

Systemic vasculitis: one year in review 2026

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ABSTRACT

Systemic vasculitides are rare, heterogeneous inflammatory diseases associated with significant morbidity due to vascular and end-organ damage. In 2025, major advances have refined pathogenic insights and therapeutic strategies across large-vessel vasculitis (LVV), ANCA-associated vasculitis (AAV), single-organ vasculitis, and cryoglobulinaemic vasculitis (CV).

Multi-omics and spatial transcriptomic approaches, imaging, and serological biomarkers are informing prognosis and management.

Glucocorticoid minimisation remains a unifying therapeutic goal. Targeted therapies such as JAK inhibitors, avacopan and anti-IL-5/IL-5R agents have demonstrated efficacy and steroid-sparing effects in both trials and real-world studies. Together, these advances mark a transition toward precision, phenotype-driven management in systemic vasculitis.

Introduction

Vasculitides are a group of rare, chronic inflammatory diseases that affect the vascular wall. They are characterised by a heterogeneous clinical presentation that depends on the calibre of the vessel most involved, warranting prompt recognition and initiation of appropriate treatment, as they may lead to stenosis, aortic dilation or dissection, and end-organ damage.

Updates on current knowledge of novel disease biomarkers for diagnosis, disease assessment, and prognosis; new available treatments; and recent epidemiological data and clinical phenotyping are therefore fundamental for physicians managing these complex entities. In this narrative review, we aim to summarise the most recent and relevant advances in this field.

As in previous years, we conducted a Medline search of English-language articles in the PubMed database from January 1, 2025, to December 31, 2025 (1, 2). The following keywords were used to identify relevant data sources: “vasculitis”, “giant cell arteritis”, “Takayasu’s arteritis”, “ANCA-associated vasculitis”, “microscopic polyangiitis”, “granulomatosis with polyangiitis”, “eosinophilic granulomatosis with polyangiitis”, “cryoglobulinemic vasculitis”, “primary central nervous system vasculitis”, “aortitis”, “periaortitis”. Selection was based on clinical relevance and the impact of the results, with a prioritisation of randomised controlled trials, when available.

What is new in large-vessel vasculitis

Large-vessel vasculitides (LVV) affect the aorta and its major branches and include giant cell arteritis (GCA) and Takayasu’s arteritis (TAK) (3). Diagnosis is based on typical imaging findings and, in the case of GCA, on temporal artery biopsy (TAB) (4). High doses of glucocorticoids (GCs) are often used to avoid complications such as anterior ischaemic optic neuropathy (AION), aortic dilation, or stenosis with subsequent ischaemia (5). Traditional clinical assessments and laboratory markers often lack specificity for vascular inflammation, particularly under immunosuppressive therapy, highlighting the critical role of advanced imaging in diagnosis, monitoring, and prognosis of LVV.

This year, multiple efforts have been made to clarify the pathogenesis of LVV, evaluate the diagnostic accuracy of imaging modalities, assess the risk of vascular complications, and develop treatments to reduce the mean cumulative GC dose.

Biomarkers and implications in the pathogenesis of LVV

Beyond classical inflammatory markers, recent multi-omics and tissue-based studies have refined the molecular landscape of GCA, identifying novel biomarkers that capture disease activity and prognosis while illuminating key pathogenic mechanisms.

At the genetic and epigenetic levels, recent genome-wide approaches revealed extensive molecular signatures within GCA-affected arteries. A large epigenome-wide association study of TABs identified thousands of differentially methylated positions and regions mapping to genes involved in T-cell activation, cytokine signalling and vascular remodelling. Convergent epigenomic and transcriptomic alterations highlighted markers of T-cell exhaustion, including HAVCR2 and SLAMF6, consistent with sustained antigenic stimulation within the vascular niche (6). In parallel, a recent Mendelian randomisation analysis of immune cell phenotypes further supported a causal contribution of innate immune subsets to GCA susceptibility. Specifically, increased HLA-DR expression on CD14+ monocytes and expansion of pro-inflammatory monocytes were associated with higher disease risk, whereas monocytic myeloid-derived suppressor cells appeared to exert a protective influence (7). Spatially resolved transcriptomic and proteomic profiling further revealed marked immunological heterogeneity across distinct layers of the arterial wall, with clear clinical correlates. Patients unable to achieve sustained clinical remission under GCs therapy showed enrichment of extracellular matrix remodelling and T-cell activation pathways, whereas an adventitial plasma cell-rich infiltrate was preferentially observed in patients with favourable outcomes, especially when accompanied by intimal macrophage accumulation (8).

Macrophages emerged as key effectors linking immune activation to structural damage and vascular remodelling in GCA. Transcriptomic analyses of treatment-naïve TABs demonstrated enrichment of phagocytic and osteoclast-like gene programs, including expression of metalloproteinases (MMP)12 and

HLA-DRA, supporting a direct role in elastic lamina degradation, medial destruction, and intimal hyperplasia (9). Extending this paradigm, a recent tissue-based and functional study identified fibroblasts as active pathogenic players in the stromal compartment. Activated CD90+ fibroblast activation protein (FAP)+ fibroblasts and PDPN+ immunofibroblasts accumulated at sites of vascular injury and displayed high proliferative capacity and responsiveness to TGF-beta and PDGFB signalling. Experimental evidence further indicated that FAP is required for TGF-beta-driven fibroblast proliferation, positioning FAP at the interface between vascular remodelling and tissue-based biomarker discovery (10). In this context, bidirectional macrophage-fibroblast crosstalk was found to be a key amplifying mechanism, with granulocyte macrophage-colony stimulating factor (GM-CSF)-driven macrophages skewing adventitial fibroblasts toward an interleukin (IL)-6-producing, matrix-degrading phenotype characterised by increased expression of MMP-3 and tenascin-C (11). Finally, systemic biomarkers reflecting age-related immune dysregulation added another dimension to disease stratification. Mosaic loss of the Y chromosome (mLOY), the most common somatic mutation in aging men, was identified as a strong independent predictor of relapse risk in male GCA patients. Higher mLOY burden was associated with enhanced IL-6 and IL-17A signalling, particularly under IL-6 receptor blockade, suggesting potential engagement of alternative inflammatory pathways (12).

