one serious adverse event attributed to vaccination, occurring in a patient with active disease at the time of immunization.

The ChAdOx1 nCoV-19 vaccine induced higher mean GMT anti-RBD IgG titers and a greater increment rate than CoronaVac after the complete schedule. This finding is consistent with previous studies that identified lower immunogenicity of inactivated vaccines

TABLE 3 Univariate and multivariate linear regression to evaluate predictors of immunogenicity response after three doses of vaccine.

IgG anti-RBD titers after the 3rd dose	Univariate				Multivariate			
	Unstandardized β coefficient	[95% CI]		*P*	Unstandardized β coefficient	[95% CI]		*P*
Gender								
Male	0	–		–	0	–		–
Female	0.211	-0.717	1.139	0.650	-0.294	-1.558	0.970	0.638
Age in years	0.007	-0.034	0.048	0.751	0.014	-0.048	0.076	0.652
Rituximab	0.257	-1.662	2.176	0.789	0.626	-2.340	3.592	0.670
TNFi and Tocilizumab	0.327	-0.649	1.302	0.505	0.145	-1.195	1.484	0.827
csDMARDs	0.119	-0.860	1.098	0.808	-0.142	-1.525	1.240	0.835
Glucocorticoids	-0.542	-1.427	0.344	0.225	-0.160	-1.451	1.131	0.802
Vasculitis subtype								
Behçet	0	–		–	0	–		–
Takayasu	-0.385	-1.621	0.851	0.533	-0.415	-1.950	1.120	0.585
AAV	-0.432	-1.628	0.764	0.470	-0.927	-2.589	0.734	0.264
Vaccination Schedule								
Heterologous	0	–		–	0	–		–
Homologous	-0.863	-1.810	0.084	0.073	-0.989	-2.314	0.336	0.138

95% CI, 95% confidence interval; AAV, ANCA-associated vasculitis; csDMARD, Conventional synthetic disease modifying antirheumatic drugs; RBD, Receptor binding domain.

10.3389/fimmu.2025.1655917

TABLE 4 Assessment of disease activity in ANCA-associated vasculitis and Behçet's disease before and after each vaccine dose.

Vasculitis	T0	T1	T2	T3
Disease activity scores				
AAV	2.50 (2.00-3.00)	3.00 (2.00-4.00)	3.00 (2.00-4.00)	4.00 (4.00-5.00)
Behçet's Disease	2.00 (2.00-2.50)	2.50 (2.00-3.00)	2.00 (2.00-2.50)	2.00 (2.00-3.00)
Active disease				
AAV, n (%)	4/12 (33.3)	0/8 (0.0)	2/12 (16.7)	2/12 (16.7)
Behçet's disease, n (%)	8/23 (34.7)	2/11 (18.2)	4/25 (16.0)	2/23 (8.7)
Takayasu arteritis, n (%)	2/11 (18.2)	1/6 (16.7)	2/12 (16.7)	1/11 (9.1)

n, Number of patients; AAV, antineutrophil cytoplasmic antibody-associated vasculitis; T0, Baseline; T1, 28 days after the 1st dose; T2, 28 days after the 2nd dose; T3, 28 days or more after the 3rd dose; *Flags significant results; results are presented as median and interquartile range (Q1-Q3) of patients presenting scores ≥ 1 and ≥ 2 for Birmingham Vasculitis Activity Score version 3 and the Brazilian simplified version of the Behçet's Disease Current Activity Form, respectively.

compared to other vaccine platforms (53, 81). However, the group vaccinated with CoronaVac had higher pre-existing viral exposure, which may have influenced the lower increment rate to vaccination observed in this group. Indeed, it is well-known that a short interval between SARS-CoV-2 infection and vaccination can result in a reduced immune response (82, 83). Despite these initial differences, seropositivity remained similar between both vaccines throughout the primary vaccination schedule.

The booster dose increased anti-RBD IgG titers in all patient groups, regardless of the initially administered vaccine platforms. It proved to be particularly important in patients with a less robust immunogenic response to the first two SARS-CoV-2 vaccine doses. A previous study including Brazilian AAV patients showed that a booster dose of CoronaVac increased antibody titers as well, indicating the benefits of the booster even with an inactivated vaccine (47). On the other hand, other studies indicate that some patients persisted unresponsive even after receiving the third dose of mRNA vaccines (45), suggesting that additional SARS-CoV-2 vaccine doses are likely needed for adequate protection in non-responders. Furthermore, the booster dose provided extra protection against mutant strains of SARS-CoV-2, such as Delta and Omicron, across various populations (45, 84).

Our population did not differ in immunogenicity between homologous and heterologous vaccine schedules. This topic has generated controversy in literature. While some studies found superiority in heterologous schedules (42, 81, 85, 86), other - including ours- did not (87), and some even favored homologous boosting (88). We believe that this variability in results of immunogenicity between homologous and heterologous vaccine schedules may be attributed to the specific characteristics of each studied population and size of the sample. It is possible that diversifying vaccine platforms does not significantly impact the immune response as long as the vaccines used are effective and administered in a schedule of at least three doses.

Our study demonstrated a low frequency of suspected or confirmed COVID-19 (16.9%) following the complete vaccination schedule and booster dose. Another study including BD patients reported 10.1% COVID-19 cases after two doses of CoronaVac and 1.4% after BNT162b2, when patients were still under social distancing measures (54). In our study, the booster dose was close to the end of social distancing measures, accompanied by modifications in population social behavior and the emergence of the Delta and Omicron SARS-CoV-2 variants. This suggests that our patients with vasculitis may have had a higher viral exposure to

TABLE 5 Comparisons of safety between CoronaVac and ChAdOx1 nCoV-19 vaccines in vasculitis patients after the complete vaccination schedule.

Adverse events	CoronaVac (n = 25)	ChAdOx1 nCoV-19 (n = 36)	*p*
Up to 28 days after the first dose			
Site-injection pain, n (%)	9/21 (42.9)	30/36 (83.3)	0.002*
Skin rashes, n (%)	0/21 (0.0)	7/36 (19.4)	0.039*
Nausea or vomiting, n (%)	5/21 (23.8)	12/36 (33.3)	0.55
Fatigue, n (%)	7/21 (33.3)	18/36 (50.0)	0.22
Headache, n (%)	9/21 (42.9)	14/36 (38.9)	0.77
Myalgia, n (%)	5/21 (23.8)	13/36 (36.1)	0.39
Arthralgia, n (%)	5/21 (23.8)	12/36 (33.3)	0.55
Fever, n (%)	4/21 (19.1)	8/36 (22.2)	1.00
Dizziness, n (%)	6/21 (28.6)	8/36 (22.2)	0.59
Up to 28 days after the second dose			
Site-injection pain, n (%)	5/19 (26.3)	14/33 (42.4)	0.37
Skin rashes, n (%)	0/19 (0.0)	3/33 (9.1)	0.29
Nausea or vomiting, n (%)	2/19 (10.5)	7/33 (21.2)	0.46
Fatigue, n (%)	6/19 (31.6)	10/33 (30.3)	0.92
Headache, n (%)	3/19 (15.8)	9/33 (27.3)	0.50
Myalgia, n (%)	5/19 (26.3)	8/33 (24.2)	1.00
Arthralgia, n (%)	3/19 (15.8)	10/33 (30.3)	0.33
Fever, n (%)	1/19 (5.3)	5/33 (15.2)	0.40
Dizziness, n (%)	3/19 (15.8)	6/33 (18.2)	1.00

N, Number of patients; *Flags significant results.

