Review

Systemic vasculitis: one year in review 2025

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ABSTRACT

Systemic vasculitides encompass a spectrum of inflammatory disorders affecting several organs and districts, with significant implications for morbidity and mortality. This annual review provides an updated overview of key advancements in vasculitis research, including emerging biomarkers, novel insights into pathogenesis, and therapeutic innovations in both large and small-vessel vasculitis. Particular attention is given to emerging concepts, including the role of cellular senescence and stromal cells in vascular inflammation, the expanding spectrum of single-organ vasculitis, and the growing recognition of VEXAS syndrome as a vasculitis-related entity.

Introduction

Systemic vasculitides represent a heterogeneous group of chronic, inflammatory diseases characterised by blood vessel inflammation, which can lead to severe organ damage and long-term morbidity. This spectrum includes large-vessel vasculitis (LVV), such as giant cell arteritis (GCA) and Takayasu's arteritis (TAK), and small-vessel vasculitis, notably anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) and cryoglobulinaemic vasculitis (CV). Recent advancements have expanded our understanding of pathogenetic mechanisms underlying vasculitis, with novel insights into the role of cellular senescence and stromal cell in the development of vascular inflammation. Additionally, the recognition of emerging entities like vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome and a renewed focus on single-organ vasculitis, such as primary central nervous system vasculitis (PCNSV), aortitis, and chronic periaortitis (PC) underscore the evolving landscape of vasculitis research and management. Similarly to the previous annual reviews of this series (1, 2), we identified in this paper the most relevant and recent evidence about pathogenesis, clinical manifestations, and therapeutic options of these entities. We conducted a Medline search of English-language articles published in the PubMed database from January 1, 2024, to December 31, 2024. The following keywords were used to identify relevant data sources: "vasculitis", "giant cell arteritis", "Takayasu's arteritis", "ANCA-associated vasculitis", "microscopic polyangiitis" (MPA), "granulomatosis with polyangiitis" (GPA), "eosinophilic granulomatosis with polyangiitis" (EGPA), "cryoglobulinemic vasculitis", "VEXAS syndrome", "primary central nervous system vasculitis", "aortitis", "periaortitis", "cellular senescence and arteritis", and "stromal cells and vasculitis or arteritis".

New insight into large-vessel vasculitis

Biomarkers and implications in the pathogenesis of LVV

The genetic bases and the potential role of immunological biomarkers in LVV are still unclear. A recent genome-wide association study identified three novel loci associated with risk of GCA, two of them (MFGE8 and VTN) involved in neoangiogenesis and one of them (CCDC25) related to neutrophil extracellular traps (3). In addition, a transcriptomic study conducted in patients with GCA found that 31 genes were downregulated and 256 genes were upregulated in temporal artery biopsies (TABs) with transmural inflammation (TMI) compared with normal TABs and TABs with inflammation limited to adventitia (4). Beyond genetic predis-

position, emerging evidence highlights the involvement of humoral immune response in the pathogenesis of GCA. In a recent study including 55 patients with GCA and 7 patients with TAK, Pesce et al identified two novel autoantigens, VSIG10L and DCBLD1, with a prevalence of 43% and 57%, respectively, and high specificity (>96%). These autoantibodies were absent in TAK patients and in age-matched healthy controls, indicating distinct pathogenic mechanisms between the two LVV subtypes, and ruling out any association with age (5). While the contribution of cell-mediated immunity is central to GCA, these findings identify a previously unrecognised role for humoral autoimmunity, suggesting that B-cell-driven responses may contribute to disease pathogenesis. Preventing the onset and progression of arterial fibrosis remains a significant challenge in patients with TAK. A recent study indicated proprotein convertase subtilisin/kexin type 5 (PCSK5) in TAK patients as a novel pro-fibrotic factor in TAK vascular fibrosis by means of activating precursor TGF-β (pro-TGF-β) to the mature form. In this regard, leflunomide (LEF) might have an anti-fibrotic value by inhibiting PCSK5 and pro-TGF-β binding, and decreasing TGF-β activation (6).