In TAK, recent transcriptomic studies highlighted a complex interplay between immune and vascular structural cells. Integrated bulk and single-cell RNA sequencing analyses of aortic tissue and peripheral blood T-cells revealed extensive CD4+ and CD8+ T-cell reprogramming, with enrichment of inflammatory, angiogenic, cytokine biosynthesis, and complement-related pathways, reflecting convergent systemic and vascular immune activation (13). Notably, transcriptional regulators such as EGR1, KLF4, RHOB and ATF3 emerged as key factors linking periph-

eral immune signatures with tissue inflammation, supporting a unifying molecular model of TAK immunopathogenesis (14). Beyond mechanistic insights, circulating biomarkers have shown potential clinical relevance. Elevated serum levels of soluble CD226, an activating receptor reflecting activation of natural killer and T-cells, were associated with disease activity, angiographic severity, steroid refractoriness, and relapse risk, while also differentiating TAK from GCA (15). Additionally, increased serum uric acid levels correlated with pulmonary artery involvement and adverse outcomes, supporting its role as a prognostic biomarker (16).

Imaging for the diagnosis of LVV

Ultrasound (US) remains a primary diagnostic tool for suspected GCA. International guidelines recommend that imaging, including US, should be performed promptly without delaying treatment (17). Although US is sensitive to changes following therapy, its performance over the course of GC treatment remains unclear. Hansen *et al.* prospectively assessed treatment-naïve GCA patients using 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT), US, and TAB. Serial US evaluations at 3- and 10-days post-GC initiation showed rapid improvement in abnormalities, with sensitivity for temporal and axillary artery assessment decreasing significantly within 10 days, from 94% before GC exposure to 92% after 3 days and 83% after 10 days. Sensitivity for temporal arteries alone dropped to 53% by day 10. This study highlights the importance of early imaging and rapid diagnosis in GCA management (18).

Recent research emphasises integrating US into GCA diagnosis and expanding training opportunities. Artificial intelligence (AI)-based tools show promise for supporting early US detection; Bauer *et al.* examined the minimum image resolution needed for reliable arterial US classification, laying groundwork for AI-assisted interpretation (19). Training in vascular US is limited and time-consuming. Innovative high-resolution 3D-printed models of axillary and temporal arteries have demon-

strated high reliability among experts in applying OMERACT US standards for GCA diagnosis and measuring intima-media thickness (IMT), providing a valuable new training resource (20).

A comparative diagnostic study by Morel *et al.* evaluated 18F-FDG PET/CT, cranial magnetic resonance imaging (MRI), temporal artery US, and biopsy against a clinical standard in suspected GCA. The combined cranial and large-vessel PET/CT showed the highest sensitivity (89%) and specificity (98%), outperforming US and MRI in certain aspects, while biopsy and cranial PET/CT displayed similar diagnostic yields (21). Similarly, van Nieuwland *et al.* assessed patients with suspected GCA using PET/CT and MRI. US effectively detected extracranial inflammation, PET/CT provided systemic insights, and MRI allowed structural evaluation correlated with PET activity. These findings support a multimodal imaging approach tailored to vessel involvement and clinical presentation (22).

The benefits of US-centred diagnostic pathways have been validated by Mukhtyar *et al.*, who studied 1,000 consecutive GCA referrals using a protocol that included extended ultrasound examination and a secondary test based on clinical probability and C-reactive protein (CRP) levels. This approach resulted in only seven misdiagnoses, underscoring the reliability and effectiveness of an ultrasound-focused, multimodal strategy within fast-track clinics (23).

New imaging techniques are also being explored in GCA. Orbital MRI detecting optic nerve sheath enhancement (ONSE) has emerged as a marker of orbital inflammation, especially in patients with visual symptoms, indicating perineural involvement and potential prognostic value (24). Similarly, optical coherence tomography angiography (OCTA) detects early retinal microvascular changes, such as reduced vessel density in the superficial peripapillary plexus, even in the absence of visual symptoms, suggesting subclinical hypoperfusion as a biomarker (25). High-resolution 3D black-blood MRI can identify intracranial arterial inflammation in about 15% of GCA patients without neurological deficits, particu-

larly affecting the intradural internal carotid artery. This suggests that intracranial involvement may be under-recognised and that advanced vessel wall MRI can improve disease characterisation (26). Standardised definitions for elementary US lesions in TAK, including increased IMT, stenosis, occlusion, aneurysm and contrast enhancement, are being systematically evaluated as a foundation for scoring systems to aid diagnosis, monitoring, and prognosis in TAK, guided by the OMERACT Ultrasound Working Group (27).

Imaging for the monitoring of large-vessel vasculitis: quantitative imaging biomarkers and prognosis

Imaging is increasingly important for monitoring and prognosis in LVV. The OMERACT GCA Ultrasonography Score (OGUS) was developed for disease monitoring in clinical research settings. It has been validated for reliability through patient-based studies involving both experts and non-experts, supporting its standardisation in assessing vascular involvement (28). A multicentre prospective study by Monti *et al.*, including 97 patients with over 800 visits, first demonstrated the prognostic utility of US: higher baseline OGUS scores predicted relapse, while rapid reduction after treatment was associated with a lower relapse risk and decreased need for additional immunosuppression. These findings support the use of OGUS assessments at diagnosis and early in therapy as part of risk stratification to identify patients at higher relapse risk (29).

In large-vessel GCA (LV-GCA), quantitative PET/CT parameters such as total inflammatory vascular volume (TIVV) and total inflammatory glycolytic volume (TIGV) showed stronger links to disease activity, earlier relapse, and aortic dilation than conventional scores like PETVAS (30). High-resolution cranial MRI provides longitudinal markers of disease activity, too. Zeng *et al.* reported that persistent or increasing vessel wall enhancement and thickness correlate with relapse, often before serologic changes, indicating the potential of MRI as a sensitive monitoring tool (31).

A multicentre retrospective study of baseline aortic imaging in 157 newly di-

agnosed GCA patients found that baseline aortic diameter, rather than overt aortitis, predicted subsequent aortic dilation, emphasising the importance of morphological assessment and ongoing monitoring (32).

Routine imaging in TAK, regardless of clinical activity, shows low rates of subclinical progression and may not provide extra prognostic value. This highlights the potential of personalised imaging schedules. In a study of 204 TAK patients, with 580 imaging assessments over a median follow-up of 72 months, radiological activity or progression was detected in 20% of scans. When clinical disease was judged inactive, only 18 out of 418 (4%) showed radiological activity or progression, suggesting low levels of subclinical progression (33).