SARS-CoV-2 during the booster phase compared to the primary series.

We also report low hospitalization (1.5%) and mortality (1.5%) rates due to COVID-19. For comparison reasons, the hospitalization rate of COVID-19 in Latin America prior to SARS-CoV-2 vaccination was 22%, with a mortality rate of 4% (89). For individuals living with vasculitis, these rates were even higher, ranging between 23% and 38% for hospitalizations and between 9% and 28% for mortality (8–11). Other studies including IMRD patients have demonstrated similar benefits of SARS-CoV-2 vaccine effectiveness, showing a reduction in hospitalizations from 25.0% to 4.8% and mortality from 5.7% to 0% in patients with a complete vaccination schedule (41, 65, 90). These studies found that COVID-19 mortality was associated with high disease activity and the use of GC, while the number of SARS-CoV-2 vaccine doses was shown to be a protective factor. To the best of our knowledge, our study is the first to demonstrate low mortality and hospitalization rates in patients with systemic vasculitis after SARS-CoV-2 vaccination. It is worth noting that the only severe case of COVID-19 occurred in a patient who did not adequately respond to the initial SARS-CoV-2 vaccine doses, reinforcing the importance of booster doses for protection against severe COVID-19 outcomes.

Robust evidence supports that immunosuppressive therapies such as GCs, MTX ≥20 mg, MMF, and RTX are major determinants of impaired SARS-CoV-2 vaccine immunogenicity (50, 58, 91–94). In GCA, for example, patients under MTX therapy have shown reduced humoral responses after two doses of the SARS-CoV-2 vaccine, with recovery only after receiving booster doses. In contrast, patients treated with tocilizumab mounted a higher antibody response (57–59). This effect was even more pronounced when MTX was combined with moderate to high doses of GC (58). In AAV, RTX-treated patients consistently exhibited lower seropositivity rates and faster antibody waning compared to non-RTX patients, even after a booster dose (48, 49). Nevertheless, SARS-CoV-2 vaccination can still induce cellular responses in RTX users, and provide partial protection, despite B-cell depletion (48, 49). In studies including BD patients, TNFi was associated with lower serological responses after one dose of CoronaVac. However, it did not affect by mRNA vaccine immunogenicity (53).

On the other hand, in our cohort, the univariate and multivariate analyses did not show that these medications significantly affected on SARS-CoV-2 vaccine immunogenicity. We acknowledge that this discrepancy is likely due to the limited number of patients taking these medications and the timing of vaccination in relation to treatment. Only five patients were on RTX, and they were all vaccinated at least six months after their last infusion, a period when B-cell repopulation is likely to occur in most patients. Regarding GCs, most of the literature describes reduced responses after the first or second dose. However, a third dose may compensate for the initial deficit (57–59). Moreover, only a few patients were taking MMF (n=8) or high-dose MTX (n=3), which limited the possibility of analyzing these drugs individually. Therefore, these findings should not be interpreted as evidence that immunosuppressive therapy has no impact on vaccine responses. Rather, they should be understood as a consequence of the small number of patients taking these drugs in our cohort, the distribution of treatments, and the possible compensatory effect of booster doses (45, 46, 48, 49, 53, 56–59).

Additionally, this is the first study to compare the vaccine response to SARS-CoV-2 among different forms of systemic vasculitis, while other studies were restricted to include only specific forms of vasculitis (45–51) or compared the immunogenicity of vasculitis with other IMDRs (95–97). In our study, patients with AAV, TAK, and BD demonstrated equivalent vaccine responses, which contrasts with most AAV series reporting lower seroconversion rates than other diseases (45, 47, 49, 51). The seropositivity rates in our AAV patients reached 69.2%, 84.2%, and 100% after each dose of SARS-CoV-2 vaccine, whereas other studies reported 0–21% after the first dose and 28–66% after the second dose (45, 47, 49, 51). We attribute this difference to the low frequency of rituximab use in our cohort. These findings reinforce the idea that impaired humoral responses in AAV are largely driven by RTX exposure rather than by the underlying disease itself (45, 46, 48, 49).

Our study is the first to evaluate the immunogenicity against SARS-CoV-2 in patients with TAK (61). We have shown clinical effectiveness, safety, and a low rate of disease relapse in this population. In a previous study, patients with TAK were included as a whole group in a large cohort of systemic autoimmune diseases, but no analyses were made regarding their vaccine response (98). Other studies have evaluated the behavior of TAK patients during the COVID-19 pandemic, and reported flare rates of 28.5%. These flares were most often associated with unsupervised discontinuation of immunosuppressive therapy or delays in medical follow-up (60). In contrast, a Chinese study found that a SARS-CoV-2 infection itself did not increase the risk of flare, with relapse rates actually lower among infected compared with uninfected patients (28). European surveys reported that most TAK patients were in remission, and no flares were attributed to either infection or vaccination (99, 100).

Furthermore, in cohort studies including different IMDR, the vasculitis group had a reduced response compared to other diseases, usually at the expense of AAV patients using RTX (95–97). In another study that compared vasculitis patients from the SAFER study with other systemic autoimmune diseases in the same cohort, there was a trend toward a lower humoral response in patients with vasculitis, inflammatory myopathies, and systemic sclerosis, while patients with Sjögren's disease and systemic lupus erythematosus tended to have a better response to SARS-CoV-2 vaccination (42).

Since this was a planned vaccination study, most patients were in remission at baseline, and this profile was maintained throughout the follow-up. The frequency of active disease remained stable in

the follow-up visits of the study. Active disease was found in 4.6% of the whole group and in 16.0%, 8.6% and 9.0% in AAV, BD and TAK patients, respectively. Additionally, the median scores for disease activity, such as BVASv3 and BR-BDCAFs were at similar levels throughout the study, reinforcing that the vaccine did not increase disease activity scores or relapses in patients in remission or with mild disease activity.

One patient with EGPA developed a severe disease relapse with a significant temporal relation after the vaccine. In this case, the disease activity was already underway at the time of the third vaccine dose and we believe that the vaccine likely influenced the worsening of the disease. Indeed, there is a theoretical risk of autoimmune disease exacerbation after COVID-19 vaccination, although severe relapses are rare, and the benefits of vaccination outweigh these risks. In this context, the American College of Rheumatology (ACR) guidelines recommend that vaccination can be administered to patients with active disease, as long as it is not severe, whereas patients presenting life-threatening manifestations or major organ dysfunction should wait for disease control before immunization (101).