Emerging role of cellular senescence in LVV

GCA affects adults over 50 years old, and aging is the strongest risk factor for GCA development. Upregulation of markers of cellular senescence, such as p16INK4A and p21WAF/Cip1, has been reported in inflamed TABs from GCA patients (7). Recently, Gorgoulis *et al*. investigated GL13, a novel marker of cellular senescence interacting with lipofuscin, in the context of GCA. Inflamed TABs from GCA patients contained significantly more GL13-positive senescent cells than normal TABs from polymyalgia rheumatica (PMR) patients, non-PMR/GCA patients, and non-inflammatory aortic aneurysmal tissue. Multi-marker immunohistochemistry identified senescence primarily in fibroblasts, macrophages, and endothelial cells, while vascular smooth muscle cells (VSMCs) were rarely affected. Senescent cells produced interleukin-6 (IL-6) and matrix metalloproteinase-9. Supernatants obtained from inflamed GCA TABs induced senescence in fibroblasts, endothelial cells, and monocytes, an effect significantly reduced by IL-6 blockade with tocilizumab (TCZ). Premature senescence has also been reported in TAK. A recent study published by Fang *et al*. identified significantly higher representation of GL13- and p16INK4A-positive cells in affected arteries compared to controls. Unlike GCA, these cells were primarily located in the medial layer and expressed α-SMA, confirming their identity as VSMCs. IL-6 signalling was found to play a crucial role in TAK by promoting the senescent phenotype and acting as a downstream effector of VSMCs senescence (8). These findings highlight cellular senescence as a key factor in LVV pathogenesis, providing insights into disease mechanisms and potential therapies.

Imaging and clinical advances

Stratifying GCA subsets is crucial for a tailored therapeutic approach and improved patient outcomes. Recent research confirmed the presence of a cranial/ophthalmic subset characterised by cranial manifestations, PMR features (9), and higher incidence of ischaemic/occlusive vascular disease (10), and an extracranial subset, affecting younger patients with frequent relapses and aneurysm risk. Vascular ultrasonography (V-US) can be useful to assess ischemic complications, revealing that cranial artery involvement is linked to anterior ischaemic optic neuropathy, while LV involvement is more often associated with stroke, acute coronary syndrome, and peripheral artery disease (11). However, V-US lacks validated quantitative scores in clinical practice. To improve disease assessment, several V-US scoring systems have been proposed. The Southend halo score, halo count, and OMERACT GCA Ultrasonography Score (OGUS) have showed good sensitivity and excellent specificity in a real-life GCA cohort (12). Notably, OGUS also predicted disease relapse at 6 months in a recent multicentric study (13). Recent evidence suggests that extra-media thickness (EMT) of the common carotid artery (CCA) adventitia may serve as a novel vascular marker for disease severity. A morphological study using V-US compared EMT and intima-media thickness (IMT) in LVV patients, distinguishing TAK from GCA. IMT, EMT and total CCA wall thickness were significantly higher in TAK, with a modest correlation between EMT and disease duration in this subgroup (14). A separate study evaluated vascular abnormalities in 24 TAK and 27 GCA patients undergoing computed tomography angiography (CTA) before and after immunosuppressive treatment. Wall thickening and vessel wall contrast enhancement (CE) improved in all patients, while structural abnormalities, such as stenoses, occlusions, dilations, aneurysms, and calcifications, remained unchanged. Pre-treatment wall thickening and CE were similar, while post-treatment stenoses and occlusions were significantly more represented in TAK patients, suggesting a greater persistence of vascular damage (15).

Positron emission/computed tomography (PET/CT) is widely used to detect vascular inflammation in LV-GCA but its interpretation is still debated. Two recent studies evaluated the ability of PET/CT to predict relapse of LV-GCA during clinical remission (16, 17). Vascular activity scores at PET/CT performed during follow-up significantly decreased in all patients, regardless of time to treatment discontinuation and subsequent relapse (17), suggesting that PET/CT may not be suited to assess disease evolution over time and guide treatment decision in LV-GCA in remission. Additionally, it is still unclear whether PET/CT in LV-GCA is reliable in patients undergoing glucocorticoid (GC) therapy. Aldasoro *et al*. applied a delayed imaging protocol (180 minutes) in patients with negative PET results at 60 minutes. Positive results at 180 minutes were observed in all cases despite ongoing GCs, proving potential improved diagnostic accuracy (18).

