Review

Systemic vasculitis: one year in review 2024

E. Treppo[1], S. Monti[2,3], P. Delvino[4,5], C. Marvisi[6], C. Ricordi[6], G. La Rocca[7], M. Moretti[7], N. Italiano[7], F. Di Cianni[7], F. Ferro[7], F. Muratore[6], C. Baldini[7], R. Talarico[7], L. Quartuccio[1], C. Salvarani[6]

[1]*Clinic of Rheumatology, Department of Medicine, University of Udine, Hospital Santa Maria della Misericordia, Udine;*
[2]*Department of Internal Medicine and Therapeutics, University of Pavia;*
[3]*Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia;*
[4]*School of Medicine, University of Milano Bicocca, Milan;*
[5]*IRCCS San Gerardo dei Tintori Foundation, Monza;*
[6]*Rheumatology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, and Università di Modena e Reggio Emilia, Modena;*
[7]*Rheumatology Unit, Azienda Ospedaliero-Universitaria Pisana, University of Pisa, Italy.*

Elena Treppo, MD
Sara Monti, MD
Paolo Delvino, MD
Chiara Marvisi, MD
Caterina Ricordi, MD
Gaetano La Rocca, MD
Michele Moretti, MD
Nazzareno Italiano, MD
Federica Di Cianni, MD
Francesco Ferro, MD
Francesco Muratore, MD
Chiara Baldini, MD, PhD
Rosaria Talarico, MD, PhD
Luca Quartuccio, MD, PhD
Carlo Salvarani, MD

Please address correspondence to:
Elena Treppo
Clinica di Reumatologia,
Dipartimento di Medicina,
Università di Udine,
Piazz.le S. Maria della Misericordia 15,
33100 Udine, Italy.
E-mail: elena.treppo@uniud.it

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ABSTRACT

Systemic vasculitides comprise a collection of rare and heterogeneous disorders capable of impacting any organ and system, posing a considerable burden of mortality and comorbidity. As with previous annual reviews of this series, this review will offer a critical overview of the latest literature on pathogenesis, biomarkers, and treatment options in both small- and large-vessel vasculitis.

Introduction

Systemic vasculitides encompass a group of rare, chronic, and multifaceted disorders characterised by inflammation of blood vessels, with the potential to affect any organ and system. These conditions can be life-threatening and frequently impose a substantial burden of disease, profoundly influencing patients' long-term outcomes and quality of life.

As in the previous annual reviews of this series (1, 2), we selected the most relevant articles published in 2023 on this topic. We performed a Medline search of English language articles published in the PubMed database from 1st January 2023 to 31st December 2023. The following key words formed the data sources: vasculitis, giant cell arteritis (GCA), Takayasu's arteritis (TAK), antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV), microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and cryoglobulinemic vasculitis (CV).

New insight into large-vessel vasculitis

Imaging update and clinical advances

One of the major novelties of the past year is the publication of the update on the EULAR recommendations on the use of imaging in large-vessel vasculitis (LVV) in clinical practice (3), supported by a systematic literature review and meta-analysis (4). Ultrasound is now proposed as the first and main imaging modality to be used for the diagnosis of GCA. Moreover, data on the role of imaging for the monitoring of the disease are emerging, and a new provisional OMERACT ultrasonographic score, the OGUS score, has been developed (5). The score has shown sensitivity to change and a correlation with markers of disease activity (6). The use of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) for the imaging of cranial arteries has achieved increasing interest in the past year. Thibault *et al*. reported on the use of this technique as a useful modality to assess both cranial and extra-cranial arteries with a limited increase in examination time (sensitivity 73%; specificity 97%) (7). An innovative approach has combined the use of FDG-PET with magnetic resonance (MR) or computed tomography (CT) angiography to assess the progression of disease in large-vessel vasculitis. The damage progression (over a period of 1.6 years follow-up) was infrequent (1% of the cohort), while baseline FDG-PET activity was the strongest predictor associated with subsequent angiographic change (8). Seitz *et al*. investigated the diagnostic performance of diffusion-weighted imaging (DWI) in comparison with black-blood MR(9). DWI showed a sensitivity of 75.9%, a specificity of 94.2% (9). Orbital MR imaging of patients with visual symptoms revealed the presence of enhancement of the optic nerve sheath (53%), intraconal fat (25%), and optic nerve/chiasm (14%). Notably, 38% of patients with unilateral visual loss displayed MR changes in the contralateral eye (10). Additionally, the EULAR working group recom-