Other studies corroborate the safety of SARS-CoV-2 vaccination concerning disease relapses in systemic vasculitis, as most of them showed low disease relapse rates after vaccination. A cohort with similar features to ours, including different types of systemic vasculitis, observed a 0.9% rate of disease relapses in 107 patients (102). In patients with AAV, no increased frequency of relapses or hospitalizations were observed after SARS-CoV-2 vaccination (45, 64). Another study also found a low frequency of relapses (i.e., 0.5%) in patients with IgAV, characterized by transient renal function impairment, but with no severe adverse events (63). Disease relapses were observed in 5.3% to 12.7% of patients with cryoglobulinemic vasculitis (61, 62) and in 7.1% of patients with GCA who underwent SARS-CoV-2 vaccination (58). Regarding SARS-CoV-2 vaccination in BD, studies conducted in Turkey reported higher relapse rates in BD (i.e., 16% to 53%) compared to our findings (54, 55). Relapses were mostly mild and mucocutaneous. However, up to 4% of BD patients experienced severe relapses, including uveitis, venous thrombosis, and even neurological involvement (54). Notably, Turkey is an endemic country for BD, providing larger and more representative samples for such studies. In relation to SARS-CoV-2 vaccination in TAK, an internet-based data collection revealed results comparable to ours, showing a low rate of disease relapse (i.e., 8%) by TAK patients after vaccination (28). These data indicate that the frequency and susceptibility to relapses upon SARS-CoV-2 vaccination may vary among different types of vasculitis. However, the overall relapse rates are low and comparable to the usual disease activity rates in this population, which reinforces the safety of SARS-CoV-2 vaccination for these patients.

The profile of AEs observed in this study was predominantly mild. Injection-site pain, fatigue, and headache were the most frequent AEs, which is similar to the literature (45, 47, 54, 55, 57, 62, 102). Additionally, age appears to be a protective factor for the frequency of AEs seemed to be lower in older compared to younger patients with vasculitis (57, 102).

4.1 Limitations

We acknowledge some limitations to this study. The main limitation is the small sample size, which, combined with the heterogeneity of vasculitis subtypes and concomitant medications, may have limited the power to perform specific analyses, such as the impact of immunosuppressive therapies on vaccine response. Consequently, the study is underpowered for such analyses. However, it provides valuable real-life data that, when combined with findings from other cohorts, may help generate more consistent evidence. Another limitation was the loss of patients during follow-up, although the patient loss in our study was similar to that reported in other studies (55). Additionally, the difficulty in monitoring and confirming COVID-19 cases was challenging, as PCR testing was not performed in all suspected cases, and over time, people ceased testing. To minimize underreporting, we included unconfirmed typical COVID-19 cases (e.g., anosmia and known contact with confirmed COVID-19 cases) and we focused on severe COVID-19 presentations. Finally, the absence of a non-vasculitis control group limits direct comparisons with the general population.

4.2 Clinical implications and future directions

Despite these limitations, our study provides novel real-life data on SARS-CoV-2 vaccination in systemic vasculitis, which is a rare and clinically diverse group of diseases. We directly compared vaccine responses across vasculitis subtypes and provided longitudinal data on TAK. Clinically, the results reinforce current recommendations to complete at least three vaccine doses to achieve adequate immunogenicity, as well as to prioritize vaccination for patients in remission, with careful timing in relation to immunobiological therapies such as RTX (103). The observed reassuring safety profile may also contribute to reducing vaccine hesitancy among patients and physicians. Although limited, the study provides valuable real-life data on rare diseases. Additionally, combining our findings with results from other cohorts may generate more consistent evidence (48, 49, 53, 58, 61, 103).

5 Conclusion

To the best of our knowledge, this is the first real-life study to compare the immunogenicity, clinical efficacy, and safety of different SARS-CoV-2 vaccines in a population comprising exclusively patients with systemic vasculitis, including the first longitudinal data reported in TAK. Our study emphasizes the importance of completing a minimum of three vaccine doses to ensure adequate immunogenicity and that vaccination is safe in patients with low disease activity or in remission, with no increased risk of relapse. Hence, our results support the recommendations to prioritize vaccination for patients in remission and to time

vaccinations according to the nadir of immunobiological drugs, such as RTX.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved the local ethics commettees of the instituions involved in this study and by COMISSÃO NACIONAL DE ÉTICA EM PESQUISA (CONEP). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

EB: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Data curation, Formal Analysis, Investigation. MF: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. PD: Data curation, Investigation, Methodology, Writing – review & editing. KM: Data curation, Investigation, Methodology, Writing – review & editing. CP: Data curation, Investigation, Methodology, Writing – review & editing. SE: Data curation, Investigation, Methodology, Writing – review & editing. NS: Methodology, Software, Supervision, Writing – review & editing. RP: Data curation, Investigation, Methodology, Writing – review & editing. AG: Data curation, Investigation, Methodology, Writing – review & editing. VAC: Investigation, Methodology, Supervision, Writing – review & editing. RR: Investigation, Methodology, Supervision, Writing – review & editing. AK: Investigation, Methodology, Supervision, Writing – review & editing. MD: Investigation, Methodology, Supervision, Writing – review & editing. VFA: Data curation, Investigation, Methodology, Writing – review & editing. OM-F: Data curation, Investigation, Methodology, Writing – review & editing. FM: Data curation, Investigation, Methodology, Writing – review & editing. VO: Data curation, Investigation, Methodology, Writing – review & editing. MG: Data curation, Investigation, Methodology, Writing – review & editing. TK: Data curation, Investigation, Methodology, Writing – review & editing. KLB: Data curation, Investigation, Methodology, Writing – review & editing. TS: Data curation, Investigation, Methodology, Writing – review & editing. JR: Data curation, Investigation, Methodology, Writing – review & editing. AR: Data curation, Investigation, Methodology, Writing – review & editing. AF: Data curation, Investigation, Methodology, Writing – review & editing. VD: Data curation, Investigation, Methodology, Writing – review & editing. VP-M: Data curation, Investigation, Methodology, Writing – review & editing. LD: Data curation, Investigation, Methodology, Writing – review & editing. RL: Data curation, Investigation, Methodology, Writing – review & editing. KS: Data curation, Investigation, Methodology, Writing – review & editing. NR: Data curation, Investigation, Methodology, Writing – review & editing. DM: Data curation, Investigation, Methodology, Writing – review & editing. JA: Data curation, Investigation, Methodology, Writing – review & editing. RT: Data curation, Investigation, Methodology, Writing – review & editing. KLT: Data curation, Investigation, Methodology, Writing – review & editing. CK: Data curation, Investigation, Methodology, Writing – review & editing. CC: Data curation, Investigation, Methodology, Writing – review & editing. MB: Data curation, Investigation, Writing – review & editing. JB: Data curation, Investigation, Writing – review & editing. RX: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. AT-C: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. VA: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. OM: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. GF: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. MP: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. ET: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. ES: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. VV: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. GP: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AS: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. This study received funding from the Brazilian Society of Rheumatology (Funding number: 392 SBR2021SAFER001), Ministério da Saúde do Brasil, MS, Departamento de Ciência e Tecnologia 393 (DECIT) and Fundação para o Desenvolvimento Científico e Tecnológico em Saúde (Fiotec). The funders were not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.