Emerging molecular imaging

New PET tracers targeting inflammatory cell receptors or proteins are emerging as a major focus of recent research, showing promise as innovative diagnostic and monitoring tools in the field of LVV. Translocator Protein (TSPO)-targeted PET imaging with 18F-DPA714, which binds to the 18 kDa translocator protein on activated inflammatory cells, offers a novel molecular imaging approach that may overcome the limitations of 18F-FDG, such as non-specific glucose uptake. This method provides immune-specific visualisation of vascular inflammation in LVV, with potential advantages in detecting subclinical disease and assessing disease activity earlier than FDG PET (34, 35).

Advances in the treatment of GCA and TAK

Recent advances have expanded therapeutic options for GCA. A large phase III randomised controlled trial (RCT) demonstrated the efficacy and safety of upadacitinib (UPA) 15 mg daily plus a 26-GC taper regimen in patients with newly diagnosed or relapsing disease. A total of 428 patients were included; 70% had a new diagnosis of GCA. UPA was administered at 7.5 mg daily in 107 patients and 15 mg daily in 209. 112 patients received placebo and a 52-week GC taper regimen. UPA at 15 mg daily was superior to placebo in achieving

sustained remission (46.4% [95% confidence interval (CI), 39.6 to 53.2] *vs.* 29.0% [95% CI, 20.6 to 37.5]; $p=0.002$) and showed a favourable GC-sparing effect, a longer time to disease flare, and improved patient-reported outcomes. No major adverse cardiovascular events occurred in the UPA groups; however, higher rates of herpes zoster infection were reported in patients receiving UPA 15 mg daily (36).

Anakinra failed to prevent disease relapses or reduce total GC exposure in a multicentre RCT and was associated with more serious adverse events than placebo, leading to premature discontinuation (37).

Data from the extension of the GUSTO trial showed that 11/13 patients treated with 52-week tocilizumab (TCZ) monotherapy following GC pulses maintained relapse-free remission for three years. TCZ remained effective upon retreatment in the two minor relapses (38).

Patients with GCA or polymyalgia rheumatica (PMR) often require prolonged GC therapy. However, a multicentre cross-sectional study at three Danish hospitals found a low risk of GC-induced adrenal insufficiency after GC discontinuation in 267 patients, suggesting that routine screening should be limited to those with overt symptoms (39). Recent research has evaluated the effectiveness of conventional and biologic disease-modifying antirheumatic drugs (c/bDMARDs) in the treatment of TAK. An open-label RCT of 111 patients with active TAK showed significantly higher response rates at 28 and 52 weeks with mycophenolate mofetil (MMF) plus methotrexate (MTX) than with intravenous cyclophosphamide (CYC) followed by azathioprine (AZA). The overall response rates at 28 and 52 weeks were 58.1% and 55.4%, respectively, in the MMF+MTX group, higher than 32.4% at both time points in the CYC+AZA group ($p=0.011$ and 0.022) (40). However, future studies with longer follow-up are needed to validate these results.

A retrospective multicentre study including 135 patients with TAK found that subcutaneous adalimumab (ADA) ($n=34$) was as effective as intravenous infliximab ($n=101$) and had a compara-

ble risk of relapse and revascularisation at six months (41). These results are important, especially when clinical settings do not permit the routine use of intravenous drugs.

Among new options for TAK patients with disease refractory to anti-TNF agents, preliminary data suggest a potential role for JAK inhibitors. In a single-arm trial of 10 patients, baricitinib induced complete responses in 6/10 patients and partial responses in 2/10. Results also showed a low incidence of adverse events at 24 and 48 weeks (42). Likewise, tofacitinib proved effective in a retrospective cohort of 33 patients refractory to TNF inhibitors or TCZ. After a 15-month follow-up, 69.7% of patients were in remission (43).

Take home messages

- Recent multi-omics and tissue-based studies highlight LVV as conditions driven by coordinated immune-stromal interactions, with biomarkers at genetic, tissue, and circulating levels providing insights into disease pathogenesis and patient stratification (8-13, 15).
- US remains the first-line tool in GCA, MRI is favoured for TAK and deeper vessel analysis, and PET offers a functional perspective of inflammation (21, 22).
- Standardised imaging protocols and scoring systems, coupled with longitudinal data, are priorities for refining imaging-guided tailored approaches in LVV (30, 31, 33).
- New PET tracers may overcome the limitations of non-specific 18F-FDG uptake (34).
- A phase III RCT has demonstrated the efficacy and safety of UPA at a dose of 15 mg daily for newly diagnosed and relapsing GCA (36).
- A large retrospective multicentre study found no differences in remission, relapse, and revascularisation rates between ADA and intravenous infliximab in patients with TAK (41).

What is new in single-organ vasculitis

By definition, single organ vasculitides affect vessels of a single organ or remain localised within a single arterial

territory (3). Herein, we report recent evidence on isolated aortitis and periaortitis and primary central nervous system vasculitis (PCNSV).

Aortitis and periaortitis

Isolated aortitis and chronic periaortitis (CP) are considered single-organ vasculitides when they occur without evidence of systemic vasculitides or other diseases, such as IgG4-related disease or Erdheim-Chester disease.

Aortitis refers to inflammation of the aorta, while CP is an inflammatory process originating in the adventitia of the aortic wall and extending into the surrounding periaortic tissue. Early diagnosis and differentiation among the different causes are essential for improving patient outcomes.

A recent retrospective study at a single centre in Spain evaluated 134 patients referred to a tertiary hospital with aortitis or CP, focusing on treatment and outcomes (44). In this series, one patient had isolated aortitis, and two had retroperitoneal fibrosis (RPF), a condition characterised by CP of the abdominal aorta. All three patients received GCs; in one RPF case, MTX was added, leading to complete remission. Notably, all other cases were caused by secondary factors such as infections, large-vessel vasculitis, or IgG4-related disease, highlighting the importance of thorough differential diagnosis because treatment varies significantly among these conditions (44).

A recent comprehensive review notes that patients with isolated aortitis, even after surgical resection of lesions, may develop new vascular lesions. Additionally, some patients with isolated aortitis might present with an alternative form of GCA (45). Mechanistic studies are needed to identify patient subtypes, predict disease progression, and determine who might benefit from immunosuppressive therapy. Therefore, close monitoring during follow-up is crucial.