mends early imaging test for patients with polymyalgia rheumatica (PMR) suspected of having LLV. González-Gay *et al*. have proposed red flags to help identify LLV suspicion in isolated PMR patients (11). During the past year, one of the largest observational cohorts ever collected, describing data on over 1000 patients with GCA, was published by the Italian Society of Rheumatology vasculitis study group. The impact of age at diagnosis was assessed demonstrating its impact on a number of clinical outcomes, including the increased risk for ischaemic complications, aneurysms formation, and development of serious infections (12). Criteria to assess response to treatment in GCA are underway. To inform the process, a recent systematic literature review analysed the definitions used across randomised controlled trials (RCTs) and observational studies concluding that definitions of response to treatment are scant and heterogeneous. Remission (often combining clinical and laboratory definitions) and relapses were the most frequent treatment outcomes (13). To further improve the assessment of the multidimensional impact of GCA, dedicated patient reported outcomes (GCA-PROMs) are being tested (14). A number of studies have been testing the real-world performance of the new 2022 ACR/EULAR classification criteria for GCA confirming their improved sensitivity compared to the previous criteria (15-17).

Similarly to GCA, recent EULAR recommendations have also addressed the role of imaging in TAK (3). In the light of the absence of new prospective data concerning the use of imaging in the management of TAK, no substantial changes were applied to the previous 2018 recommendations. Avoiding the use of radiation, MR imaging has been confirmed as first imaging modality to detect parietal inflammation and/or luminal abnormalities in the diagnostic process of suspected-TAK patients. FDG-PET, CT or ultrasound may be considered as alternative diagnostic approaches, the latter being of limited value for evaluating the thoracic aorta. Conventional angiography is not recommended for the diagnosis of TAK and should be considered only for endovascular procedures. Since unanimous consensus on the definition of disease activity is lacking, clinical assessment and the differentiation between active disease and chronic damage represents a major challenge in the management of TAK. In a recent study, Marvisi *et al*. proposed a novel type of disease-specific activity index, the Takayasu's Arteritis Integrated Disease Index (TAIDAI), whose peculiarity is to reflect, through a hierarchical approach, the intricate correlation between clinical manifestations, imaging, and laboratory findings (sensitivity 96.3%; specificity 79.2%) (18). Furthermore, TAIDAI significantly correlated with physician and patient global assessment, PET Vascular Activity Score (PETVAS), and inflammatory markers. Monitoring the long-term course of LVV through a multi-modal approach may represent a promising modality to predict vascular progression over time. In a recent prospective, observational study including 50 patients with GCA and 76 patients with TAK, PET signs of active inflammation documented by the PETVAS score were identified in 66% and 50% of patients enrolled in years 2-5 and >5 years after diagnosis, respectively. Divergent patterns of vascular PET activity were observed between GCA and TAK, with higher PETVAS score reported in GCA compared to TAK in both the earlier and later phases of the disease (0-1 year: 22 *vs*. 17; p=0.004; 2-5 years: 21 *vs*. 15, p<0.0001; >5 years: 18 *vs*. 14; p<0.005). PETVAS score significantly decreased throughout the disease course in GCA but not in TAK (19). Additionally, a decrease FDG uptake of the vessel walls could be spuriously associated by the use of statin therapy, suggesting a potential protective role on vascular inflammation (20). At present, there are no established classification or diagnostic criteria for clinically isolated aortitis (CIA). It remains uncertain whether the treatment approach for CIA should differ from that of patients with GCA or TAK. The demographic profile of patients, primarily comprising white females over 70, suggests that CIA might represent a smoldering or limited phenotype of GCA (21).

Biomarkers and implications in thepathogenesis

Specific diagnostic, prognostic, and monitoring biomarkers other than C-reactive protein (CRP) are still lacking for GCA. Last year, an Italian study conducted last year identified that polymorphism in the CRP gene, specifically rs1205 and rs3093068, exert an influence on GCA susceptibility and its outcomes (22). Specifically, carriers of the allele T of rs1205 genotype exhibited a shorter glucocorticoid (GC) treatment duration, lower cumulative GC dose, and higher prevalence of long-term remission (22). Conversely, carriers of the allele C of rs3093068 genotype displayed significantly higher CRP at diagnosis (22). Moreover, the IL6-174 G/C and interferon gamma polymorphisms were found to have no impact on the phenotypic expression of GCA (cranial or extra-cranial manifestations) (23, 24). Results from the clinical trial GUSTO (NCT03745586) have reported, for the first time, data on untreated patients naive to GC (25). The trial identified IL-6 independent biomarkers (CCL7, CXCL9 and MMP12) that reflect disease activity despite CRP normalisation (25). Whole transcriptome analysis was performed to assess an *in situ* spatial profiling of molecules involved in temporal artery biopsies (TABs) of patients with GCA. Over 12000 genes were found to be upregulated in the arteries, with differential expression according to different arterial layers. Interestingly, the immune-related functions and vascular remodeling were limited to the intima and media (26). A genetic approach was also used to estimate the proportion of misdiagnosis in patients with a clinically confirmed diagnosis of GCA, not supported by TAB or imaging. Through HLA genotyping from 663 patients with GCA, the authors estimated that around two-thirds of TAB-negative cases and one-third of cases without TAB results may have been overdiagnosed, re-defining the sensitivity of TAB up to 88% (27). Metabolomic studies revealed that distinct profiles can be identified between activity and remission in patients with GCA. In more detail, N-acetylglycoproteins and cholines of bound phospholipids, could serve as predictive