Acknowledgments

The authors thank the Network of Observational Studies for monitoring the effectiveness, safety of vaccination against COVID-19 in Brazil, linked to the Fundação Oswaldo Cruz, Fiocruz, Instituto de Tecnologia em Imunobiológicos, Departamento de Assuntos Médicos, Estudos Clínicos e Vigilaência Pós Registro, for the technical and operational support. To the participating centers: Universidade Federal do Espírito Santo (UFES),Universidade Federal de São Paulo (UNIFESP), Universidade Federal de Minas Gerais (UFMG), Universidade Federal da Paraíba (UFPB), Universidade Federal Fluminense (UFF), Universidade Federal de Juiz de Fora (UFJF), Universidade federal de Goiás (UFG), Universidade Federal do Rio Grande do Sul (UFRGS), Hospital universitário da Universidade Federal do Amazonas (UFAM); Hospital Geral da universidade Federal do Ceará (UFCE), EDUMED research center de Curitiba Associates with Universidade Federal do Paraná (UFPR), Serviços Especializados em Reumatologia da Bahia (SER) e centros de refereência em Gastroenterologia com pesquisadores cadastrados do GEDIIB). To the collaborating researchers integrating the SAFER-study task force: AR, Adriana Maria Kakehasi, Adriana Ribas Andrade, AS, Aline Teixeira de Landa, AG, Ana Luisa Souza Pedreira, Ana Paula Neves Burian, André Gustavo Cunha Trolese, AT-C, Andrese Aline Gasparin, Andrieli Caroline Mehl, AF, Anna Carolina Simões Moulin, Antonio Luiz Boechat, Artur José Azevedo Pereira, Bárbara Oliveira Souza, Barbara Polli, Camila da Silva Cendon Duran, CP, Carolina Strauss Estevez Gadelha, Catherine Pancotto, CC, Clara Lyra de Andrade Stefanon, Clarissa Ruas Yasuda, CK, Cyrla Zaltman, Danielle Cristina Filgueira Alves Batista, Débora Cerqueira Calderaro, DM, Edgard Torres dos Reis-Neto, Eduardo Yasuda, ES, Erica Vieira Serrano, EB, Fernanda Dazilio dos Reis, Filipe Faé, FM, Flavia Zon Pretti, Gabriel Smith Sobral Vieira, Gabriela Guimarães Nogueira, GP, Gilda Aparecida Ferreira, Guilherme LevíTres, Heitor Filipe Surlo, Helena da Silva Corona, Isabella Vargas de Souza Lima, Isac Ribeiro Moulaz, João Gabriel Leão Sperancini Amaral, João Pedro Sarcinelli Chagas, JA, Jonathan Willian Da Silva Rodrigues, José Geraldo Mill, JR, Julia Fagundes Fracasso, JB, Juliana Ribeiro de Oliveira, KLT, KLB, KM, KS, Laís Pizzol Pasti, Laissa Fiorotti Albertino, LD, Laura Gonçalves Rodrigues Aguiar, Leonardo Barbosa da Silva, Leonardo Rodrigues Campos, Lucélia Paula Cabral Schmidt, Ludmila Arrebola Rubin de Celis Mori, Luigi Marangão Calil, Luiza Helena Coutinho Ribeiro, Luiza Lorenzoni Grillo, Lunara Baptista Ferreira, Maisa Brito Nunes, MP, Marcos Mavignier Sousa Dias, MB, MD, Maria da Penha Gomes Gouvea, Mariana de Oliveira Macabú, MF, Marina Deorce de Lima, Mittermayer Barreto Santiago, Nadja Maria Santiago de Mattos, NR, NS, Natália Seixas de Melo, Nicole Pamplona Bueno de Andrade, Nilzio Antonio da Silva, OM, OM-F, Paula dos Santos Athayde, Pedro Matos, Pietra Zava Lorencini, Pollyana Vitoria Thomaz da Costa, PD, Rafaela Cavalheiro do Espírito Santo, Ranielly Correêa Lube Santos Brum, RL, Rebeca Silva Moreira da Fraga, Regiane Lima, RR, Renata Henriques de Azevedo, RX, Roberta Beatriz Nazareth Alagia, Rodrigo Cutrim Gaudio, RP, Rosely Holanda da Silva Sanches, Russian Teixeira Rebello, Sabrina de Souza Ramos, Samira Tatiyama Miyamoto, SE, TS, TK, Thaisa de Moraes Ribeiro Espirito Santo, Valderilio Feijó Azevedo, Valéria Bezerra da Silva, VV, VO, Vanessa Hax, VP-M, VD, Vinícius de Pádua Sanders Medeiros, VAC, Viviane Angelina de Souza, Yasmin Gurtler Pinheiro de Oliveira. We also thank all the patients who participated in this study and the nurses for their support with patient care and sample collection.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that Generative AI was used in the creation of this manuscript. For grammatical support.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2025.1655917/full#supplementary-material

References

1. Eder L, Croxford R, Drucker AM, Mendel A, Kuriya B, Touma Z, et al. COVID-19 hospitalizations, intensive care unit stays, ventilation, and death among patients with immune-mediated inflammatory diseases compared to controls. *J Rheumatol*. (2022) 49:523–30. doi: 10.3899/jrheum.211012

2. Kroon FPB, Najm A, Alunno A, Schoones JW, Landewé RBM, MaChado PM, et al. Risk and prognosis of SARS-CoV-2 infection and vaccination against SARS-CoV-2 in rheumatic and musculoskeletal diseases: a systematic literature review to inform EULAR recommendations. *Ann Rheum Dis*. (2022) 81:422–32. doi: 10.1136/annrheumdis-2021-221575

3. Santos CS, Morales CM, Álvarez ED, Castro CÁ, Robles AL, Sandoval TP. Determinants of COVID-19 disease severity in patients with underlying rheumatic disease. *Clin Rheumatol*. (2020) 39:2789–96. doi: 10.1007/s10067-020-05301-2

4. Marques CDL, Kakehasi AM, Pinheiro MM, Mota LMH, Albuquerque CP, Silva CR, et al. High levels of immunosuppression are related to unfavourable outcomes in hospitalised patients with rheumatic diseases and COVID-19: First results of ReumaCoV Brasil registry. *RMD Open*. (2021) 7:e001461. doi: 10.1136/rmdopen-2020-001461corr1

5. Gomides APM, de Albuquerque CP, da Mota LMH, Devidé G, Dias LH, Duarte ALBP, et al. Factors associated with hospitalizations for Covid-19 in patients with rheumatoid arthritis: data from the Reumacov Brazil registry. *Adv Rheumatol*. (2022) 62:13. doi: 10.1186/s42358-022-00244-5

6. Ugarte-Gil MF, Alarcón GS, Izadi Z, Duarte-García A, Reátegui-Sokolova C, Clarke AE, et al. Characteristics associated with poor COVID-19 outcomes in individuals with systemic lupus erythematosus: data from the COVID-19 Global Rheumatology Alliance. *Ann Rheum Dis*. (2022) 81:970–8. doi: 10.1136/annrheumdis-2021-221636

7. Hoff LS, Ravichandran N, Shinjo SK, Day J, Sen P, Junior JG, et al. COVID-19 severity and vaccine breakthrough infections in idiopathic inflammatory myopathies, other systemic autoimmune and inflammatory diseases, and healthy controls: a multicenter cross-sectional study from the COVID-19 Vaccination in Autoimmune Diseases (COVAD) survey. *Rheumatol Int*. (2023) 43:47–58. doi: 10.1007/s00296-022-05229-7

8. Rutherford MA, Scott J, Karabayas M, Antonelou M, Gopaluni S, Gray D, et al. Risk factors for severe outcomes in patients with systemic vasculitis and COVID-19: A binational, registry-based cohort study. *Arthritis Rheumatol*. (2021) 73:1713–9. doi: 10.1002/art.41728

9. Samanta J, Naidu G, Deo P, Mittal S, Prasad CB, Das D, et al. Managing ANCA-associated vasculitis during COVID-19 pandemic: a single-center cross-sectional study. *Rheumatol Int*. (2022) 42:2159–66. doi: 10.1007/s00296-022-05177-2

10. Antovic A, Bruchfeld A, Ekland J, Lövström B, Hugelius A, Börjesson O, et al. Risks and treatment related aspects of COVID-19 infection in patients with ANCA-associated vasculitis. *Scand J Rheumatol*. (2023) 52:418–23. doi: 10.1080/03009742.2022.2109337

11. Sattui SE, Conway R, Putman MS, Seet AM, GianFrancesco MA, Beins K, et al. Outcomes of COVID-19 in patients with primary systemic vasculitis or polymyalgia rheumatica from the COVID-19 Global Rheumatology Alliance physician registry: a retrospective cohort study. *Lancet Rheumatol*. (2021) 3:e855–64.