Advances in the treatment of GCA and TAK

TCZ is the first choice GC-sparing agent in severe/refractory GCA and in patients at risk for GCs-induced adverse events (AEs). However, the efficacy of TCZ and the optimal tapering strategy in clinical practice are still a research topic. The results from of an extension of the TOPAZIO trial showed that one year of TCZ monotherapy was effective in maintaining clinical remission even after drug discontinuation, although PET vascular score (PETVAS) significantly increased 6 months after discontinuation, suggesting emerging subclinical vascular inflammation (19). In this context, progressive TCZ tapering may be preferable over abrupt discontinuation, as the latter was associated with a significantly shorter time to relapse (20). In a recent real-life study comparing TCZ and methotrexate (MTX), TCZ allowed a faster GCs discontinuation, without increasing the risk of relapse at 6 and 12 months (21). Beyond TCZ, there is a need for further GCs-sparing agents in GCA. Broadening therapeutic options, JAK inhibitors (JAK-I) have gained attention as a promising strategy in GCA. In a recent retrospective analysis of 35 patients with relapsing GCA, JAK-I showed promising results in terms of efficacy, and a phase III randomised controlled trial (RCT) of upadacitinib in GCA is currently ongoing to confirm these data (22). Current treatment of TAK is based on conventional and biological disease-modifying anti-rheumatic drugs (csDMARDs/bDMARDs), with LEF emerging as a potential option based on efficacy data. A recent retrospective cohort study compared the efficacy of LEF and adalimumab (ADA), showing similar outcomes in terms of complete response, time to relapse, and angiographic progression after a median of 15-month follow-up. However, mild to moderate AEs were reported only in the LEF group, highlighting the need for further evaluation of its safety profile (23). Expanding the comparison of bDMARDs, a recent RCT compared the efficacy of ADA and TCZ in active, severe TAK. At 6 months, ADA demonstrated higher efficacy rate (85.71% *vs*. 52.63%, p=0.02), with comparable secondary endpoints, including response rate at 9 and 12 months, risk of relapse, and safety profile (24).

Take home messages

- Novel genetic loci and cellular senescence markers provide insights into GCA and TAK pathogenesis and potential therapeutic targets (3, 4, 6-8). The recognition of novel GCA-related autoantigens could offer a new non-invasive tool to enhance the diagnostic process (5).
- Vascular ultrasound, CTA, and PET/CT improve disease assessment, with preliminary evidence of a possible prognostic role, but their role in guiding treatment decisions remains debated (12-18).
- TCZ tapering, JAK-I, and DMARD comparisons offer new perspectives for GCA and TAK management and GC-sparing strategies (19, 21-24).

Vascular inflammation and beyond: the expanding role of stromal cells in vasculitis

Various research groups are investigating fibroblast activation protein (FAP), a serine-protease highly expressed by active fibroblasts in inflammation and atherosclerosis. Xu *et al*. evaluated soluble and transmembrane FAP in treatment-naïve GCA, finding lower plasmatic levels in active disease compared to PMR and controls, with normalisation upon remission. In inflamed GCA-related TABs, FAP was highly expressed across all vessel layers, correlating with intimal occlusion. FAP-positive fibroblasts co-expressed IL-6 and metalloproteinase-9, supporting their role in vascular inflammation and remodelling (25). A novel PET tracer targeting FAP, 68Ga-FAP-inhibitor (FAPI)-46, has been proposed for vasculitis imaging. Recently, Rohrich *et al*. found higher aortic FAPI uptake in GCA- and TAK-related aortitis compared to controls, regardless of clinical activity. Notably, FAPI-PET/CT allowed the detection of persistent fibroblast activity during long-term remission, even when magnetic resonance imaging (MRI) inflammatory scores were low, suggesting ongoing fibroblast-driven pathology (26). Zhong *et al*. compared 18F-FAPI and 18F-FDG in PET/CT imaging in 17 LVV and 10 AAV treatment-naïve patients. 18F-FAPI demonstrated superior lesion detection (161/168 *vs*. 145/168) and a moderate correlation with inflammatory markers. Notably, FAPI-PET/CT identified persistent lesions despite clinical remission, reinforcing its potential role in vasculitis monitoring (27).

Single-organ vasculitis

Single-organ vasculitis refers to vasculitic disorders confined to a single organ, occurring without systemic involvement or features of systemic vasculitis (28).

Primary central nervous system vasculitis

PCNSV is a rare vasculitis confined to the brain and spinal cord, leading to diverse neurological syndromes. A recent review examined its clinical, radiological, and histopathological features (29). Diagnostic criteria for PCNSV remain undefined, with brain biopsy representing the gold standard for diagnostic confirmation and differential diagnosis. However, sensitivity is relatively low (30-50% nondiagnostic/normal findings), likely due to irregular lesion distribution and LV involvement, which precludes safe biopsy. Despite this, the risk of biopsy-related severe complications is relatively low. Imaging modalities, such as MRI, CTA, MR angiography, and conventional angiography, play a crucial role for diagnosis of PCNSV. High-probability findings include the smooth-wall segmental stenosis of multiple cerebral arteries, occasionally combined with post-stenotic dilatation or beading. Aneurysms are uncommon in PCNSV. A retrospective study of 216 patients with PCNSV found aneurysms in 5.5% of cases, half in the internal carotid artery, with no size changes during follow-up. No clinical differences were observed between PCNSV patients with and without aneurysms (30). Clinical management of PCNSV remains challenging, underscoring the need for future research into its underlying pathophysiology, biomarkers, and improved diagnostic/therapeutic approaches.

Aortitis and chronic periaortitis

Aortitis and CP are inflammatory conditions affecting the aorta and its surrounding structures. Aortitis involves inflammation of one or more aortic layers, while CP affects the periaortic region, including the thoracic aorta, abdominal aorta, and iliac arteries (31, 32). Both conditions may occur without features of systemic vasculitis. In non-infectious aortitis, the thoracic aorta is most frequently affected (33). The development of vascular inflammation at this level may ultimately lead to cardiovascular complications, such as aneurysm, aortic dissection, and thrombotic luminal occlusion. In a recent multicentre study, Espitia *et al*. evaluated the impact of histopathological patterns (granulomatous/giant cell pattern, lymphoplasmacytic pattern, suppurative pattern, and mixed inflammatory pattern) on cardiovascular mortality in 197 patients with biopsy-proven non-infectious aortitis. Among these, 48% were diagnosed with clinically isolated aortitis, 37% with GCA, and 8% with TAK, with diagnoses evenly distributed across histological patterns. The granulomatous/giant cell pattern increased mortality by 4.7 times, primarily due to aortic dissection/rupture, regardless of aetiology. Cardiovascular complications accounted for more than 60% of deaths, underscoring the need for prompt intervention (34).

VEXAS syndrome-related vasculitis

VEXAS syndrome is a recently defined clinical entity causing hematologic and autoinflammatory symptoms (35). Previous evidence suggested the potential occurrence of vasculitic manifestations in the context of VEXAS syndrome (36, 37). Sullivan *et al*. recently examined the prevalence and clinical characteristics of vasculitis in the cohort of VEXAS patients followed up at Mayo Clinic (38). Among 89 enrolled patients, 23.6% had a confirmed diagnosis of vasculitis, primarily affecting small vessels (19.1%), while the involvement of medium-sized or LV was rare (both 2.2%). Importantly, the study identified ANCA-positivity in a subset of patients, which could potentially delay the diagnosis of VEXAS syndrome. Although LV involvement is uncommon, the authors propose classifying VEXAS syndrome as a form of variable vessel vasculitis. This has critical clinical implications, as VEXAS is a life-threatening condition, requiring prompt recognition and timely intervention to improve outcomes.

Take home messages

- Although brain biopsy remains the diagnostic gold standard for PC-NSV, imaging modalities play a key role in detecting vascular abnormalities (29).
- In aortitis and CP, histopathological patterns may influence disease prognosis, with granulomatous inflammation significantly increasing the risk of aortic rupture and mortality (34).
- Vasculitis occurs in about a quarter of patients with VEXAS syndrome, often affecting small vessels, with ANCA-positivity potentially delaying diagnosis (38).