markers of disease activity. Moreover, metabolic fingerprinting could be applied to discriminate between GCA and PMR (28). Despite the lack of recognised disease-specific autoantibodies in GCA, a relevant role for B-cells has been demonstrated in the pathogenesis of the disease. According to the study from Graver *et al*., B-cells produce cytokines (*e.g*. IL-6, IL-1β, TNF-α, IL-23, YKL-40 and MMP-9) that are able to steer macrophages towards a pro-inflammatory phenotype; this effect would be reverted once remission is achieved (29). Extrusion of mitochondria can also occur in the context of platelet activation and neutrophil cell death and can be immunogenic and inflammatory. Plasma from GCA patients was demonstrated to promote increased mitochondrial-mediated cytokine production, platelet activation and reduced clearance contributing to disease activity and inflammation (30).

Similarly, while the T cell-mediated immune response has long been recognised as a central player in the immunopathogenesis of TAK, recent evidence shed light on the potential contribution of B-cells and humoral response. In a recent retrospective Chinese study, both median peripheral CD3-CD19+ B-cells and mean immunoglobulins G (IgG) were significantly higher when comparing patients with TAK with healthy controls (31). Patients with active TAK had higher mean serum IgG levels compared to those in clinical remission. Immunosuppressive treatment induced a statistically significant reduction of serum IgG levels, with a positive correlation between serum IgG and both inflammatory markers and disease activity clinimetric indexes, before and after immunosuppressive treatment (31). Preventing the establishment and progression of arterial fibrosis is a relevant unmet need in TAK. The potential role of glycoprotein non-metastatic melanoma protein B (GPNMB) in sustaining TAK-related vascular fibrosis was recently assessed by Dai *et al*. (32). Macrophage-derived GPNMB, via binding with integrin αVβ1, has been shown to play a primary role in promoting the expression of extracellular matrix in the adventitial fibroblasts (32).

GCA/TAK treatment update

Following the publication of GiACTA trial, tocilizumab (TCZ) has emerged as the primary choice for immunosuppressive therapy in GCA patients, being the only drug approved for this condition. Increasing real-world data support its use in patients with severe or refractory disease or those at increased risk of GC-related adverse effects. In a study by Matza *et al*., TCZ therapy led to long-term remission and allowed for GC discontinuation in most patients, while maintaining a satisfactory safety profile (33). As the efficacy of TCZ has been well-established, recent literature has predominantly focused on determining the optimal duration of immunosuppressive and steroid therapy after achieving complete disease remission and subsequent tapering strategies, which remain an unmet need (34). A North American study by Samec *et al*. followed a large cohort of GCA patients treated with TCZ for an extended period and observed a relapse rate exceeding 50% after abrupt discontinuation following a median treatment duration of 16.8 months (35). An Italian group implemented a tapering regimen involving weekly TCZ for the first 12 months after diagnosis, followed by every-other-week administration for additional 12 months before discontinuation (36). During the 6-month follow-up after withdrawal, they observed a relapse rate of 26% (36). Given the high relapse rates associated with early TCZ discontinuation, the GCA Spanish Collaborative Group proposed a tapering algorithm based on a multicentric real-life study (37). After achieving prolonged disease remission with TCZ treatment, the optimisation of drug administration involved reducing the dose or increasing the dosing interval in approximately half of the patients. The authors observed similar remission rates, frequency of relapses, and occurrence of serious adverse events between the optimised and non-optimised groups, with a lower proportion of serious infections and cumulative GC doses in the optimised group (37). In addition to TCZ, other biologic immunosuppressive drugs are being investigated for their potential application in GCA patients. Sarilumab advanced to phase 3 in a multicentre clinical trial that was prematurely terminated due to low enrolment during the COVID-19 pandemic (38). Although the limited available data showed a promising steroid-sparing effect of the 200 mg dosage and a good safety profile. Another GCA clinical trial conducted recently involved a phase 2 double-blind, placebo-controlled investigation on secukinumab (SEK) (39). The authors observed a 70% remission rate in the SEK group compared to 20% in placebo group, with no significant safety concerns (39). Regarding Janus kinase (JAK) inhibitors, an ongoing randomised phase 3 study of upadacitinib in GCA (ClinicalTrials.gov; NCT03725202) is currently in the recruitment stage (40). Additionally, results from a retrospective Swedish case series involving 15 GCA patients treated with baricitinib and tofacitinib are now available (41). These patients received JAK inhibitors for an average of 19 months, and no disease relapses were observed during drug administration. However, one patient experienced a GCA relapse one month after JAK inhibitor withdrawal, following a sustained remission lasting more than two years (41). In term of safety profile, one pulmonary embolism and two major infections were observed in patients with relevant prior risk factors (41).