12. Watts RA, Robson J. Introduction, epidemiology and classification of vasculitis. *Best Pract Res Clin Rheumatol*. (2018) 32:3–20. doi: 10.1016/j.berh.2018.10.003

13. de Souza AWS, Zarur EB, Pimentel-Quiroz VR, Sanchez-Torres A, Ugarte-Gil MF, Sato EI. Different epidemiologic profiles of systemic vasculitis between Brazil and Peru-preliminary results in two referral centers from both countries. *Clin Rheumatol*. (2022) 41:635–9. doi: 10.1007/s10067-021-06032-8

14. Vieira M, Ochtrop MLG, Sztajnbok F, Souto Oliveira Elias C, Verztman JF, Bica BERG, et al. The epidemiology of takayasu arteritis in Rio de Janeiro, Brazil: A large population-based study. *J Clin Rheumatol*. (2023) 29:E100–3. doi: 10.1097/RHU.0000000000001964

15. Pearce FA, Craven A, Merkel PA, Luqmani RA, Watts RA. Global ethnic and geographic differences in the clinical presentations of anti-neutrophil cytoplasm antibody-associated vasculitis. *Rheumatol (Oxford)*. (2017) 56:1962–9. doi: 10.1093/rheumatology/kex293

16. Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. *Nat Rev Rheumatol*. (2022) 18:22–34. doi: 10.1038/s41584-021-00718-8

17. Garen T, Lerang K, Hoffmann-Vold AM, Andersson H, Midtvedt Ø, Brunborg C, et al. Mortality and causes of death across the systemic connective tissue diseases and the primary systemic vasculitides. *Rheumatol (Oxford)*. (2019) 58:313–20. doi: 10.1093/rheumatology/key285

18. Phillip R, Luqmani R. Mortality in systemic vasculitis: a systematic review. *Clin Exp Rheumatol*. (2008) 26:S94–104.

19. Tavares ACFMG, de Melo AKG, Cruz VA, de Souza VA, de Carvalho JS, MaChado KLLL, et al. Guidelines on COVID-19 vaccination in patients with immune-mediated rheumatic diseases: a Brazilian Society of Rheumatology task force. *Adv Rheumatol*. (2022) 62:3. doi: 10.1186/s42358-022-00234-7

20. Yamana TK, Galanti M, Pei S, Di Fusco M, Angulo FJ, Moran MM, et al. The impact of COVID-19 vaccination in the US: Averted burden of SARS-COV-2-related cases, hospitalizations and deaths. *PloS One*. (2023) 18:e0275699. doi: 10.1371/journal.pone.0275699

21. Kirwan PD, Charlett A, Birrell P, Elgohari S, Hope R, Mandal S, et al. Trends in COVID-19 hospital outcomes in England before and after vaccine introduction, a cohort study. *Nat Commun*. (2022) 13:4834. doi: 10.1038/s41467-022-32458-y

22. Suthar AB, Wang J, Seffren V, Wiegand RE, Griffing S, Zell E. Public health impact of covid-19 vaccines in the US: observational study. *BMJ*. (2022) 377:e069317. doi: 10.1136/bmj-2021-069317

23. Tu W, Zhang P, Roberts A, Allen KS, Williams J, Embi P, et al. SARS-CoV-2 infection, hospitalization, and death in vaccinated and infected individuals by age groups in Indiana, 2021–2022. *Am J Public Health*. (2023) 113:96–104. doi: 10.2105/AJPH.2022.307112

24. Tharwat S, Abdelsalam HA, Abdelsalam A, Nassar MK. COVID-19 vaccination intention and vaccine hesitancy among patients with autoimmune and autoinflammatory rheumatological diseases: A survey. *Int J Clin Pract*. (2022) 2022:1–10. doi: 10.1155/2022/5931506

25. Chen J, Cai W, Liu T, Zhou Y, Jin Y, Yang Y, et al. The COVID-19 vaccine: Attitudes and vaccination in patients with autoimmune inflammatory rheumatic diseases. *Rheumatol Autoimmun*. (2022) 2:82–91. doi: 10.1002/rai2.12028

26. Vieira Rezende RP, Braz AS, Guimarães MFB, Ribeiro SLE, Abreu Vieira RMR, Bica BE, et al. Characteristics associated with COVID-19 vaccine hesitancy: A nationwide survey of 1000 patients with immune-mediated inflammatory diseases. *Vaccine*. (2021) 39:6454–9. doi: 10.1016/j.vaccine.2021.09.057

27. Butt IN, van Eeden C, Kovacs Burns K, Saxinger L, Clifford A, Redmond D, et al. Understanding COVID-19 vaccine hesitancy in vasculitis patients. *Front Public Health*. (2023) 11. doi: 10.3389/fpubh.2023.1301492

28. Kong X, Dai X, Ma L, Wang J, Sun Y, Jiang L. COVID-19 vaccine uptake, hesitancy and clinical effects on patients with Takayasu's arteritis: A web-based questionnaire survey from a large cohort. *Front Immunol*. (2023) 14. doi: 10.3389/fimmu.2023.1030810

29. Baier E, Olgemöller U, Biggemann L, Buck C, Tampe B. Dual-positive MPO- and PR3-ANCA-associated vasculitis following SARS-CoV-2 mRNA booster vaccination: A case report and systematic review. *Vaccines (Basel)*. (2022) 10:653.

30. Miskovic R, Radovic S, Arandjelovic S, Plavsic A, Reljic V, Peric J, et al. Onset of leukocytoclastic vasculitis following covid-19 vaccination: case based comprehensive review. *Rheumatol Int*. (2024) 44:2621–35. doi: 10.1007/s00296-024-05718-x

31. Sanker V, Mylavarapu M, Gupta P, Syed N, Shah M, Dondapati VVK. Post COVID-19 vaccination medium vessel vasculitis: a systematic review of case reports. *Infection*. (2024) 52:1207–13. doi: 10.1007/s15010-024-02217-w

32. Mettler C, Terrier B, Treluyer JM, Chouchana L. Risk of systemic vasculitis following mRNA COVID-19 vaccination: a pharmacovigilance study. *Rheumatology*. (2022) 61:e363–5. doi: 10.1093/rheumatology/keac323/6596033

33. Jarrot PA, Mirouse A, Ottaviani S, Cadiou S, Salmon JH, Liozon E, et al. Polymyalgia rheumatica and giant cell arteritis following COVID-19 vaccination: Results from a nationwide survey. *Hum Vaccin Immunother*. (2024) 20:2334084. doi: 10.1080/21645515.2024.2334084