Furthermore, recent studies have assessed the role of 18F-FDG PET/CT imaging in monitoring RPF and predicting relapse (46, 47). Bayerl *et al.* evaluated various PET metrics, including standardised uptake volume (SUV)_{max}, SUV_{mean}, SUV_{peak}, and metabolic active

volume (MAV), along with morphological measures such as thickness (CTrim) and cranio-caudal extension (CTcc), to predict metabolic progression (defined as at least a 30% increase in peak SUV corrected for lean body mass) in 50 patients. All PET parameters correlated with morphological features, with baseline MAV being the strongest predictor of disease progression (47). Interestingly, other studies have shown that baseline FDG uptake, assessed with the 4-point visual scale relative to liver uptake, correlates with remission. In one study involving 115 patients, baseline factors such as smoking (odds ratio [OR] 0.34, 95% CI 0.11–0.99) and atypical RPF localisation (*e.g.* pelvic) (OR 0.11, 95% CI 0.02–0.52) were negatively associated with remission, while pre-treatment FDG activity on PET was positively linked (OR 11.51, 95% CI 1.35–98.20). Moreover, thoracic vessel involvement and positive PET findings at the end of treatment independently predicted relapse (hazard ratios [HR] 2.61 and 3.47, respectively) (46).

These findings suggest that 18F-FDG PET/CT can serve as a biomarker for assessing disease activity in RPF. The differences in PET parameters emphasise the need for standardised imaging evaluation. Further research should determine whether semi-quantitative analyses align more closely with disease activity than visual assessments. Recently, case reports have highlighted the potential of fibroblast activation protein alpha inhibitor (FAPI) as a novel imaging agent for RPF. FAPI binds with high affinity to activated fibroblasts' surface protein, potentially enhancing PET/CT accuracy in fibrosis evaluation (48, 49). Regarding treatment, an open-label, randomised phase III trial compared MTX plus low-dose prednisone (LowPred) with standard-dose prednisone (stand-Pred) in RPF. The prednisone doses differed from month 3 onward (0.125 mg/kg *vs.* 0.25 mg/kg), starting at 1 mg/kg. MTX was initiated at the end of month 1, up to 20 mg/week. Forty patients were randomised: 29 received MTX + LowPred, and 31 received standPred. The remission rate difference was 9.1% (95% CI -9.9% to 27.3%), confirming non-inferiority. Time to remission was

similar (log-rank $p=0.549$), and both groups showed comparable reductions in RPF thickness and relapse rates. No significant difference in adverse events was observed (50).

Primary central nervous system vasculitis

Primary central nervous system vasculitis (PCNSV) is a rare, poorly understood vasculitis limited to the central nervous system. Although cerebral vasculitis is more commonly described, a proportion of patients may present with spinal cord involvement. A recent retrospective cohort study of 216 consecutive patients with PCNSV evaluated at the Mayo Clinic from 1983 to 2023 examined clinical, laboratory, radiologic and pathologic findings, along with management and outcomes in patients with spinal cord involvement compared with those with cerebral vasculitis (51). Diagnosis was histologic or based on imaging. 10/216 (4.6%) had spinal cord involvement, with cerebral involvement in 9 cases. One patient (0.5%) had isolated spinal cord vasculitis. Histological evidence of vasculitis was found in all 10. MRI showed thoracic abnormalities in 8 patients, cervical spine involvement in 2, conus medullaris involvement in 3, and cauda equina enhancement in 4. Compared with patients with cerebral vasculitis, patients with spinal cord vasculitis presented more often with paraparesis/tetraparesis and were more likely to have at least 1 relapse ($p<0.001$). Histological findings were more often necrotising ($p=0.01$) and granulomatous vasculitis ($p=0.03$). On MRI, meningeal enhancement was often present (OR=10.50). Spinal cord involvement was more commonly associated with the presence of lymphoma (OR=6.49), specifically Hodgkin lymphoma diagnosed simultaneously with PCNSV.

No differences between the 2 groups were observed in long-term remission, treatment response, high disability scores (modified Rankin Scale score, 4–6), or death at last follow-up.

These findings define a rare clinical phenotype that appears to differ from the more “classic” presentation of cerebral vasculitis.

Another retrospective study evaluated

the differences in clinical and imaging between PCNSV with small-vessel and large-vessel vasculitis. 47 PCNSV patients (29 with small vessels-PCNSV, 18 with large vessels-PCNSV) who met the 1988 Calabrese and Mallek diagnostic criteria, with a follow-up duration ≥ 1 year, were enrolled. Patients with small-vessel vasculitis had more severe initial neurological impairment (baseline modified Rankin Scale mRS score: 3 *vs.* 2, $p=0.043$) and a longer median time from onset to treatment initiation (154 days *vs.* 58.5 days, $p=0.013$). They present more often with tumour-like lesions (41.4% *vs.* 5.6%, $p=0.008$), whereas patients with large-vessel involvement presented with cerebrovascular stenosis, of which 94.4% exhibited circumferential vascular wall enhancement and had a higher incidence of ischaemic infarction (66.7% *vs.* 20.7%, $p=0.002$). Multivariate analysis confirmed that time from onset to treatment was an independent risk factor for poor 1-year prognosis (mRS score > 2) in both subtypes (OR=1.012, $p=0.021$ for small-vessel vasculitis and OR=1.048, $p=0.040$ for large-vessel vasculitis) (52)

There are no RCTs available for PCNSV, and current treatment approaches are based on guidelines for other vasculitides. Typically, in severe cases, CYC or rituximab (RTX) in association with GCs are the preferred options. A recent case report described a male patient with small-vessel PCNSV who experienced rapid disease progression despite induction therapy with CYC; he was subsequently treated with 1 g of RTX administered two weeks apart. This combined therapeutic regimen, including CYC, RTX, and GCs, adapted from treatment protocols from ANCA-associated vasculitis (AAV), resulted in sustained remission (53, 54). Further data are required to identify patients with more aggressive disease and to determine the most effective therapeutic strategies for these cases.

Take home messages

- Isolated aortitis and chronic periaortitis should be considered isolated organ vasculitis only after careful exclusion of secondary causes at diagnosis and during follow-up (44).

- PET/CT is now considered an important imaging biomarker for predicting disease remission and relapse in RPF. Among the novel ligands, FAPI is the more promising for evaluating the extent of fibrosis (46, 47).
- MTX plus low-dose prednisone is non-inferior to standard-dose prednisone in the treatment of RPF (50).
- Isolated spinal cord involvement in PCNSV represents a different subtype of disease compared with patients with cerebral involvement (51).