In the past year, the first Pan American League of Associations for Rheumatology (PANLAR) guidelines for the treatment of TAK were published, emphasising the importance of evidence-based approaches in managing of this condition (42). Both TNF-I and TCZ may be considered for inducing and maintaining remission in TAK (43). According to ACR guidelines, TNF-I are preferred over TCZ in refractory TAK; in contrast, EULAR recommendations suggest that either TNF-I or TCZ could be used as treatment options in refractory TAK. A meta-analysis conducted by Kang *et al*. supported the favourable outcome of TCZ in refractory TAK patients, although only one RCT was included in the review (44). Another systematic review with meta-analysis found similar clinical responses, angiographic stabilisation, and safety profiles between TCZ and TNF-I based on observational

data (43, 45). The ACT-Bridge study assessed the safety and effectiveness of a 52-month course of subcutaneous TCZ therapy in a Japanese TAK cohort (46). Relapse was observed in 20% of patients, with disease duration of less than 2 years significantly associated with a lower relapse-free proportion. In 83% of relapse-free patients, the GC dose at the last follow-up was less than 10 mg/day, and adverse events were reported by 40% of patients (46). Another multicentre retrospective study observed complete remission in 70% of patients with TAK receiving TCZ for at least 3 months (47). The risk of relapse was significantly higher in patients on subcutaneous TCZ compared to intravenous TCZ, while safety profile was similar between the two groups (47). Moreover, the exploration of new therapeutic agents for TAK continues. The efficacy of SEK was compared to TNF-I in a prospective, open-label study involving 53 patients refractory to two immunosuppressive drugs (48). The SEK group achieved overall response at 6 months, and SEK effectiveness was comparable to TNF-I at 3, 6 and 48 months. In a real-world setting, the efficacy of csDMARDs in TAK patients was also evaluated. Results from an open-label RCT suggested that mycophenolate mofetil (MMF) might be superior to methotrexate (MTX) in terms of clinical and angiographic outcomes, despite the small size sample and short observation period (49).

Take home messages

- The 2023 EULAR recommendations provided an updated support for the use of imaging in LVV, strengthening the role of axillary ultrasound and FDG-PET in the diagnostic process of GCA and highlighting the value of combining different imaging modalities for monitoring disease activity and vascular abnormalities during follow-up (3).
- TAIDAI is a new promising disease-specific index aimed at incorporating different clinical, laboratory and imaging findings in patients with TAK (18).
- Given the high relapse rates associated with early TCZ discontinuation in GCA, optimising drug administration by reducing the dose or increasing the dosing interval may represent a viable strategy for managing GCA patients (33, 35-37).

New insights into cryoglobulinaemic vasculitis

Epidemiology and pathophysiology update

Cryoglobulinaemic vasculitis (CV) has historically been linked to hepatitis C virus (HCV). In a recent multicentric study including 450 treatment naïve chronic HCV patients, MC patients had lower levels of CD4+ and CD8+ compared to HCV patients without MC (50). It's understood that while some HCV-infected patients present cryoglobulins (CGs), but not all of them manifest symptoms. Conversely, some patients exhibit typical symptoms of mixed cryoglobulinaemia (MC) but do not have detectable CGs. It has been demonstrated that symptomatic patients without detectable cryoprecipitate exhibit similar serological parameters to patients with circulating type II CGs (51). Specifically, higher average levels of IgG1 and IgG3, k/λ ratio, IgM/IgG-rheumatoid factor (RF) have been observed in these patients compared to asymptomatic HCV-patients without CGs (51). Moreover, considering the short half-life of IgG3, this observation supports the hypothesis that the risk of clonal expansion is higher when CGs are formed by two IgG subclasses, namely IgG1 and IgG3. It is also well known that the detection of CGs in routine laboratory medicine is challenging, requiring strict pre-analytical conditions. As initial screening strategy for suspected cryoglobulinemia, Stoyanov and colleagues have demonstrated the effectiveness and high sensitivity of serum protein electrophoresis and RF analysis for detecting MC (52). Similarly, C4 has been shown to be the strongest predictor of cryoglobulinemia in a monocentric study cohort (53). According to C4 concentration and RF positivity/negativity, the accuracy of CHAID decision tree model for predicting cryoglobulinaemia was 82.9%. Specifically, the model accurately predicted the absence of CGs in patients with C4 value of >0.316g/L and in patients with C4 value between 0.150 and 0.326g/L who were negative for RF (53).