34. Ramdani Y, Largeau B, Jonville-Bera AP, Maillot F, Audemard-Verger A. COVID-19 vaccination as a trigger of IgA vasculitis: A global pharmacovigilance study. *J Rheumatol*. (2023) 50:564–7. doi: 10.3899/jrheum.220629

35. MaChado PM, Lawson-Tovey S, Strangfeld A, Mateus EF, Hyrich KL, Gossec L, et al. Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry. *Ann Rheum Dis*. (2022) 81:695–709. doi: 10.1136/annrheumdis-2021-221490

36. Mageau A, Ferré VM, Goulenok T, Charpentier C, Delory N, Francois C, et al. Severely impaired humoral response against SARS-CoV-2 variants of concern following two doses of BNT162b2 vaccine in patients with systemic lupus erythematosus (SLE). *Ann Rheumatic Dis*. (2022) 81:1194–6. doi: 10.1136/annrheumdis-2022-222498

37. Krasselt M, Wagner U, Nguyen P, Pietsch C, Boldt A, Baerwald C, et al. Humoral and cellular response to COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases under real-life conditions. *Rheumatology*. (2022) 61:SI180–8. doi: 10.1093/rheumatology/keac089

38. Tang W, Gartshteyn Y, Ricker E, Inzerillo S, Murray S, Khalili L, et al. The use of COVID-19 vaccines in patients with SLE. *Curr Rheumatol Rep*. (2021) 23:79. doi: 10.1007/s11926-021-01046-2

39. Sieiro Santos C, Calleja Antolin S, Moriano Morales C, Garcia Herrero J, Diez Alvarez E, Ramos Ortega F, et al. Immune responses to mRNA vaccines against SARS-CoV-2 in patients with immune-mediated inflammatory rheumatic diseases. *RMD Open*. (2022) 8:e001898. doi: 10.1136/lupus-2022-elm2022.188

40. Cruz VA, Guimarães C, Rêgo J, MaChado KLLL, Miyamoto ST, Burian APN, et al. Safety of CoronaVac and ChAdOx1 vaccines against SARS-CoV-2 in patients

with rheumatoid arthritis: data from the Brazilian multicentric study safer. *Adv Rheumatol*. (2024) 64:1–8. doi: 10.1186/s42358-024-00397-5

41. Calderaro DC, Valim V, Ferreira GA, MaChado KLLL, Ribeiro PDC, Ribeiro SLE, et al. Predictors of hospitalization in breakthrough COVID-19 among fully vaccinated individuals with immune-mediated rheumatic diseases: data from SAFER-study. *Vaccines*. (2024) 12:1031.

42. MaChado KLLL, Burian APN, Martins-Filho OA, Mill JG, Ferreira LB, Tapia KRL, et al. Immunogenicity and safety according to immunosuppressive drugs and different COVID-19 vaccine platforms in immune-mediated disease: data from SAFER cohort. *Vaccines*. (2024) 12:1367.

43. Sartori NS, MaChado KLLL, Miyamoto ST, Pretti FZ, Gouveia M da PG, de Oliveira YGP, et al. Immunogenicity of SARS-CoV-2 vaccination schedules including a booster dose in patients with systemic lupus erythematosus: data from a prospective multicenter study. *Vaccines (Basel)*. (2025) 13:127. doi: 10.3390/vaccines13020127

44. Teles C, Borges A, Magalhães A, Barra C, Silva I, Tomé P, et al. Effectiveness and immunogenicity of SARS-CoV-2 booster vaccine in immunosuppressed systemic autoimmune disease patients: A prospective study. *Med Clin (Barc)*. (2025) 164:106920. doi: 10.1016/j.medcli.2025.106920

45. Speer C, Töllner M, Benning L, Klein K, Bartenschlager M, Nusshag C, et al. Third COVID-19 vaccine dose with BNT162b2 in patients with ANCA-associated vasculitis. *Ann rheumatic Dis*. (2022) 81:593–5.

46. Kant S, Azar A, Geetha D. Antibody response to COVID-19 booster vaccine in rituximab-treated patients with anti–neutrophil cytoplasmic antibody–associated vasculitis. *Kidney Int*. (2022) 101:414–5. doi: 10.1016/j.kint.2021.11.012

47. Pereira RMR, Dagostin MA, Caparbo VF, Sales LP, Pasoto SG, Silva CA, et al. Anti-SARS-CoV-2 inactivated vaccine in patients with ANCA-associated vasculitis: Immunogenicity, safety, antibody decay and the booster dose. *Clinics*. (2023) 78:100150. doi: 10.1016/j.clinsp.2022.100150

48. Egri N, Calderón H, Martinez R, Vazquez M, Gómez-Caverzaschi V, Pascal M, et al. Cellular and humoral responses after second and third SARS-CoV-2 vaccinations in patients with autoimmune diseases treated with rituximab: specific T cell immunity remains longer and plays a protective role against SARS-CoV-2 reinfections. *Front Immunol*. (2023) 14. doi: 10.3389/fimmu.2023.1146841

49. Marty PK, Van Keulen VP, Erskine CL, Shah M, Hummel A, Stachowitz M, et al. Antigen specific humoral and cellular immunity following SARS-CoV-2 vaccination in ANCA-associated vasculitis patients receiving B-cell depleting therapy. *Front Immunol*. (2022) 13. doi: 10.3389/fimmu.2022.834981

50. Carruthers JE, Wells J, Gupta A, Kallon D, Cox A, Pina N, et al. Response to vaccination against SARS-CoV-2 in patients with antineutrophil cytoplasmic antibody-associated vasculitis with renal involvement. *Front Med (Lausanne)*. (2022) 8. doi: 10.3389/fmed.2021.817845

51. Floyd L, Elsayed ME, Seibt T, von Bergwelt-Baildon A, Seo P, Antiochos B, et al. SARS-CoV-2 vaccine response in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis. *Kidney Int Rep*. (2022) 7:629–32. doi: 10.1016/j.ekir.2021.12.004

52. Furer V, Eviatar T, Zisman D, Peleg H, Paran D, Levartovsky D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: A multicentre study. *Ann Rheum Dis*. (2021) 80:1330–8. doi: 10.1136/annrheumdis-2021-220647

53. Ozdede A, Nohut OK, Atli Z, Tok YT, Guner S, Yilmaz E, et al. Higher antibody responses after mRNA-based vaccine compared to inactivated vaccine against SARS-CoV-2 in Behcet's syndrome. *Rheumatol Int*. (2022) 42:1741–50. doi: 10.1007/s00296-022-05164-7

54. Ozdede A, Guner S, Ozcifci G, Yurttas B, Toker Dincer Z, Atli Z, et al. Safety of SARS-CoV-2 vaccination in patients with Behcet's syndrome and familial Mediterranean fever: a cross-sectional comparative study on the effects of M-RNA based and inactivated vaccine. *Rheumatol Int*. (2022) 42:973–87. doi: 10.1007/s00296-022-05119-y

55. Apaydin H, Erden A, Güven SC, Armağan B, Konak HE, Polat B, et al. Effects of anti-SARS-CoV-2 vaccination on safety and disease exacerbation in patients with Behçet syndrome in a monocentric cohort. *Int J Rheum Dis*. (2022) 25:1068–77. doi: 10.1111/1756-185X.14387