What is new in

ANCA-associated vasculitis

AAV encompass a diverse group of conditions that affect small- to medium-sized blood vessels. These include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (3). The clinical presentations of AAV can vary significantly. MPA mainly targets the kidneys, while GPA and EGPA are characterised by extravascular granulomatous inflammation, primarily involving the respiratory tract. In more severe cases, AAV may be associated with capillaritis, most frequently manifesting as glomerulonephritis (GN) or alveolar haemorrhage. Advances in treatment options, along with non-invasive biomarkers for diagnosis, prognosis, and damage assessment, are urgently needed.

Novel biomarkers and clinical features update in MPA and GPA

Recent studies have identified several promising novel biomarkers and molecular features that could improve phenotypic classification and prognosis in AAV. In a retrospective analysis of 109 patients with newly diagnosed AAV, serum cystatin C (a protease inhibitor indicative of renal function) demonstrated diagnostic and prognostic value. Its levels were significantly associated with the Birmingham Vasculitis Activity Score (BVAS), age, and the Five Factor Score (FFS). A cystatin C level of ≥ 2.56 mg/L at diagnosis was linked to a markedly increased risk of all-cause mortality (HR=5.994, 95% CI 1.66, 21.525) (55).

A new diagnostic biomarker is serum

Metnrl, also known as IL-41, an immunomodulatory cytokine primarily expressed in barrier tissues. Serum Metnrl was significantly elevated in patients with MPA and GPA compared to healthy controls (56). It also showed positive correlations with BVAS and renal function markers such as creatinine, cystatin C, and eGFR, suggesting further investigation into its role as a marker for renal involvement in AAV (56).

Beyond serum biomarkers, kidney transcriptomics uncovered a robust 12-gene signature that better predicts kidney failure than the traditional Berden classification (57). Further molecular studies on kidney biopsies revealed differences between MPA/MPO-AAV and GPA/PR3-AAV in the same cohort (57). Similar to findings in lupus nephritis, the interferon (IFN) signature appears to play a role in AAV-related glomerulonephritis. Transcriptomic analysis showed a stronger type I IFN signature in MPA compared to GPA, which correlated with increased kidney fibrosis independently of baseline kidney function. Importantly, a high IFN-I signature was associated with poorer kidney survival, serving as an independent prognostic biomarker for adverse renal outcomes in AAV.

Finally, single-cell transcriptome analyses identified two neutrophil populations (immature neutrophils and a subset expressing type II IFN signature genes [NeuT2ISG]) that were elevated in patients with new-onset MPA compared to controls (58). The NeuT2ISG subset differs from mature neutrophils upon stimulation with IFN- γ and TNF. A greater proportion of NeuT2ISG was linked to persistent vasculitis symptoms, and higher serum IFN- γ levels at disease onset were associated with increased relapse risk.

Regarding clinical updates, a nationwide retrospective study in Japan (J-CANVAS) involving 729 newly diagnosed MPA and GPA patients found that phenotype-based classification more accurately predicts all-cause mortality than serotype alone. Patients with MPA-MPO had the highest risk of death (HR 3.45, 95% CI 1.09, 11.0). Analyses of 24-week remission rates with treatments like CYC and RTX showed no

significant differences across phenotypic or serological subgroups (59).

New evidence on therapeutic management in MPA and GPA

The 2025 British Society for Rheumatology (BSR) guidelines for managing AAV have been published. While RTX and CYC continue to be the preferred immunosuppressive agents for active, organ- or life-threatening AAV, the guidelines highlight the importance of reducing GC exposure to minimise treatment-related toxicity. In this context, the C5a receptor inhibitor avacopan is recommended as a GC-sparing adjunct for eligible patients (60). The effectiveness and safety of avacopan have also been supported by real-world studies (61–63). Furthermore, *post-hoc* analyses of the ADVOCATE trial in patients treated with CYC confirmed avacopan's efficacy, demonstrating sustained remission at both 26 and 52 weeks. These analyses also showed improvements in kidney function and a lower relapse rate (-0.7 , 95% CI: -17.5 to -17.3) in patients receiving avacopan compared to GCs, reaffirming its safety profile (64).

A randomised, double-blind, placebo-controlled trial assessing abatacept combined with a 12-week GC taper for relapsing, non-severe GPA (n= 65, with 34 in the treatment group and 31 in the placebo group) did not demonstrate efficacy. No significant differences emerged in treatment failure rates (defined as BVAS ≥ 1), time to complete remission, duration of GC-free remission, relapse severity, damage prevention, patient-reported quality of life, or safety outcomes, including infections (65).

A multicentre retrospective cohort study from Japan comparing the long-term efficacy and safety of RTX *versus* CYC for severe AAV remission induction (n=178) found higher 10-year survival rates and remission rates with RTX ($p=0.04$ and $p=0.017$, respectively). The rates of end-stage kidney disease (ESKD) progression and relapse were similar between groups, while infection-related mortality was significantly lower in the RTX group (0% *vs.* 15.2%, $p=0.007$) (66).

The best approach to GC tapering remains debated. In a multicentre retro-

spective cohort, a reduced GC regimen based on PEXIVAS and combined with major immunosuppressants (RTX in 74% of patients, CYC in 30%, plasma exchange in 17%) was associated with a higher risk of a composite outcome (death, ESKD, AAV progression before remission, or relapse within 12 months) compared to standard-dose GCs (HR 2.03; 95% CI 1.08, 3.83). Notably, the increased risk was mainly due to higher rates of disease progression or relapse rather than death or ESKD alone. This risk was particularly heightened in patients with baseline serum creatinine >300 µmol/L and in those receiving RTX as induction therapy (67). Conversely, a Japanese real-world study comparing PEXIVAS reduced versus standard GC tapering regimens, after propensity score matching, found no significant difference in relapse-free survival between the two approaches (68).

Novel biomarkers and clinical features update in EGPA

A distinct proteomic signature was observed in EGPA, characterised by increased plasma levels of serine proteinase inhibitor A3 (SERPINA3), alpha-fibrinogen (FGA), alpha-1 acid glycoprotein 1 (AGP1), inter-alpha-trypsin inhibitor heavy chain H3, and serum amyloid A1 compared to healthy controls. Notably, levels of SERPINA3, FGA, and AGP1 correlated with disease activity, and a combination of SERPINA3 and AGP1 effectively distinguished EGPA from other immune-mediated conditions (AUC=0.918) (69). Additionally, lower serum concentrations of anti-C5aR antibody were associated with major relapse events (70). Emerging evidence supports viewing EGPA as part of a T2-eosinophilic disease continuum that includes hypereosinophilic syndromes, asthma, and nasal polyposis. A Japanese retrospective study identified a significant correlation between serum IgE levels and both cutaneous vasculitis and cardiomyopathy in a small cohort of EGPA patients (71). In a large retrospective cohort of patients with severe asthma, Puan *et al.* reported an EGPA prevalence of 3.9%, highlighting the overlap between

severe asthma and early EGPA phenotypes (72). Furthermore, higher serum IgG4 levels have been observed in EGPA and hypereosinophilic syndrome patients compared with those with T2-eosinophilic asthma, suggesting IgG4 may help identify progression from airway-limited disease to systemic vasculitis (73).

Cardiac involvement is a major factor influencing prognosis in EGPA and remains the leading cause of mortality. Cardiac MRI is currently the most sensitive method to detect both active inflammation and subclinical cardiac involvement. A systematic review found myocardial fibrosis via late gadolinium enhancement in 50.9% of 963 EGPA patients, most often with subendocardial or endocardial distribution (22.6%), followed by intramyocardial (13.2%) and subepicardial regions (10%) (74). Two main phenotypes of cardiac involvement have recently been described: eosinophilic myocarditis (EGPA-EM) and chronic inflammatory cardiomyopathy (EGPA-ICM). EGPA-EM indicates an acute eosinophil-driven myocarditis, characterised by cardiac injury with positive Lake Louise MRI criteria or late gadolinium enhancement and eosinophil infiltration on endomyocardial biopsy. Patients with EGPA-EM tend to have higher eosinophil counts and IgE levels, lower ANCA positivity, and less frequent lung and ENT involvement, but higher troponin levels, reduced left ventricular ejection fraction (LVEF), more ST-T changes, and a worse short-term prognosis with increased mortality. EGPA-ICM reflects a more indolent, remodelling phenotype, characterised by cardiac injury potentially associated with features of chronic inflammatory cardiomyopathy on MRI (notably late gadolinium enhancement) and the absence of eosinophilic infiltration on biopsy. ICM patients show similar disease involvement to EGPA patients without cardiac issues, with preserved LVEF and longer durations of cardiac symptoms. A seven-item LATE-EAST score has been proposed to aid in phenotypic classification (75). Distinguishing these phenotypes has important implications for management and short-term outcomes. Additionally, coronary

vasospasm leading to myocardial infarction with non-obstructive coronary arteries (MINOCA) has emerged as a rare but significant presentation (76). Gastrointestinal (GI) involvement in EGPA, associated with a worse prognosis, requires early recognition. The most common signs include abdominal pain, diarrhoea, nausea and vomiting. Independent predictors are eosinophilic tissue infiltration of any organ, weight loss and myalgia, while asthma and ENT lesions are less common (77). Similar analyses between eosinophilic gastroenteritis and EGPA-GI showed no significant demographic or symptom differences, but weight loss may be a risk factor for EGPA. Also, EGPA patients tend to have higher baseline IgE levels, erythrocyte sedimentation rate (ESR), and CRP, along with more systemic symptoms like fever and rash. These findings underscore the importance of maintaining suspicion for gastrointestinal involvement in EGPA, even with nonspecific symptoms. Finally, nailfold videocapillaroscopy (NVC) has been explored as a supportive tool for diagnosis and assessing disease activity in EGPA. Scream *et al.* identified four significant capillaroscopic changes: neoangiogenesis (72%), pericapillary stippling (66%), rolling (100%), and inverted capillary apex (52%). However, their clinical usefulness appears limited to a supplementary role because no clear links to pulmonary function tests or CRP levels have been established (78).

New evidence on therapeutic management in EGPA

In the recent BSR guidelines, the use of RTX or CYC was confirmed for life- or organ-threatening EGPA to induce remission, extrapolating robust data from GPA and MPA (60). However, in 2025, the REOVAS trial provided the first randomised controlled evidence on the role of RTX for remission induction in EGPA. In this trial, GCs plus RTX (1 g 2 weeks apart) were compared with GCs alone or in combination with CYC in severe forms. At 6 months, remission rates (BVAS=0 with a prednisone dose of 7.5 mg/day or less), relapse rates, average daily GC dose, and rates

of adverse events were similar across treatment arms, demonstrating non-superiority of RTX over conventional induction strategies (79).

Similarly, the traditional role of CYC in combination with GCs for EGPA without life-threatening manifestations has been questioned by a target trial emulation study comparing GCs plus CYC with GCs alone for newly diagnosed EGPA with FFS=0. At 12 months, the risk of overall relapse (defined as BVAS >0 and the need for treatment escalation, excluding asthma or ear-nose-throat [ENT] exacerbations) was similar between the two groups. Although safety data were limited, these results warrant further investigation to determine whether routine use of CYC in EGPA warrants reconsideration in favour of eosinophil-targeted therapies (80).

In the recent guidelines, anti-IL-5/IL-5R-directed therapies are preferred for non-life- or non-organ-threatening EGPA, while alternative induction therapy with MTX, MMF, or AZA may be considered when anti-IL-5/IL-5R is unavailable or used as adjunctive therapy. For maintenance of remission, anti-IL-5/IL-5R-directed therapies are recommended as first-line options, while RTX, MTX, MMF, or AZA may be considered as alternatives when anti-IL-5/IL-5R is unavailable or used as adjunctive maintenance therapy, depending on disease phenotype. Overall, current international guidelines consistently support a phenotype-driven treatment strategy while allowing flexibility based on disease severity and drug availability (60).

This is supported by real-world practice. A recent web survey of Japanese rheumatologists, pulmonologists, and neurologists demonstrated that mepolizumab (MEPO) is frequently used in combination with GCs for remission induction and is the most frequently selected regimen for both maintenance and relapse management (81).

The pivotal MIRRA and MANDARA trials established the safety and efficacy of MEPO and benralizumab (BEN) in both newly diagnosed and relapsing or refractory EGPA (82, 83). Subsequent 2025 publications have consolidated their long-term role.

The open-label extension of the MIRRA trial confirmed durable remission, sustained GC sparing, and a favourable safety profile for MEPO. Treatment-related adverse events were experienced by 43% of patients, with injection site reaction the most frequent (17%), and no new safety signals were identified versus the initial part of MIRRA (84).

Real-world data from the Japanese MARS study involving 118 patients confirmed these findings. All patients had previously completed 96 weeks of MEPO treatment and continued receiving four-weekly MEPO 300 mg subcutaneously for a further 96 weeks. The study demonstrated high remission rates at week 192 (64% of patients achieved remission with GCs \leq 4 mg/day and 34% achieved steroid-free remission), substantial reduction in GC use, a good safety profile (58% of patients experienced adverse events and 22% experienced serious adverse events, but none were MEPO-related), and sustained effectiveness of MEPO regardless of disease duration, ANCA status, or immunosuppressant use (85). The open-label extension data from the MANDARA trial showed that switching from MEPO to BEN after one year during the study period led to blood eosinophil depletion and GC sparing. Moreover, treatment with BEN was associated with durable remission, GC discontinuation, blood eosinophil depletion, and low relapse rates (86). *Post-hoc* analyses of the MANDARA trial provided further insight into GC-sparing effects. Although cumulative GC exposure and timing of GC reduction were similar between BEN and MEPO, GC withdrawal was more frequent in the BEN group than in the MEPO group, without differences by ANCA status or immunosuppressive use (87). Using a more stringent remission definition (BVAS=0 and GC dose of 0 mg/day) at weeks 36 and 48, a significantly greater proportion of patients achieved steroid-free remission with BEN than with MEPO, suggesting a potentially stronger steroid-sparing effect of IL-5R blockade (88).

Further, a real-world comparative study published in 2025 suggested higher complete remission rates with BEN than

with MEPO, despite similar disease activity, daily oral GC dose, and asthma functional parameters. BEN induced a deeper reduction in blood eosinophil count than MEPO, and the safety profile was comparable (89). These data have been confirmed by a recent systematic review showing high remission rates at 12 and 24 months after BEN introduction and a significant GCs-sparing effect, with GCs discontinuation in 32% to 68% of patients (90).

The clinical relevance of GCs minimisation beyond traditional remission definitions is supported by patient-reported outcomes (PROs). A recent multicentre study demonstrated rapid and sustained improvement in patient global assessment and all AAV-PRO domains following MEPO initiation, with GCs exposure exerting a stronger influence on patient perception than disease remission itself, damage accrual, MEPO dose, or ANCA status (91).

Beyond systemic disease control, persistent ENT involvement remains a major therapeutic challenge. A single-centre study found that approximately half of patients on biologics underwent endoscopic sinus surgery for nasal polyposis, often requiring a switch in biologics or initiation of dual-biologic therapy (92). Moreover, surgery was performed more frequently in patients on MEPO and BEN than on RTX or dupilumab. Similar findings have been reported in patients with otitis media (93). Another single-centre study highlighted that all patients with secondary failure on BEN experienced uncontrolled ENT symptoms (94). In this context, emerging reports describe the use of dupilumab monotherapy in EGPA, showing good ENT and vasculitis response. Cases of hypereosinophilia were described, leading to dupilumab discontinuation without vasculitis relapse (95).

The optimal treatment duration is another unmet need. Step-down strategies have been explored. A real-life single-centre study evaluating MEPO reduction to 100 mg/4 weeks in patients in sustained remission (BVAS=0, an Asthma Control Test >20, and steroid-free status for at least one year) showed maintenance of vasculitis and asthma control, although around half of the

patients required dose escalation or adjunctive local therapy for ENT relapse, highlighting the need for tailored long-term management (96).

Finally, novel therapeutic approaches are emerging. Preliminary data on the use of tofacitinib demonstrated encouraging remission rates, eosinophil reduction, and GC tapering in a small study of 11 patients, suggesting a potential future role for JAK inhibition in EGPA (97).

Take home messages

- Different serological biomarkers have demonstrated a diagnostic and prognostic role (cystatin C) in AAV and in the evaluation of kidney involvement (IL-41). Transcriptomic analyses have shown a high IFN signature associated with poor kidney survival and a major risk of relapse (55, 56, 58).
- The integration of novel proteomic biomarkers (SERPINA3, FGA, SAA1) with established immunological features (peripheral eosinophilia, IgE, IgG4, ANCA) may improve diagnostic sensitivity and risk stratification in EGPA (69, 71, 72).
- A clearer definition of cardiac and gastrointestinal involvement in EGPA is crucial for early recognition and subsequent treatment (75, 77).
- Various therapeutic strategies to reduce GCs are now available. Avacopan for MPA and GPA; MEPO and BEN for EGPA (60).
- BEN appears to be associated with higher rates of complete remission than MEPO (89, 90).
- The REOVAS trial has demonstrated that RTX is not superior to CYC and other conventional strategies in inducing remission for EGPA (79).

What is new in cryoglobulinaemic vasculitis

Cryoglobulinaemic vasculitis (CV) is a small-vessel vasculitis with a highly heterogeneous clinical presentation, ranging from mild, limited cutaneous vasculitis to severe end-organ damage. Hepatitis C and B viruses (HCV and HBV) play an important role in pathogenesis, but their role is now minor thanks to the widespread use of direct-

acting antivirals (DAAs) and vaccines. Updated epidemiological data, advancements in the pathogenesis, clinical phenotyping, and treatment are herein reported.

Epidemiology and pathophysiology novelties

A nationwide registry analysis in Spain spanning 25 years revealed a significant decrease in hospitalisations due to HCV-related cryoglobulinaemia after 2015. This decline was accompanied by a proportional increase in cases linked to autoimmune diseases, haematological disorders, and HBV (98). These findings clearly indicate a shift in the CV landscape away from a predominantly viral aetiology, with important implications for diagnosis, management, and long-term monitoring.

Beyond epidemiological observations, substantial progress has been made in understanding the pathogenesis of CV. A pivotal *in vitro* study demonstrated that cryoglobulins do not directly damage endothelial cells. Instead, vascular injury is mediated by macrophages that ingest cryoglobulins, leading to the release of pro-inflammatory cytokines such as TNF- α and IL-1 β . Notably, mixed cryoglobulins (types II and III) exhibited greater inflammatory potential than type I, supporting the idea that immune activation, rather than mere vascular blockage, plays a central role in CV development (99).