It is noteworthy that CGs remain detectable in a substantial proportion of HCV-cured patients and HCV-independent relapses of vasculitis can occur in concomitance with events such as infections or cancer. Recently, it has been demonstrated how the simultaneous engagement of BCR by autoantigen and of TLR9 by CpG drives the proliferation and differentiation of CD21low B cell clones, providing an explanation for the virus-independent survival of pathogenic CD21low B cell clones *in vivo* (54). Thus, in a healthy condition continual low-level stimulation by physiologic levels of ICs and of microbial or apoptosis-related nucleic acids may support survival of pathogenic B cell clones, whereas overproduction of these ligands may overactivated cells leading to clinical relapse.

MC can also be associated with autoimmune diseases, mainly Sjögren's syndrome (SS). In a retrospective multicentric study including systemic lupus erythematosus (SLE) patients with biopsy-proven CV, a higher prevalence of SSj was found compared with SLE patients without CV (55), highlighting the possibility of multiple causes of vasculitis.

Clinical features and treatment update

In terms of clinical features, cryoglobulinaemia may lead to life-threatening manifestation such as rapidly progressive glomerulonephritis (RPGN), gastrointestinal (GI), and cardiac involvement. In a Chinese cohort of HBV-related MC, renal involvement was observed at a higher rate compared to previously described Western cohorts (56). Kidney biopsies revealed that endocapillary proliferative GN was another typical pathology of HBV-related MC, in addition to the classic membranoproliferative GN (56). Furthermore, renal involvement and IgG CGs have been identified as independent poor prognostic factors of cryoglobulinaemia type I in a large multicentre study (57).

Quartuccio *et al*. published the evidence- and consensus-based recommendations of the Italian Study Group of Cryoglobulinaemia (GISC) on

rituximab (RTX) in MC (58). An RTX-based regimen is effective and safe for both severe and non-severe clinical manifestation of MC, and it appears to be successful in treating relapsing disease. RTX is equally effective in infectious and non-infectious CV, although caution is advised in HBV patients (56, 58). Refractory manifestations such as challenging ulcers and renal involvement can also improve through the use of double filtration plasmapheresis technique in combination with RTX (59). A case report documented the efficacy of the Bruton's tyrosine kinase (BTK) inhibitor, specifically Ibrutinib, in a refractory mixed essential cryoglobulinaemia that progressed into a Waldenström macroglobulinaemia (WM) (60). The BTK inhibitor achieved complete resolution of symptoms, despite the persistence of CGs/IgM paraprotein. Overall, managing monoclonal gammopathy and cryoglobulinaemia can present diagnostic and treatment challenges, particularly in case of uncommon manifestations (61, 62).

In general, patients with MC may be classified among "frail" populations with a high risk of disease exacerbation in the presence of triggering factors. A multicentre prospective survey study conducted in Italy, which included 430 MC patients, revealed that the cumulative prevalence of SARS-CoV-2 infection was higher among MC patients compared to the general Italian population (11.9% *vs*. 8%, $p<0.005$) (63). Similarly, although not statistically significant, the COVID-19-related death rate was higher in MC patients compared to general population (5.9% *vs*. 2.76%). Moreover, MC relapses following COVID-19 vaccination were observed in 5% of cases, with a significantly higher frequency noted in essential MC compared to HCV-related MC (63). However, the prevalence of MC relapses triggered by vaccination was significantly lower than that caused by COVID-19 infection (5% *vs*. 14%, $p=0.0285$) (63). After the first two doses of vaccine, no response was recorded in 24% of cases. The absence of detectable seroconversion was hampered by immunosuppressive treatment, *i.e.*, recent RTX therapy and GCs. Overall, data showed a good risk safety of anti-SARS-CoV-2 vaccine in systemic vasculitis (64).

Take home messages

- Despite challenges in routine detection, serum electrophoresis, RF analysis, and C4 concentration assessment offer predictive value for MC, even under suboptimal pre-analytical conditions (52).
- An RTX-based regimen is effective and safe for both severe and non-severe clinical manifestation of MC, and it appears to be successful in treating relapsing disease (58).
- Ibrutinib may be a therapeutical option in selected case of refractory mixed essential cryoglobulinaemia (60).