56. Monti S, Fornara C, Delvino P, Bartoletti A, Bergami F, Comolli G, et al. Immunosuppressive treatments selectively affect the humoral and cellular response to SARS-CoV-2 in vaccinated patients with vasculitis. *Rheumatol (Oxford)*. (2023) 62:726–34. doi: 10.1093/rheumatology/keac365

57. Delvino P, Bozzalla-Cassione E, Biglia A, Quadrelli VS, Bartoletti A, Montecucco C, et al. Safety of BNT162b2 mRNA COVID-19 vaccine in a cohort of elderly, immunocompromised patients with systemic vasculitis. *Clin Exp Rheumatol*. (2022) 40:853. doi: 10.55563/clinexprheumatol/xj2pqk

58. Bartoletti A, Fornara C, Delvino P, Franchi G, Ferrari A, Baldanti FP, et al. Humoral and T-cell immune response following three doses of SARS-CoV-2 mRNA vaccine in giant cell arteritis: analysis of a prospective cohort. *Clin Exp Rheumatol*. (2024) 42:942. doi: 10.55563/clinexprheumatol/mlatyf

59. van Sleen Y, van der Geest KSM, Buisman AM, Sandovici M, van Baarle D, Brouwer E. Humoral SARS-CoV-2 vaccine responses in patients with giant cell arteritis and polymyalgia rheumatica: decay after primary vaccination and effects of the booster. *Arthritis Care Res (Hoboken)*. (2024) 76:105–10. doi: 10.1002/acr.25173

60. Karakaş A, Yüce İnel T, Önen F, Sari İ. The effect of COVID-19 pandemic in a large series of patients with Takayasu arteritis. *Turk J Med Sci*. (2022) 52:565–70. doi: 10.55730/1300-0144.5347

61. Visentini M, Gragnani L, Santini SA, Urraro T, Villa A, Monti M, et al. Flares of mixed cryoglobulinaemia vasculitis after vaccination against SARS-CoV-2. *Ann rheumatic Dis*. (2022) 81:441–3. doi: 10.1136/annrheumdis-2021-221248

62. Vacchi C, Testoni S, Visentini M, Zani R, Lauletta G, Gragnani L, et al. COVID-19 vaccination rate and safety profile in a multicentre Italian population affected by mixed cryoglobulinaemic vasculitis. *Clin Exp Rheumatol*. (2023) 41:787–91. doi: 10.55563/clinexprheumatol/ldv88a

63. Zan J, Ma J, Man Q, Liu X, Yu D, Zhang Y, et al. Safety evaluation of COVID-19 vaccine in patients with IgA nephropathy or IgA vasculitis nephritis. *Kidney Int Rep*. (2022) 7:1435–6. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8977377/.

64. Turner D, Luxton G, Yong K, Sammel A. The impact of coronavirus-19 vaccination on anti-nuclear cytoplasmic antibody vasculitis hospitalisations in a Sydney health network. *Intern Med J*. (2024) 54:483–7. doi: 10.1111/imj.16343

65. Bakasis AD, Mavragani CP, Voulgari PV, Gerolymatou N, Argyropoulou OD, Vlachoyiannopoulos PG, et al. COVID-19: Clinical features and outcomes in unvaccinated 2-dose and 3-dose vaccinated against SARS-CoV-2 patients with systemic autoimmune and autoinflammatory rheumatic diseases. *J Autoimmun*. (2022) 131:102846. doi: 10.1016/j.jaut.2022.102846

66. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American College of Rheumatology 1990 criteria for the classification of takayasu arteritis. *Arthritis Rheum*. (2010) 33:1129–34. doi: 10.1002/art.1780330811

67. International Study Group for Behçet's Disease. Criteria for diagnosis of Behcet's disease. *Lancet*. (1990) 335:1078–80.

68. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. (2013) 65:1–11. doi: 10.1002/art.37715

69. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis*. (2007) 66:222–7. doi: 10.1136/ard.2006.054593

70. Quartuccio L, Isola M, Corazza L, Ramos-Casals M, Retamozo S, Ragab GM, et al. Validation of the classification criteria for cryoglobulinaemic vasculitis. *Rheumatology*. (2014) 53:2209–13. doi: 10.1093/rheumatology/keu271

71. Mills JA, Michel BA, Bloch DA, Calabrese LH, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of henoch-schönlein purpura. *Arthritis Rheum*. (2010) 33:1114–21. doi: 10.1002/art.1780330809

72. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum*. (2010) 33:1122–8. doi: 10.1002/art.1780330810

73. Shionoya S. Diagnostic criteria of Buerger's disease. *Int J Cardiol*. (1998) 66 Suppl 1:S243–5. doi: 10.1016/S0167-5273(98)00175-2

74. Calabrese LH, Mallek JA. Primary angiitis of the central nervous system: Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Med (United States)*. (1988) 67:20–39. doi: 10.1097/00005792-198801000-00002

75. Pileggi GS, Da Mota LMH, Kakehasi AM, De Souza AW, Rocha A, de Melo AKG, et al. Brazilian recommendations on the safety and effectiveness of the yellow fever vaccination in patients with chronic immune-mediated inflammatory diseases. *Adv Rheumatol*. (2019) 59:17. doi: 10.1186/s42358-019-0056-x

76. Brenol CV, da Mota LMH, Cruz BA, Pileggi GS, Pereira IA, Rezende LS, et al. Consenso 2012 da Sociedade Brasileira de Reumatologia sobre vacinação em pacientes com artrite reumatoide. *Rev Bras Reumatol*. (2013) 53:13–23.

77. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients with novel coronavirus disease 2019. *Clin Infect Dis*. (2020) 71:2027–34. doi: 10.1093/cid/ciaa344

78. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham vasculitis activity score (version 3). *Ann Rheum Dis*. (2009) 68:1827–32. doi: 10.1136/ard.2008.101279

79. Neves F de S, Caldas CAM, de Medeiros DM, de Moraes JCB, Gonçalves CR. Adaptação transcultural da versão simplificada (s) do Behçet's Disease Current Activity Form (BDCAF) e compara¸tiao do desempenho das versões Brasileiras dos dois instrumentos de avaliação da atividade da Doença de Behçet: BR-BDCAF e BR-BDCAF(s). *Rev Bras Reumatol*. (2009) 49:20–31. doi: 10.1590/S0482-50042009000100003

80. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. *Ann Intern Med*. (1994) 120:919–29. doi: 10.7326/0003-4819-120-11-199406010-00004

81. Assawasaksakul T, Lertussavavivat T, Sathitratanacheewin S, Oudomying N, Vichaiwattana P, Wanlapakorn N, et al. Comparison of immunogenicity and safety of inactivated, adenovirus-vectored, and heterologous adenovirus-vectored/mRNA vaccines in patients with systemic lupus erythematosus and rheumatoid arthritis: A prospective cohort study. *Vaccines (Basel)*. (2022) 10:853. doi: 10.3390/vaccines10060853

82. Herring MK, Romine JK, Wesley MG, Ellingson KD, Yoon SK, Caban-Martinez AJ, et al. Severe acute respiratory syndrome coronavirus 2 infection history and

antibody response to 3 Coronavirus disease 2019 messenger RNA vaccine doses. *Clin Infect Dis*. (2023) 76:1822–31. doi: 10.1093/cid/ciac976