New insights into ANCA-associated vasculitis

GPA and MPA: novel biomarkers and clinical features update

Among AAV, clinical phenotype, laboratory findings, and outcome of GPA and MPA vary widely. A cluster analysis from the FAIRVASC project identified five clusters (39): three with kidney involvement: [1) severe renal disease; 2) myeloperoxidase (MPO)-ANCA-positivity with limited extra-renal disease; 3) proteinase-3 (PR3)-ANCA-positivity with widespread extrarenal disease]; a PR3-ANCA-positive multisystemic inflammatory cluster; and a fifth cluster with predominant ear, nose, and throat (ENT) involvement and low inflammatory markers. While ANCA play a crucial role in the pathogenesis of AAV, their usefulness as disease activity biomarkers is still uncertain. Rah *et al*. recently found that single ANCA titres at diagnosis did not correlate with Birmingham Vasculitis Activity Score (BVAS), Five Factor Score (FFS), acute phase reactants, or relapse rate (40). However, first-year cumulative MPO-ANCA titres ≥720,8 IU/mL was linked to all-cause mortality and a lower cumulative survival in MPA, suggesting that serial MPO-ANCA measurements in the first year may help predict long-term survival. Recent evidence also highlights the prognostic role of early vasculitis-related organ damage in AAV. A study conducted by Koo *et al*. found that a total Vasculitis Damage Index ≥3, assessed three months after diagnosis, was significantly associated with higher all-cause mortality, particularly in patients with pulmonary, renal, cardiovascular, and musculoskeletal damage (41). Additionally, a newly developed predictive model for diffuse alveolar haemorrhage (DAH) in AAV identified age, low haemoglobin levels, low platelet count, erythrocyte sedimentation rate, and haematuria as independent risk factors, demonstrating strong discriminatory power (AUC-ROC 0.852) (42). This model underscores the relevance of haematological and inflammatory markers in identifying AAV patients at risk of DAH. Alpha-1 antitrypsin is the main natural inhibitor of PR3 and its deficiency has been associated with PR3-positive AAV (43). Ceruloplasmin, an acute phase reactant, physiologically binds and inhibits MPO. Camboulive *et al*. analysed ceruloplasmin levels in AAV patients before immunosuppressive treatment, finding that MPO-positive patients with low ceruloplasmin levels had significantly worse survival. Conversely, PR3-positive patients showed no difference in ceruloplasmin levels (44). These findings suggest that low ceruloplasmin levels may contribute to a more severe AAV phenotype by enhancing oxidative stress and tissue damage through increased MPO activity and interaction with MPO-ANCA. Activated neutrophils expressing MPO and PR3 on their surface drive ANCA production. Additionally, monocytes also express PR3 and MPO in their lysosomes and on their surface. Smargianaki et al. recently found that active AAV patients had lower frequency of total and intermediate (CD14+/CD16+) monocytes compared to those in remission, likely due to cell recruitment in inflamed tissues. Notably, rituximab (RTX) appeared to influence monocyte subpopulations, as higher frequencies

of classical (CD14-/CD16+) and intermediate monocytes were observed in RTX-treated patients (45).

GPA/MPA: evolving treatment strategies and emerging therapeutic insights

Recent American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) recommendations have established RTX as the therapeutic cornerstone of MPA and GPA, both in severe and non-severe phenotypes (46, 47). The 2024 Kidney Disease Improving Global Outcomes (KDIGO) guidelines align closely, recommending RTX or cyclophosphamide (CyC) plus GCs or avacopan as the preferred induction therapy, with RTX-CyC combination therapy reserved in selected cases (48). RTX can be preferred for remission maintenance and relapsing diseases. Plasma exchange (PLEX) should be considered for patients with serum creatinine >3.4 mg/dl, dialysis-dependence, or with rapidly increasing serum creatinine and, unlike EULAR recommendations, for patients with respiratory failure secondary to severe DAH.

Over the last decade, the MAINRITSAN trials have demonstrated the pivotal role of RTX in maintenance treatment for AAV (49-51). Long-term follow-up and pooled analysis of patients enrolled in these trials showed that an 18-month fixed RTX regimen achieved higher remission rates at 84 months than azathioprine (AZA) or 18-month tailored RTX, while extending RTX to 36 months did not further reduce relapses compared with the 18-month fixed RTX regimen (52). However, the optimal strategy for RTX maintenance treatment in AAV is still unclear. The recent MAINTANCAVAS trial aimed to compare RTX maintenance treatment tailored to B-cell repopulation versus ANCA rise in patients completing at least 2 years of fixed-schedule RTX. Compared to therapeutic approach based on ANCA rise/return, B-cell repopulation tailored approach resulted in fewer relapses, with comparable safety profile (53). Regarding B-cell kinetics during RTX therapy, a recent study found that preserved renal function and female sex were associated with faster B-cell repopulation, which may influence treatment strategies (54). A retrospective study including patients with life-threatening GPA/MPA, the efficacy of RTX was comparable to intravenous CyC, with similar in-hospital mortality but a lower risk of fungal infections and *Pneumocystis Jirovecii* pneumonia. However, RTX was associated with a slightly higher risk of severe renal dysfunction requiring dialysis (55). A post-hoc analysis of the PEXIVAS trial, enrolling patients with severe GPA/MPA, showed that neither the use of PLEX nor a reduced GCs tapering regimen influenced relapse risk (56). As previously noted, GCs still play a key role during induction therapy, A recent Japanese emulated target trial including patients with AAV-related severe glomerulonephritis or DAH suggested that intravenous methylprednisolone 1.0 g/day pulses improved 48-week mortality compared to 0.5 g/day and non-intravenous pulse regimens (57). However, long-term data from LoVAS trial including newly diagnosed AAV patients without severe glomerulonephritis or DAH showed no difference in mortality or relapse rates between initial high- and reduced-dose GCs induction regimens over 24 months, with fewer AEs reported in the reduced-dose arm (58). In recent years, avacopan has emerged as an effective GC-sparing agent in AAV. In a recent post-hoc analysis of the ADVOCATE trial, Geetha *et al*. focused on the efficacy and safety of avacopan in patients receiving RTX-based induction regimen, finding that avacopan achieved similar 26-week remission rates, but higher 52-week remission rates compared to prednisone taper, with better renal outcomes and lower GCs toxicity (59). However, the ADVOCATE trial excluded patients with severe renal impairment or DAH. In this regard, Chalkia *et al*. recently described 8 patients with severe DAH-related respiratory failure successfully treated with avacopan combined with RTX and/or CyC (60). Similarly, Zimmermann *et al*. reported high remission rates and kidney function improvement in real-world patients, including those with eGFR <15 ml/min or previous DAH, with a safety profile comparable to that of the ADVOCATE trial (61). Lastly, spatial, and single-cell transcriptomics on AAV kidney biopsies identified ustekinumab has as a promising treatment candidate. In four relapsing patients with ANCA-associated glomerulonephritis, ustekinumab combined low-dose CYC and GCs, allowed a clinical response (62).

EGPA: update on clinical features, biomarkers, and treatment

EGPA is a subtype of AAV characterised by eosinophilic and vasculitic manifestations. MPO-ANCA, following neutrophil activation, can induce necrotizing small-vessel vasculitis and glomerulonephritis in animal models (63). However, their pathogenic role in EGPA remains unproven, and the triggers for ANCA production are still unknown. A mouse model recently demonstrated that allergic airway disease caused by house dust mites or ovalbumin, combined with a single intravenous dose of MPO-ANCA IgG, led to lung histologic abnormalities resembling EGPA (64). These findings suggest that environmental and endogenous interactions may contribute to disease onset. Additionally, a recent systematic review found that smoking may act as a protective factor in EGPA, particularly in MPO-ANCA-negative patients (65). Clinical data revealed higher arterial and venous thromboembolism rates compared to the general population in patients with EGPA (66). Natorska *et al*. investigated the intrinsic coagulation pathway, finding that increased factor XI level (>130%) were associated with higher eosinophil count, lower neutrophil percentage, and reduced clot permeability, reinforcing the role of factor XI in EGPA-related prothrombotic state and its potential therapeutic relevance.

Asthma and nasal polyposis are common prodromal manifestations of EGPA. Given their high prevalence in the general population, a recent study aimed to identify blood and sputum biomarkers distinguishing between severe hypereosinophilic asthma (SEA) and EGPA-related asthma. However, granulocyte-monocyte colony-stimulating

factor in sputum was the only biomarker significantly elevated in EGPA patients compared to those with SEA (67). The classical dichotomy between vasculitic and eosinophilic manifestations reflects two complementary treatment approaches: traditional immunosuppressive and eosinophil-targeted therapies. Current recommendations suggest GCs combined with CyC or RTX for remission induction of severe EGPA (46, 47). A recent target trial emulation study confirmed that adding CyC to GCs reduces vasculitic relapses at 12 months and asthma/ENT symptoms at 24 months (68). However, comparative data concerning the efficacy of csDMARDs in EGPA are lacking. A recent retrospective study investigated the effectiveness and safety of MTX and AZA as induction therapy for non-severe EGPA and maintenance treatment for severe disease. Compared to AZA, MTX led to earlier remission during the induction phase and provided a greater GC-sparing effect during maintenance phase (69). Although intravenous immunoglobulins (IVIg) are widely used for autoimmune-related peripheral neuropathy, specific indications for EGPA remain undefined. A retrospective study recently showed that IVIg add-on therapy was associated with better long-term neurological symptoms control, reduced overall and neurological relapses, and improved disability outcomes compared to standard of care (70). Following the publication of the MIRRA trial, mepolizumab (MEPO), an anti-IL5 monoclonal antibody, has become a therapeutic cornerstone in EGPA, particularly for eosinophilic manifestations. Recent studies have examined the long-term outcomes of EGPA patients receiving MEPO. A retrospective multicentre study conducted in Japan reported a 5-year retention rate of 78.7%, significantly higher in patients previously on immunosuppressants (71). Another retrospective study from the Japanese REVEAL registry, demonstrated increased 5-year survival rates in patients treated with MEPO (100% *vs*. 81.3%, p=0.012) (72). Preliminary evidence suggested the efficacy of benralizumab (BEN), an anti-IL5-receptor monoclonal antibody, as an alternative treatment option in EGPA (73, 74). The MANDARA trial, a noninferiority, phase III RCT, compared BEN 30 mg to MEPO 300 mg administered every 4 weeks for 52 weeks in relapsing or refractory non-life/organ-threatening EGPA. Remission rate, time to first relapse, and GC-free periods were comparable, confirming BEN's noninferiority to MEPO. Serious AEs were reported in 6% and 13% of patients treated with BEN and MEPO, respectively (75). Beyond IL-5 blockade, tezepelumab (TEZ), a thymic stromal lymphopoietin (TSLP)-inhibitor, is being investigated in EGPA. TSLP is an epithelial-derived cytokine, driving type-2 inflammation by activating dendritic cells, eosinophils, and mast cells. A recent study described two patients with severe, refractory EGPA-related asthma treated with TEZ 210 mg subcutaneously every 4 weeks. One patient experienced significant improvement of both respiratory and ENT symptoms, while the other showed worsening respiratory function, requiring treatment discontinuation. Notably, slight increases of blood absolute eosinophil count and persistent sputum eosinophilia raises concerns about TSLP inhibition-induced eosinophil rebound (76). Further research is needed to assess the long-term efficacy and safety of TEZ in EGPA.

Take home messages

- Cluster analysis refined GPA and MPA phenotypes, while MPO-ANCA cumulative titres and low ceruloplasmin levels emerged as potential prognostic markers (39, 40, 44).
- RTX is established as the preferred remission maintenance therapy, with B-cell repopulation-based RTX regimens reducing relapses (52, 53). Avacopan is an effective GC-sparing option, showing benefits also in severe renal and pulmonary involvement (60, 61).
- MEPO remains a first-line biologic (71, 72) in EGPA, while BEN demonstrated its non-inferiority in non-severe disease (75). TEZ, targeting TSLP, is a promising therapeutic alternative, although concerns about eosinophil rebound warrant further investigation (76).

Cryoglobulinaemic vasculitis

Epidemiology and pathophysiology novelties

CV is a rare disease for which the only available classification criteria were published in 2014 by Prof De Vita's research group (77). Laboratory findings are essential for both diagnosis and disease monitoring, playing a key role in guiding clinical management. A recent monocentric cross-sectional study corroborated findings from earlier research, indicating that high serum cryoglobulin (CG) concentrations can often characterise an oligo- or asymptomatic disease course, whereas low CG values and/or reduced complement levels typically correlate with severe and active CV. Specifically, Codes-Mendez *et al*. found that haematological diseases exhibited the highest mean serum protein cryoprecipitate levels, despite presenting with milder clinical manifestations (78). However, the prevalence of type I IgM cryoglobulinaemia appears to be higher than previously described in IgM monoclonal gammopathy. In a large screening study conducted over a 9-year period, 33% of the 534 patients with monoclonal IgM disorders tested positive for CGs, and 25% were found to have type I IgM CGs. Among patients with type I CGs, about 50% were symptomatic. Notably, most symptomatic patients had an underlying IgM monoclonal gammopathy of undetermined significance rather than Waldenström macroglobulinemia or non-Hodgkin lymphoma (NHL) (79). Serum CGs can be detected in up to 40% of patients with chronic hepatitis C virus (HCV) infection, though only 5% of these individuals develop HCV-associated CV. Similarly, a recent study conducted in Taiwan, a region considered hyperendemic for hepatitis B virus (HBV) infection, reported that one-third of HBV carriers tested positive for CGs, but only 4% developed HBV-associated CV (80). Furthermore, RF-positivity has been identified as an independent predictor of HBV-associated CV development (80). A recent study analysed B cell receptor (BCR) repertoires in chronic HCV patients before and after antiviral therapy, identifying a persistent B cell

signature with high mutation rates, resembling lymphoma-associated BCRs. Notably, some BCR mutations, linked to highly neutralising HCV antibodies, were also present in aggressive lymphomas, exhibiting lower activation thresholds. Single-cell RNA sequencing further revealed persistent oncogenic signalling in these B cells, even after viral clearance, suggesting that HCV-related B cell dyscrasias and lymphoma risk persist beyond HCV elimination (81).