New insights into ANCA-associated vasculitis

Novel biomarkers and clinical features update

ANCAs, specifically proteinase-3 (PR-3) and myeloperoxidase (MPO), are widely recognised as the hallmark antigens in AAV. Recent reports have indicated the presence of additional antigens beyond PR3 and MPO that are associated with EGPA, expanding our understanding of the disease spectrum. In a study involving 73 EGPA patients, Arnold and colleagues discovered that 6.8% of patients exhibited positivity for Pentraxin 3 (PTX3) and 2.7% for olfactomedin 4 (OLM4) ANCA, alongside PR3 or MPO, further diversifying the antigenic profile in EGPA (65). Patients with PTX3-ANCA positivity had a higher prevalence of ENT, pulmonary, GI, and PNS involvement, but a lower prevalence of renal and CNS involvement compared to PTX3-ANCA negative patients. On the other hand, patients with OLM4-ANCA positivity had multiorgan involvement. Assessing disease activity in AAV patients traditionally relies on ANCA titers (66), though they lack sensitivity and specificity. Immune cell activation by ANCAs necessitates co-ligation of IgG's Fc and Fab fragments. Altered glycosylation of the Fc fragment may contribute to autoimmune conditions like AAV. Researchers investigated Fc glycosylation patterns, finding that relapsing PR3-ANCA patients had higher Fc-bisection at diagnosis and decreased Fc-sialylation before relapse. Moreover, PR3-ANCA patients experiencing ANCA rise and subsequent relapse showed lower IgG Fc-fucosylation levels 9 months before relapse, indicating Fc glycosylation patterns may offer more insight into disease activity than ANCA titers (67). Additionally, a model incorporating calprotectin, which indicates neutrophil activation and is highly expressed in neutrophil extracellular traps (NETs), along with CD163, has shown promise in identifying active disease(68). Conversely, serum soluble interleukin-7 receptor alpha (sIL-7Rα) levels showed an inverse correlation with Birmingham Vasculitis Activity Score (BVAS), erythrocyte sedimentation rate (ESR), and CRP (69). Divergent findings regarding complement levels have surfaced. While a prior investigation linked hypocomplementemia, indicative of alternative pathway activation, to diminished renal survival, a recent study examining sera samples from 74 MPA patients at disease onset discovered a contrasting result (70). This study identified high serum C4 levels as potential predictive biomarkers for end-stage renal disease (ESRD) in MPA patients. Additionally, multivariate analysis revealed both serum C4 and creatinine levels as independent risk factors for ESRD in MPA patients. Consequently, stratifying patients based on C4 levels could prove effective in assessing their risk of progressing to ESRD (70). Tao *et al*. recently expanded our understanding of NETosis in AAV, particularly in GN, by studying various genes associated with NETosis and constructing a NETosis Score through bioinformatic analysis (71). This score effectively distinguished between high and low-risk patients, with six NETosis-related genes identified as significantly correlated with renal disease (71). Additionally, a new molecule, cyclophilin D (CypD), has been discovered to regulate NETosis. CypD, found in the mitochondrial matrix, governs the production of reactive oxygen species (ROS) and metabolism. Studies on murine AAV models demonstrated that genetic deletion of CypD reduced organ damage (72).

Renal involvement remains a significant complication of AAV, with kidney biopsy as the gold standard for prognosis assessment (73, 74). ESRD is strong associated with histological findings (75). However, biopsy may not always be feasible or may carry risks. In a pilot study by Satrapova *et al*. urinary levels of five inflammation and kidney fibrosis biomarkers were collected from 45 AAV patients with renal involvement at biopsy (76). DKK-3 and PRO-C6 levels predicted renal fibrosis extent, peaking in the sclerotic class and lowest in the focal class, while C3M was higher in focal classes (76). These biomarkers correlated with renal function at follow-up; higher DKK-3 and PRO-C6 levels were associated with worse renal function, while higher C3M levels correlated with better function. Urinary CD163 levels were elevated in all cases of crescentic GN. Combining urinary biomarkers with serum creatinine distinguished biopsy classes with 92.5% accuracy (76). Furthermore, urinary levels of various T cell subpopulations have been examined alongside proteins like MCP-1, CD163, and CD25 to differentiate between active AAV and remission (77). Active renal AAV patients exhibited significantly elevated urinary T cell counts, particularly in crescentic GN, surpassing MCP-1 and sCD163 in indicating active disease (77). Higher Treg and Th17 levels correlated with treatment response, while increased Th17 and lacking Treg were associated with relapse within six months (77). These findings underscore the role of T cells in AAV-related renal damage and suggest potential benefits of IL17 blockade in identified patient subsets. The renal involvement in GPA and MPA was also correlated with serum concentrations of sTyro-3 and sAxl, that are members of receptor protein tyrosine kinases (78).

Lung involvement is another intriguing aspect that can precede, concur and follow a AAV diagnosis. In a recent study involving an Italian cohort, usual interstitial pneumonia (UIP) emerged as the prevailing pattern among p-ANCA patients (47.7%) (79). It often precedes the AAV diagnosis, and the prognosis is typically more influenced by interstitial lung disease (ILD) than vasculitis. Conversely, non-specific interstitial pneumonia (NSIP) was predominantly observed cases of c-ANCA positivity and ANCA negativity (79). It is frequently detected concurrently with diagnosis of AAV or in the course of the disease.