At cellular and molecular levels, single-cell and genomic studies have provided mechanistic insights, showing that HCV-associated CV is a model of virus-induced autoimmunity driven by persistent, self-reactive B-cell clones. These clones acquire thousands of somatic mutations, including alterations associated with lymphoma, and persist even after the virus is eradicated. They produce IgM rheumatoid factor with increased affinity for IgG and pathogenic insolubility (100). Importantly, these findings decisively separate CV pathogenesis from molecular mimicry against viral antigens, supporting the use of B-cell-targeted therapies and emphasising the need for ongoing lymphoma surveillance even after achieving sustained virological response.

The recognition of monoclonal-driven immune damage has broadened the conceptual framework of CV. Recently, Quartuccio *et al.* proposed a new category called monoclonal gammopathy of rheumatologic significance (MGRhS), providing a unified model for CV and other autoimmune phenotypes caused by small but aggressive B-cell clones, highlighting that even low levels of monoclonal components can promote systemic inflammation and organ damage (101).

Finally, advancements in diagnostic methods remain a key priority. Laboratory case studies suggest that automated blood cell counters and peripheral blood smears can detect early, temperature-dependent abnormalities indicative of cryoglobulinaemia. These potential early signs may precede standard cryoprecipitation tests and help reduce diagnostic delays (102).

Clinical features and treatment update

Clinical features of CV continue to exhibit significant heterogeneity, ranging from mild skin manifestations to severe, life-threatening multi-organ involvement. Recent cohort studies have clarified predictors of disease severity at diagnosis, consistently identifying palpable purpura, Raynaud's phenomenon, underlying haematologic disorders, and elevated cryoprecipitate levels as key indicators of aggressive disease. Notably, clinical features seem to carry greater prognostic weight than absolute cryoglobulin levels, supporting a phenotype-driven rather than laboratory-driven approach to risk stratification (103). Renal, neurological, and pulmonary involvement remain primary determinants of morbidity and mortality. Cryoglobulinaemic GN is a major prognostic factor, especially in patients with an associated monoclonal component, reinforcing the concept of monoclonal-driven organ damage (104). Correspondingly, cryoglobulinaemia has been confirmed as an independent predictor of lymphoma in Sjögren's disease (105, 106).

Long-term follow-up studies after successful antiviral therapy have further refined the natural history of HCV-associated CV. A prospective cohort

with a median follow-up of five years (up to over ten years) showed that cryoglobulin disappearance is often delayed even after sustained virological response, particularly in type II disease, with median times to disappearance of around 36 months compared to 12 months in type III cryoglobulinaemia. Importantly, severe vasculitic manifestations and non-Hodgkin lymphoma may still occur or relapse after sustained viral response (SVR), highlighting the need for prolonged clinical and immunological monitoring even in patients with apparent virological and biochemical remission (107). Notably, peripheral neuropathy showed little or no improvement despite cryoglobulin disappearance, emphasising the limited reversibility of established nerve damage (107). Additionally, recent reports have documented the first case of CV recurrence in a patient with persistently undetectable serum HBV-DNA during treatment with nucleotide analogues, suggesting that disease reactivation can occur independently of active viral replication, possibly triggered by immune mechanisms, and potentially associated with seasonal influenza vaccination (108). From a treatment standpoint, B-cell-targeted therapy with RTX remains the cornerstone for moderate-to-severe CV (109). Long-term data in patients with essential or connective tissue disease-associated CV who achieve remission after RTX show high relapse rates over time, exceeding 70% at five years. Factors like purpura at presentation and previous flares strongly predict relapse. Maintenance RTX strategies seem to reduce early relapse but do not entirely prevent late recurrence, highlighting the chronic, relapsing nature of CV (110).

The expansion of targeted haematologic therapies has introduced new clinical challenges. Recent reports describe paradoxical CV flares following clone-directed treatments such as daratumumab in patients with IgM-producing plasma cell clones. These flares appear related to sudden cryoglobulin release or qualitative changes in cryoglobulin properties rather than absolute levels, further supporting that cryoglobulin burden does not linearly correlate with

disease activity (111). Overall, these findings underscore that CV encompasses a spectrum of immune-mediated disorders driven by diverse pathogenic mechanisms. Early identification of monoclonal and immunological drivers, careful therapeutic planning, and long-term clinical and haematologic monitoring are essential to optimise outcomes in the post-DAA era.

Take home messages

- The epidemiology of CV has markedly shifted in the post-DAA era, with a declining burden of HCV-related disease and a proportional increase in autoimmune- and haematologic-associated forms, requiring updated diagnostic and surveillance strategies (98).
- Recent mechanistic studies have definitively established CV as a prototype of immune-mediated, clone-driven disease, sustained by persistent autoreactive B-cell populations and independent of molecular mimicry against viral antigens (99,100).
- Monoclonality represents a central driver of disease severity and prognosis, linking cryoglobulinaemic glomerulonephritis, systemic organ damage, and lymphoma risk, particularly in SjD (101).
- Despite SVR, cryoglobulin disappearance may be delayed and severe vasculitic manifestations or lymphoproliferative complications can still occur, underscoring the need for long-term clinical and immunological follow-up (107).
- RTX remains the cornerstone therapy for moderate-to-severe CV; however, high relapse rates and paradoxical flares during clone-directed treatments highlight the chronic, relapsing nature of the disease and the importance of individualised, mechanism-based therapeutic strategies (109, 110).

Conclusions

Over the past year, research in systemic vasculitis has accelerated the transition from descriptive disease characterisation to mechanism-driven precision medicine. The integration of multi-omics technologies, advanced imaging

modalities, and refined clinical phenotyping is reshaping our understanding of pathogenic networks and identifying actionable therapeutic targets. Early recognition of high-risk molecular and clinical signatures now represents a critical step toward individualised treatment strategies aimed at preventing relapse and irreversible vascular or end-organ damage.

Although GCs remain foundational in disease control, their cumulative toxicity is no longer considered an unavoidable trade-off. The expanding availability of targeted biologics and small-molecule inhibitors (supported by both randomised trials and real-world evidence) signals a paradigm shift toward safer, steroid-sparing approaches. Collectively, these advances mark the progressive emergence of a precision-based, phenotype-driven model of care and herald a transformative era in the management of systemic vasculitis.

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