Clinical features and treatment update

CV may present with a wide range of hepatic and extra-hepatic manifestations. A recent Italian case-control study identified an association between cryoglobulinemia, cholestasis, and an increased number of intrahepatic plasma cells in HCV patients before virus eradication, independent of viral load, cirrhosis, and other comorbidities. Notably, after HCV eradication, cryoglobulinemia and cholestasis persisted in 54% and 25% of patients, respectively (82). Similarly to renal involvement, it can be hypothesised that immune complexes may contribute to both vasculitic injury and direct hepatic damage. Among HCV-related extra-hepatic manifestations, peripheral nerve system (PNS) involvement is common, affecting 22.5% of patients. Skin biopsy obtained from HCV-infected patients suggest an improvement of nerve density after antiviral treatment, approaching that of healthy individuals (83). Ocular involvement is not uncommon in CV, with a prevalence of 28% in a retrospective study, primarily represented by dry eye unrelated to Sjögren's syndrome (SjS) and Purtscher-like retinopathy. Treatment allowed resolution of major vasculitic signs, in combination with improved ocular symptoms in 87.5% of patients (84). Though rare (prevalence <5%), pulmonary involvement has a major impact on disease prognosis. A recent monocentric study found higher RF titres and increased frequencies of cutaneous, renal, and peripheral neuropathy in patients with lung involvement (85). The most common radiological finding was diffuse bilateral patchy ground-glass opacities. Compared to those without pulmonary involvement, affected patients had significantly worse two-year overall survival and progression-free survival.

Direct acting antivirals drugs (DAAs) are the standard of care for chronic HCV infection, including HCV-associated CV. However, CGs may persist or reappear despite DAA-induced viral clearance (86). Additionally, serum CGs can emerge in DAA-treated patients, even in those previously negative for CGs (87). In such cases, liver cirrhosis and neoplasms were independently associated with positive CGs three months post-treatment (87). A recent study comparing three antiviral protocols found a lower rate of constitutional relapses with interferon (INF)-based regimens compared to INF-free treatment, suggesting superior clinical and immunological effects of INF over DAAs. This finding supports its antiproliferative activity, which not only halts B-cell clonal expansion but also eradicates HCV and prevents B-cell antigen stimulation. However, no significant differences were observed in DNA damage, DNA repair markers, or B cells activators (BAFF and APRIL), between INF-based and INF-free protocols (88). RTX is the cornerstone of CV treatment, especially for severe or life-threatening manifestations (85). An Italian monocentric study compared three different therapeutic approaches for SjS-related CV, including two RTX-based and one non-RTX-based regimens. An early RTX approach started within 6 months from CV diagnosis, followed by a 6-month, fixed, maintenance regimen, while a late RTX approach was employed after 6 months, with on-demand retreatment based on disease activity. RTX-treated patients showed significant improvement in the cutaneous, PNS, and articular EULAR SjS disease activity index (ESSDAI) domains compared to non-RTX-based regimens (89). However, no significant differences were observed in glandular and nodal ESSDAI domains. Notably, early RTX induction improved glandular and nodal ESSDAI domains, although no effect was seen on biological domains. The incidence of new-onset mucosa-associated lymphoid tissue-NHL was similar across the three groups. These findings highlight RTX primary benefits in controlling vasculitic and inflammatory manifestations, rather than lymphoproliferative complications.

Take home messages

- HCV-related CV may persist after viral clearance due to lingering B cell abnormalities. RF and ESSDAI ≥5 are key risk factors for lymphoma in SjS-related CV (81).
- DAAs effectively treat HCV but may not fully eradicate CGs or prevent relapses. Liver cirrhosis and cancers are risk factors for positive CG post-treatment (86, 87).
- IFN has shown superior immunological benefits compared to DAAs, possibly due to its antiproliferative effects on B cells (88).
- RTX remains the cornerstone for severe CV cases. Early RTX induction offers better outcomes for glandular and nodal domains in SjS-CV but primarily addresses vasculitic and inflammatory symptoms rather than lymphoproliferative complications (89).

Conclusions

Recent advances have enhanced our understanding of systemic vasculitis, particularly in pathogenesis, biomarkers, and treatment approach. The role of cellular senescence, stromal cells, and genetics is increasingly recognised, while novel imaging and classification improve diagnostics and research standardisation. Treatment paradigms continue to evolve, with biologics, GCs-sparing strategies, and targeted therapies offering promising alternatives. Despite these advances, challenges remain in optimising long-term disease control and minimising adverse events. Future research should focus on personalised medicine approaches to enhance patient outcomes.

Competing interests

C. Baldini has received consultancy fees from GSK, Roche, Sanofi, Amgen, Novartis, Johnsson and Johnsson, BMS, Aurina. The other authors have declared no competing interests.

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