Recent research has also delved into genetics and proteomics in the context of AAV. While genetics significantly influences ANCA specificity (PR3 versus MPO), it may have differing impacts than clinical classification. A study involving 588 AAV patients revealed a robust link with the HLA-DPB1/DPA1 locus in both male and female patients with PR3-ANCA positive AAV (80). Conversely, for MPO-ANCA positive AAV, a significant difference was noted in association with the lead HLA-DQB1/HLA-DQA2 locus. This association was notably stronger in females compared to males, indicating potential sex-related differences in AAV susceptibility and genetic influences (80). In a study by Brick *et al*., analysing samples from 85 pre-symptomatic AAV patients, distinct cytokine profiles were observed in PR3-ANCA and MPO-ANCA subgroups (81). MPO-ANCA positivity strongly correlated with CSF-1, a cytokine affecting macrophage development, consistent with renal involvement in MPO-ANCA+ patients (81). TNFSF14, MCP-1, and CD244 were also identified, indicating T cell involvement in MPO-ANCA+ vasculitis. Conversely, PR3-ANCA positivity inversely correlated with CXCL5 and DNER, suggesting potential impairment in macrophage response in this subgroup (81). Additionally, proteomics analysis of kidney specimens from MPO-AAV patients revealed high expression of C5-C9 in glomeruli with fibrinoid necrosis foci, explaining the therapeutic benefit of anti-complement therapies in this subset (82).

GPA/MPA treatment update

In the last decade, RTX has progressively replaced cyclophosphamide (CYC) and azathioprine (AZA) as the anchor drug in remission induction and maintenance respectively (83). The RITAZER-EM trial demonstrated RTX superiority over AZA in remission maintenance also following induction treatment with RTX itself in relapsing AAV (84). However, the optimal RTX administration scheme is still debated. Interestingly, a recent ancillary study of the MAINRITSAN-II trial showed that low 3-months plasma RTX concentrations are an independent risk factor for relapses, suggesting the potential usefulness of serum RTX concentration measurement in clinical practice (85). Furthermore, Wallace *et al*. recently developed and validated a new simulation model to project outcomes of AAV remission maintenance treatment (86).

Following the results of the ADVOCATE trial, the C5a1R inhibitor avacopan is poised to revolutionise steroid-sparing strategies in GPA and MPA (87). Recent recommendations suggest considering avacopan alongside RTX or CYC for remission induction, aiming for rapid GC tapering within one month (87, 88). Furthermore, post-hoc analyses of the ADVOCATE trial highlighted a greater improvement of glomerular-filtration-rate (eGFR) in patients with baseline eGFR<20ml/min and in health-related quality of life respectively, in AAV patients in the avacopan arm compared to those in the GC arm of the trial (89, 90). In addition, in a retrospective study on AAV-related pulmonary-renal syndrome, low-dose GC pulses and rapid tapering proved effective in inducing remission in all cases (91). Moreover, a meta-analysis confirmed that low-dose GC regimens are associated with a lower risk of infections without compromising clinical efficacy (92).

Difficult-to-treat and refractory subsets of AAV, particularly localised and granulomatous forms, pose significant therapeutic challenges due to high resistance rates and frequent flares. A recent retrospective study found that patients with localised AAV were more often refractory to RTX induction therapy (93). Additionally, Moroni *et al*. demonstrated the effectiveness of either RTX or CYC in treating subglottic stenosis (SGS), resulting in longer relapse-free intervals after endoscopic dilation (94). FDG-PET has also shown to play a role in predicting progression to bronchial stenosis and response to treatment of endobronchial involvement in GPA (95). Furthermore, a nationwide French retrospective study on GPA identified

the presence of orbital mass as a risk factor for CYC induction failure in GPA (96). In a promising development, daratumumab, an anti-CD38 monoclonal antibody, induced remission in two severe cases of AAV refractory to RTX and CYC treatment, suggesting potential efficacy in future clinical trials (97).

EGPA treatment update

In recent years, the management of EGPA has evolved significantly due to the recognition of its high disease burden (98). In 2023, updated recommendations from EULAR refined EGPA management strategies (99). RTX was deemed a viable alternative to CYC in the induction regimen, particularly for patients with organ- or life-threatening manifestations. On the other hand, mepolizumab (MEPO) emerged as a preferred option for inducing remission in cases of relapsing or refractory EGPA without severe organ involvement, and it was also advocated for maintenance therapy (99). These recommendations find resonance in evidence-based guidelines which emphasise the role of GC monotherapy in managing non-severe EGPA cases (100).

The long-term efficacy and safety of MEPO 300 mg administered every 4 weeks in EGPA have been investigated. An interim analysis of the MARS study, a 96-week Japanese trial involving 118 patients who had been on MEPO treatment for at least 96 weeks, revealed promising findings (101). The median GC dose decreased significantly from 6.9 (prior to MEPO initiation) to 3.0 (at baseline) and further to 2.0 mg/day at weeks 45-48. Notably, the proportion of patients able to discontinue GCs increased from 8% to 32% and 38%, respectively. Only 5% of patients experienced EGPA relapse, and no drug-related adverse events were reported (101). Similar positive outcomes were reported by Masumoto and colleagues (102). A post hoc analysis of the MIRRA trial reaffirmed the efficacy of MEPO, even in the vasculitic phenotype of EGPA (103). The use of a low-dose MEPO regimen (100 mg monthly) remains a subject of debate in the literature, with recent studies shedding further light on this topic (104). However, there has been no interventional study to date directly comparing the efficacy of low-dose *versus* conventional-dose MEPO. Alternative biologic agents, such as benralizumab (BENRA), have been explored. In a retrospective study conducted by the French Vasculitis Study Group involving EGPA patients with non-severe refractory or relapsing manifestations, BENRA induced a complete response in 49% of patients (defined as BVAS=0 and a prednisone dose ≤4 mg/day) and a partial response in 36% (BVAS=0 and a prednisone dose ≥4 mg/day), with 38% of patients able to discontinue GCs, particularly in those who were naïve to MEPO (105). Similarly, another retrospective study by the European EGPA Study Group showed that BENRA resulted in complete response and partial response rates of 46.4% and 18.8%, respectively, after 12 months of follow-up, with a mean prednisone dose of 2.5 mg/day (106). However, 16% of patients reported adverse events, and 13% discontinued BENRA(106). A recent comparative study evaluating the efficacy of anti-IL-5/IL-5Rα drugs in treating EGPA found that after 12 months, 42.3% of patients treated with BENRA and 34.8% receiving MEPO achieved complete remission, with no significant difference observed between the two groups (107). Additionally, MEPO and BENRA have been also successfully used in cases of refractory eosinophilic fasciitis (108, 109).

Treatment options for severe asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) have expanded to include dupilumab, which has demonstrated promising efficacy both in CRSwNP and asthma (110-112). It's worth noting that case reports have linked the onset of EGPA to hyper-eosinophilia following dupilumab administration (110-112). In an observational multicentre study, dupilumab was introduced in 92% of cases for refractory ENT symptoms, with 41% of patients achieving a complete response and 24% experiencing a partial response overall (113). Notably, EGPA relapses occurred in 31% of cases on dupilumab, with 88% of these cases associated with blood eosinophilia (113). Additionally, in patients with asthma Kushima *et al*. showed that peripheral blood eosinophil count (PBEC) commonly increased after dupilumab introduction and then reduced but, when eosinophils continued to rise within 6 months, a higher risk of development of EGPA was observed (114). Previous therapy with anti-IL-5/IL-5Rα drugs was linked to a significantly lower PBEC at dupilumab initiation, although this effect was not sustained during follow-up (114). Furthermore, patients with a PBEC above 1500 cells/μL at 3 months after starting dupilumab exhibited a higher risk of developing EGPA (114). It's noteworthy that EGPA onset has also been reported during therapy with omalizumab, BENRA, and MEPO in asthma patients, suggesting that their GC-sparing effect might unmask the natural trajectory from asthma to EGPA (115). While MEPO has revolutionised EGPA treatment, further research is necessary to delineate the safety and efficacy profiles of other drugs targeting type 2 inflammation in EGPA.

Unmet needs in AAV

Despite the great amount of consolidated evidence, there are still numerous unmet needs in AAV management, which have been the focus of research efforts in 2023 (116). The AAV patients-reported outcomes (PRO) questionnaire plays a complementary role alongside BVAS and Vasculitis Damage Index (VDI), capturing aspects of the patient experience that may not be captured by traditional measures (117). Studies have demonstrated the influence of factors such as sex, GC therapy, and disease history (*e.g*. disease duration, previous relapses) on patients' perception of their disease (118-120). Furthermore, since AAV is a multisystemic disorder, managing comorbidities, both pre-existing and subsequent to the diagnosis of AAV, is crucial (121). Severe infections remain the primary cause of mortality in AAV, especially within the first year of diagnosis. Recent retrospective multicentre studies have reinforced the association between low IgG levels following remission induction treatment and an increased risk of severe infections. Older age and the use of oral GCs appear to be independent risk factors for hypogammaglobulinaemia after induc-

tion treatment with RTX (122, 123). All these findings highlight the importance of implementing GC-sparing regimens in the management of AAV.

Take home messages

- GC-sparing strategies are poised to revolutionise the management of AAV (87).
- The optimal administration scheme for RTX in maintenance therapy for AAV remains a topic of debate. The potential usefulness of measuring serum RTX concentrations in clinical practice has been suggested (85).
- In EGPA, MEPO safety has been demonstrated in long-term follow-up analyses (101-103), and BENRA showed a good profile of efficacy and safety in refractory cases (105, 106).

Conclusions

Over the past year, the field of vasculitis has seen a surge in new research contributions spanning pathogenesis, biomarkers, and novel treatments. These endeavours represent a concerted effort to deepen our comprehension of these rare diseases, paving the way for more effective management strategies and ultimately improving outcomes for those affected by vasculitis.

Competing interests

C. Baldini has acted as principal investigator in RCTs promoted by GSK and Roche, and has received consultancies for GSK. The other authors have declared no competing interests.

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