83. García-Pérez J, Bermejo M, Ramírez-García A, de la Torre-Tarazona HE, Cascajero A, Castillo de la Osa M, et al. Longer intervals between SARS-CoV-2 infection and mRNA-1273 doses improve the neutralization of different variants of concern. *J Med Virol*. (2023) 95:e28679. doi: 10.1002/jmv.28679

84. Frodlund M, Nived P, Chatzidionysiou K, Södergren A, Klingberg E, Hansson M, et al. The serological immunogenicity of the third and fourth doses of COVID-19 vaccine in patients with inflammatory rheumatic diseases on different biologic or targeted DMARDs: a Swedish nationwide study (COVID-19-REUMA). *Microbiol Spectr*. (2024) 12:e0298123. doi: 10.1128/spectrum.02981-23

85. Chu C, Schönbrunn A, Fischer D, Liu Y, Hocher JG, Weinerth J, et al. Immune response of heterologous versus homologous prime-boost regimens with adenoviral vectored and mRNA COVID-19 vaccines in immunocompromised patients. *Front Immunol*. (2023) 14. doi: 10.3389/fimmu.2023.1187880

86. Honfi D, Gémes N, Szabó E, Neuperger P, Balog J, Nagy LI, et al. Comparison of homologous and heterologous booster SARS-CoV-2 vaccination in autoimmune rheumatic and musculoskeletal patients. *Int J Mol Sci*. (2022) 23:11411. doi: 10.3390/ijms231911411

87. Nangsue C, Srisurapanont K, Sudjaritruk T. A Comparison of the Immunogenicity and Safety of an Additional Heterologous versus Homologous COVID-19 Vaccination among Non-Seroconverted Immunocompromised Patients after a Two-Dose Primary Series of mRNA Vaccination: A Systematic Review and Meta-Analysis. *Vaccines (Basel)*. (2024) 12:468. doi: 10.3390/vaccines12050468

88. Gallardo-Nelson MJ, Cruces M, Gómez YM, Fuenzalida C, Silva J, Aravena-Traipi L, et al. 4th booster-dose SARS-CoV-2 heterologous and homologous vaccination in rheumatological patients. *Front Immunol*. (2024) 15. doi: 10.3389/fimmu.2024.1427501

89. Isnardi CA, Alpizar-Rodriguez D, Calderaro DC, Marques CDL, Pons-Estel GJ, Xavier RM, et al. Factors associated with mortality in patients with immune-mediated rheumatic diseases and COVID-19 from Latin America: data from Argentina, Mexico, and Brazil. *J Clin Rheumatol*. (2024) 30:E9–17. doi: 10.1097/RHU.0000000000002038

90. Liew J, GianFrancesco M, Harrison C, Izadi Z, Rush S, Lawson-Tovey S, et al. SARS-CoV-2 breakthrough infections among vaccinated individuals with rheumatic disease: results from the COVID-19 Global Rheumatology Alliance provider registry. *RMD Open*. (2022) 8:e002187.

91. Araujo CSR, Medeiros-Ribeiro AC, Saad CGS, Bonfiglioli KR, Domiciano DS, Shimabuco AY, et al. Two-week methotrexate discontinuation in patients with rheumatoid arthritis vaccinated with inactivated SARS-CoV-2 vaccine: a randomised clinical trial. *Ann Rheum Dis*. (2022) 81:889–97. doi: 10.1136/annrheumdis-2021-221916

92. Medeiros-Ribeiro AC, Bonfiglioli KR, Domiciano DS, Shimabuco AY, Da Silva HC, Saad CGS, et al. Distinct impact of DMARD combination and monotherapy in immunogenicity of an inactivated SARS-CoV-2 vaccine in rheumatoid arthritis. *Ann Rheum Dis*. (2022) 81:710–9. doi: 10.1136/annrheumdis-2021-221735

93. De Santis M, Motta F, Isailovic N, Clementi M, Criscuolo E, Clementi N, et al. Dose-dependent impairment of the immune response to the moderna-1273 mRNA vaccine by mycophenolate mofetil in patients with rheumatic and autoimmune liver diseases. *Vaccines (Basel)*. (2022) 10:801. doi: 10.3390/vaccines10050801

94. Kashiwado Y, Kimoto Y, Ohshima S, Sawabe T, Irino K, Nakano S, et al. Immunosuppressive therapy and humoral response to third mRNA COVID-19 vaccination with a six-month interval in rheumatic disease patients. *Rheumatol (Oxford)*. (2024) 63:725–33. doi: 10.1093/rheumatology/kead275

95. Furer V, Eviatar T, Zisman D, Peleg H, Braun-Moscovici Y, Balbir-Gurman A, et al. Predictors of immunogenic response to the BNT162b2 mRNA COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases treated with rituximab. *Vaccines (Basel)*. (2022) 10:901.

96. Ferri C, Ursini F, Gragnani L, Raimondo V, Giuggioli D, Foti R, et al. Impaired immunogenicity to COVID-19 vaccines in autoimmune systemic diseases. High prevalence of non-response in different patients' subgroups. *J Autoimmun*. (2021) 125:102744. doi: 10.1016/j.jaut.2021.102744

97. Jena A, Mishra S, Deepak P, Kumar-M P, Sharma A, Patel YI, et al. Response to SARS-CoV-2 vaccination in immune mediated inflammatory diseases: Systematic review and meta-analysis. *Autoimmun Rev*. (2022) 21:102927. doi: 10.1016/j.autrev.2021.102927

98. Braun-Moscovici Y, Kaplan M, Braun M, Markovits D, Giryes S, Toledano K, et al. Disease activity and humoral response in patients with inflammatory rheumatic diseases after two doses of the Pfizer mRNA vaccine against SARS-CoV-2. *Ann Rheum Dis*. (2021) 80:1317–21. doi: 10.1136/annrheumdis-2021-220503

99. Tomelleri A, Sartorelli S, Campochiaro C, Baldissera EM, Dagna L. Impact of COVID-19 pandemic on patients with large-vessel vasculitis in Italy: a monocentric survey. *Ann Rheum Dis*. (2020) 79:1252–3. doi: 10.1136/annrheumdis-2020-217600

100. Comarmond C, Leclercq M, Leroux G, Marques C, Le Joncour A, Domont F, et al. Correspondence on 'Impact of COVID-19 pandemic on patients with large-vessels vasculitis in Italy: a monocentric survey.'. *Ann Rheum Dis*. (2023) 82:e30–0.

101. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American college of rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 3. *Arthritis Rheumatol*. (2021) 73:e60–75.

102. Simoncelli E, Conticini E, ColaFrancesco S, Gattamelata A, Spinelli FR, Garufi C, et al. Multicentre case-control study evaluating the safety of anti-SARS-CoV-2 vaccines in a cohort of patients with systemic vasculitis. *Clin Exp Rheumatol*. (2023) 41:922–7. doi: 10.55563/clinexprheumatol/if8nka

103. Valim V, MaChado KLLL, Miyamoto ST, Pinto AD, Rocha PCM, Serrano EV, et al. Planned yellow fever primary vaccination is safe and immunogenic in patients with autoimmune diseases: A prospective non-interventional study. *Front Immunol*. (2020) 11. doi: 10.3389/fimmu.2020.01382

Frontiers in Immunology

Explores novel approaches and diagnoses to treat immune disorders.

The official journal of the International Union of Immunological Societies (IUIS) and the most cited in its field, leading the way for research across basic, translational and clinical immunology.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact