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IMMUNOPATHOGENESIS OF OCULAR MANIFESTATIONS OF GRANULOMATOSIS WITH POLYANGIITIS AND POTENTIAL TARGETS FOR NOVEL BIOLOGICAL THERAPIES

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is a phenotypically heterogeneous form of ANCA-associated vasculitis characterized by two partially overlapping processes: extravascular granulomatous inflammation and necrotizing vasculitis of small- and medium-sized vessels. This dual pathobiology is particularly relevant in ocular disease, where some manifestations primarily reflect active vasculopathy and endothelial injury, whereas others result from locally destructive granulomatous inflammation extending from the sinonasal tract, orbit, sclera, and ocular adnexa. Ocular involvement is reported in approximately one quarter to one third of patients in contemporary pooled analyses, with higher rates in ophthalmology-based cohorts and in head-and-neck–limited disease. The most common manifestations include scleritis, episcleritis, orbital inflammatory mass or pseudotumor, peripheral ulcerative keratitis, and lacrimal system involvement; optic neuropathy, retinochoroidal inflammation, and visual loss are less frequent but potentially sight-threatening.

The immunopathogenesis of ophthalmic GPA involves dysregulated B- and T-cell responses, ANCA-mediated neutrophil activation, neutrophil extracellular trap formation, complement amplification, and local tissue-destructive programs mediated by macrophages, plasma cells, fibroblasts, and matrix metalloproteinases. Rituximab remains the best-established biologic therapy, particularly for vasculitic ocular manifestations and peripheral ulcerative keratitis, although granulomatous orbital lesions may be relatively treatment-resistant. Future therapeutic strategies should target BAFF/APRIL/BCMA/TACI signaling, CD38-positive plasma cells, IL-6/IL-6R, IL-21/Tfh/ICOS pathways, Th17/IL-23 signaling, C5a/C5aR-mediated complement activation, NETosis, and monocyte-driven tissue invasion. A layered therapeutic approach combining control of ANCA-dependent inflammation with suppression of local granulomatous tissue destruction may be especially promising, although ocular-specific randomized trials remain lacking.

KEYWORDS

Granulomatosis With Polyangiitis, Ocular Involvement, ANCA-Associated Vasculitis, Immunopathogenesis, Biological Therapy

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Introduction

Granulomatosis with polyangiitis (GPA) is a systemic autoimmune disease belonging to the group of ANCA-associated vasculitides (AAV), in which necrotizing vasculitis coexists with extravascular granulomatous inflammation. Contemporary classifications and reviews emphasize that serological classification based on ANCA specificity—particularly PR3-ANCA versus MPO-ANCA—better reflects certain clinical and biological differences than the syndromic diagnosis alone. The PR3-ANCA phenotype is more frequently associated with granulomatous disease, upper respiratory tract involvement, and ocular manifestations (Hellmich et al., 2024; Lyons et al., 2012; Müller et al., 2021).

The eye and orbit represent a distinctive “model organ” in GPA for two main reasons. First, ocular structures may be damaged both by systemic vasculitis and by a local granulomatous process extending from the nasal cavity, paranasal sinuses, and orbital tissues. Second, ophthalmic involvement clearly illustrates the discrepancy between inflammatory activity and irreversible tissue damage: even a short diagnostic delay may result in corneal perforation, compressive optic neuropathy, or permanent destruction of the orbital walls (Byszewska et al., 2023; Holle et al., 2013; Sfiniadaki et al., 2019). In a multicentre collaborative study including 63 patients, ocular involvement was reported in 35% of cases, with scleritis, orbital mass/orbital pseudotumor, and episcleritis being the most common manifestations (Dammacco et al., 2023). By contrast, a systematic review of rheumatic diseases estimated the prevalence of ocular involvement in GPA at approximately 26%, highlighting the heterogeneity of definitions and cohort selection (Byszewska et al., 2023).

From a translational perspective, ophthalmic GPA is also important because it likely represents one of the most granulomatous ends of the AAV spectrum. This suggests that therapies directed solely against circulating B cells and ANCA may be insufficient in some orbital and sclerocorneal cases, particularly when local plasma-cell niches, monocyte/macrophage activation, invasive fibroblast programs, and alternative complement pathway activation persist (Akiyama et al., 2019; D. R. W. Jayne et al., 2021; Kesel et al., 2012; Mueller et al., 2014). This concept is supported by histopathological data from the upper respiratory tract and by the clinical refractoriness observed in some orbital masses (Holle et al., 2013; Voswinkel et al., 2006; Zhao et al., 2012).

Methodology

This narrative review summarizes current evidence on the immunopathogenesis of ocular manifestations in granulomatosis with polyangiitis (GPA) and potential targets for novel biologic and targeted therapies. A literature search was performed primarily in PubMed/MEDLINE, including publications available up to 2026.

The search strategy included combinations of the following terms: “granulomatosis with polyangiitis”, “Wegener granulomatosis”, “ANCA-associated vasculitis”, “ocular involvement”, “orbital inflammation”, “scleritis”, “peripheral ulcerative keratitis”, “optic neuropathy”, “immunopathogenesis”, “neutrophil extracellular traps”, “complement C5a”, “BAFF”, “APRIL”, “IL-6”, “IL-17”, “IL-21”, “rituximab”, “belimumab”, “abatacept”, “tocilizumab”, “avacopan”, and “biologic therapy”.

Original studies, clinical trials, reviews, retrospective cohorts, case series, and selected case reports were included if they addressed GPA-related ocular disease, immunological mechanisms, histopathology, or targeted treatment. Priority was given to peer-reviewed PubMed-indexed articles, recent reviews, multicentre studies, and randomized controlled trials. Studies not directly related to GPA, ocular involvement, ANCA-associated vasculitis, immunopathogenesis, or targeted therapy were excluded. The literature was analyzed qualitatively and organized thematically into sections on pathogenesis, ocular manifestations, established biologic therapy, and future therapeutic targets.

Pathogenesis and Immunological Mechanism

The pathogenesis of GPA should not be viewed as a linear process; rather, it is better understood as a multilayered immunopathological model. At its core lies a genetic and environmental predisposition, upon which chronic activation of mucosal immunity, progression from localized to systemic disease, and the development of autoreactive responses against proteinase 3 (PR3) and, less frequently, myeloperoxidase (MPO) are superimposed (Lyons et al., 2012; Müller et al., 2021). Contemporary reviews emphasize that GPA is distinguished among ANCA-associated vasculitides by its particular tendency to produce extravascular granulomatous inflammation, which differentiates it from more purely vasculitic phenotypes (Müller et al., 2021; Robson et al., 2022).

At the adaptive immune level, local lymphoid-like structures have been identified within granulomatous lesions, together with affinity maturation of B-cell receptors and mucosal microniches enriched in autoantigens and B-cell survival factors (Mueller et al., 2014; Voswinkel et al., 2006; Zhao et al., 2012). Voswinkel et al. demonstrated clonal expansion and enhanced somatic hypermutation of immunoglobulin genes in endonasal lesions, supporting the concept of local maturation of the humoral immune response (Voswinkel et al., 2006). Zhao et al. showed the presence of chronically activated B cells and mucosal inflammation rich in autoantigens and B-cell survival factors (Zhao et al., 2012). Mueller et al. further demonstrated that plasma cells within granulomas display features of autoreactivity, express APRIL, BCMA, and TACI, and show strong RANKL expression, potentially linking plasma-cell survival with local tissue destruction (Mueller et al., 2014).

Within the T-cell compartment, classical studies demonstrated a predominant Th1 signature in GPA granulomas, characterized by increased IFN-γ expression and a relative deficiency of Th2-type responses (Csernok et al., 1999). More recent studies have expanded this model rather than replaced it, indicating additional involvement of the Th17/IL-23 and Tfh/IL-21 axes (Abdulahad et al., 2013; Nogueira et al., 2010). Csernok et al. documented Th1 predominance within granulomatous lesions, whereas Lamprecht et al. reported increased monocytic production of IL-12 and TNF-α, which normalized after treatment with cyclophosphamide and glucocorticoids (Csernok et al., 1999; Lamprecht, Kumanovics, et al., 2002). Nogueira et al. showed that IL-17A and IL-23 levels are elevated, correlate with more severe disease activity, and may persist despite standard immunosuppression (Nogueira et al., 2010). Abdulahad et al. demonstrated an increased frequency of IL-21-producing cells and an imbalance in the circulating T follicular helper/regulatory T-cell ratio, which is partially reversed following B-cell depletion (Abdulahad et al., 2013).

At the effector level, neutrophils remain central to disease pathogenesis (Müller et al., 2021; Walulik et al., 2023). PR3-ANCA and MPO-ANCA activate previously primed neutrophils, enhancing degranulation, reactive oxygen species production, and neutrophil extracellular trap (NET) formation (Söderberg & Segelmark, 2016; Walulik et al., 2023). NETs may themselves serve as a source of autoantigens, promote antigen-presenting cell maturation, and perpetuate autoreactivity (Söderberg & Segelmark, 2016). Schreiber et al. demonstrated that necroptosis regulates NET generation and mediates complement activation, endothelial injury, and autoimmune vasculitis (Schreiber et al., 2017). Pruchniak et al. further showed impaired NET generation and degradation in patients with GPA (Pruchniak et al., 2019). These mechanisms are particularly relevant to ocular tissues, where even subtle shifts in the inflammatory balance within the sclera, cornea, or orbital microcirculation may result in rapidly progressive necrosis or perforation (Byszewska et al., 2023).

Complement activation, especially through the C5a/C5aR axis, provides a mechanistic link between neutrophil-driven inflammation and tissue injury (Brilland et al., 2020). Contemporary mechanistic studies and clinical trials have confirmed that the alternative complement pathway is not merely an epiphenomenon, but an amplifier of ANCA-mediated neutrophil activation. This observation has direct therapeutic relevance, as the efficacy of avacopan in AAV provides clinical validation of this pathway. However, it should be emphasized that ocular GPA still lacks trials specifically designed to evaluate C5aR blockade using ophthalmic endpoints (D. R. W. Jayne et al., 2021).

A distinct pathogenic layer is represented by local tissue destruction, which is particularly relevant in orbital and sinonasal-adjacent disease (Holle et al., 2013). Kesel et al. showed that cartilage destruction in GPA may be driven by fibroblasts producing MMP-1, MMP-3, MMP-13, IL-6, and IL-8, and that this process may occur relatively independently of leukocyte influx (Kesel et al., 2012). Akiyama et al. demonstrated that NETs in locally aggressive head and neck disease induce a tissue-invasive monocyte phenotype dependent on S100A8/S100A9 and MMP-9 (Akiyama et al., 2019). From a pathophysiological perspective, this provides a compelling model for orbital GPA characterized by bone erosion, fibrosis, midfacial deformity, and compressive optic neuropathy (Akiyama et al., 2019; Byszewska et al., 2023).

Finally, two forms of immunological “locality” should be distinguished in ocular GPA. The first is a predominantly vasculitic form, in which scleritis, peripheral ulcerative keratitis, and retinal or choroidal vascular lesions predominate (Byszewska et al., 2023). The second is a more granulomatous form, characterized by orbital mass formation, lacrimal gland involvement, lacrimal drainage system disease, orbital wall erosion, and compressive optic neuropathy (Byszewska et al., 2023; Holle et al., 2013). In the latter phenotype, ANCA expression may be weaker or even absent, making biopsy and imaging particularly important for diagnosis (Tan et al., 2014).

Ocular Manifestations

The ophthalmic spectrum of granulomatosis with polyangiitis may involve virtually all ocular and periocular structures, including the conjunctiva, episclera, sclera, cornea, uvea, retina, optic nerve, lacrimal gland, lacrimal drainage system, and orbit (Sfiniadaki et al., 2019). In one of the largest contemporary open-access multicentre collaborative study, ocular involvement was reported in 35% of patients, with bilateral manifestations present in 32% of cases. The most frequent findings were scleritis, orbital mass or orbital pseudotumor, and episcleritis. Importantly, ocular and systemic manifestations may develop simultaneously; however, in some patients, ophthalmic disease precedes the diagnosis of fully established systemic GPA (Dammacco et al., 2023). In a small subset of cases, an orbital mass may occur without overt systemic manifestations (Dammacco et al., 2023; Holle et al., 2013).

Scleritis and episcleritis are among the most clinically relevant “red eye” presentations in GPA (Sfiniadaki et al., 2019). Episcleritis is usually relatively mild, whereas scleritis—particularly necrotizing scleritis—is associated with a high risk of scleral thinning, perforation, and coexisting peripheral ulcerative keratitis (Mohanan-Earatt & Biswas, 2023; Schonberg & Stokkermans, 2026). In the ophthalmic cohort reported by Gheita et al., scleritis or episcleritis occurred in as many as 87% of patients with ocular GPA, illustrating the strong influence of cohort selection on reported epidemiological patterns (Dammacco et al., 2023; Gheita & Abd El Latif, 2019). From a pathophysiological perspective, scleritis is closely related to active ANCA-mediated disease, with prominent involvement of neutrophils, the microvasculature, and matrix metalloproteinases, although it may also coexist with contiguous granulomatous inflammation extending from adjacent tissues (Holle et al., 2013).

Peripheral ulcerative keratitis and corneoscleral melting are among the most vision-threatening ocular complications of GPA. Clinically, they represent a destructive interaction between limbal vasculopathy,

neutrophil-mediated stromal injury, protease activation, and secondary fibrosis (Hassanpour et al., 2022). Available therapeutic data suggest that rituximab is particularly useful in GPA-associated peripheral ulcerative keratitis, especially in cases refractory to cyclophosphamide or in relapsing disease associated with an imminent risk of corneal perforation (Ebrahimiadib et al., 2016).

Orbital involvement carries a distinct pathobiological significance (Holle et al., 2013). It may present as an inflammatory mass or orbital pseudotumor, extension from sinonasal disease, extraocular muscle inflammation, lacrimal gland involvement, orbital wall erosion, and secondary compressive optic neuropathy (Holle et al., 2013; Ismailova et al., 2018). Orbital GPA is particularly associated with a locally aggressive phenotype and a high risk of permanent structural damage. Holle et al. demonstrated that orbital masses are associated with a more refractory disease course and a greater burden of local damage (Holle et al., 2013). Similarly, Ismailova et al. identified orbital pain, diplopia, restricted ocular motility, ocular redness, reduced visual acuity, and orbital wall destruction as clinically useful indicators of this phenotype (Ismailova et al., 2018).

Optic neuropathy in GPA may be ischemic, inflammatory, or compressive in origin (Salman et al., 2024). In clinical practice, the inflammatory-compressive form involving the orbital apex or optic nerve sheath is often the most vision-threatening and diagnostically challenging. Contemporary case-based reviews indicate that optic neuropathy may develop even when routine diagnostic findings are limited, and therefore requires a high index of clinical suspicion (Clément et al., 2021).

Retinal, choroidal, and uveal manifestations are less frequent, but their presence is diagnostically important because they increase the likelihood of active systemic vasculitis (Sfiniadaki et al., 2019). These manifestations may include retinal vasculitis, retinal hemorrhages, cotton-wool spots, venous thrombosis at the optic disc, and, rarely, exudative retinal detachment secondary to choroidal involvement (Byszewska et al., 2023). Recent publications emphasize that these findings likely belong closer to the “vasculitic injury” end of the disease spectrum than to the “granulomatous mass effect” phenotype (Byszewska et al., 2023; Müller et al., 2021).

Current Biological Therapies

From the perspective of the highest-quality evidence, rituximab remains the only biologic agent with a clearly established role in GPA (Hellmich et al., 2024; Stone et al., 2010). The RAVE trial demonstrated that rituximab was non-inferior to cyclophosphamide for remission induction in ANCA-associated vasculitis, with superiority observed in the subgroup of patients with relapsing disease (Stone et al., 2010). The RITUXVAS trial confirmed the efficacy of rituximab-based regimens in patients with renal involvement, while the MAINRITSAN studies established rituximab as a key agent for remission maintenance (Guillevin et al., 2014; Jones et al., 2010). Updated EULAR recommendations, reflecting the post-randomized trial era, position rituximab alongside cyclophosphamide as a first-line option for remission induction in severe AAV. In clinical practice, rituximab is often preferred in patients with GPA who have a high risk of relapse, particularly those with PR3-ANCA-positive disease (Hellmich et al., 2024).

In ophthalmic GPA, rituximab has the strongest observational evidence among biologic therapies (Taylor et al., 2009). In GPA-associated peripheral ulcerative keratitis (PUK), case reports and small series suggest rapid suppression of corneal necrosis and, in some patients, more effective disease control than cyclophosphamide alone (Ebrahimiadib et al., 2016). In orbital disease, the data are less consistent. Regression of inflammatory infiltrates and radiological improvement may occur; however, permanent optic nerve damage is often irreversible if treatment is initiated too late. Contemporary clinical observations therefore suggest that rituximab is most effective when introduced before fibrosis and structural tissue destruction become established (Holle et al., 2013).

Belimumab was considered a biologically plausible candidate because of the role of BAFF in B-cell and plasmablast survival, as well as the local expression of BAFF/APRIL within granulomatous lesions (Mueller et al., 2014; Zhao et al., 2012). However, the BREVAS trial did not demonstrate a reduction in relapse risk when belimumab was added to azathioprine and glucocorticoids for remission maintenance in AAV. This finding suggests that isolated BAFF blockade at this stage of disease may be insufficient, rather than indicating that the BAFF/APRIL axis is biologically irrelevant (D. Jayne et al., 2019).

Abatacept, which inhibits T-cell costimulation, has a strong mechanistic rationale in GPA, particularly in disease dominated by granulomatous inflammation (Müller et al., 2021). An open-label study in patients with non-severe relapsing GPA produced an encouraging efficacy signal (Langford et al., 2014). However, a more recent randomized placebo-controlled trial did not confirm a reduction in relapse risk, severe worsening, or failure to achieve remission. Thus, abatacept may remain a rescue option in highly selected cases, but current evidence does not support its routine use (Langford et al., 2025).

Biologic blockade of TNF-α, particularly with etanercept, has not fulfilled initial expectations (Wegener's Granulomatosis Etanercept Trial (WGET) Research Group, 2005). Despite a strong theoretical rationale in granulomatous diseases, randomized data for etanercept were negative, and the WGET trial raised safety concerns regarding solid malignancies (Stone et al., 2006; Wegener's Granulomatosis Etanercept Trial (WGET) Research Group, 2005). Infliximab showed clinical responses in some small prospective open-label series of refractory GPA, but the level of evidence remains low and does not justify routine use (Lamprecht, Voswinkel, et al., 2002).

Tocilizumab does not have an established role in GPA, although it remains immunobiologically and clinically interesting (Hellmich et al., 2024). Studies in AAV have demonstrated activation of the IL-6 axis, and isolated case reports have described successful treatment of GPA with tocilizumab, including cases refractory to standard immunosuppression and belimumab (Berti et al., 2015; Tang et al., 2023). At present, however, this approach should be considered experimental or rescue therapy rather than standard treatment (Hellmich et al., 2024; Tang et al., 2023).

An important terminological distinction concerns avacopan. Avacopan is not a biologic agent, but a targeted small-molecule inhibitor of the C5a receptor (Garg & Frishman, 2023). It is nevertheless relevant to this discussion because it clinically validates the complement pathway, particularly the C5a/C5aR axis, as one of the most promising therapeutic targets in GPA (Hellmich et al., 2024; D. R. W. Jayne et al., 2021).

Potential Novel Biological Targets

Future therapeutic strategies for ophthalmic manifestations of granulomatosis with polyangiitis should move beyond the concept of a single dominant pathogenic "driver" toward an approach tailored to the prevailing immunopathological program (Müller et al., 2021). In practical terms, three major pathogenic axes can be distinguished: the humoral immune response and plasma-cell niches, neutrophil- and complement-mediated effector injury, and local granulomatous–stromal tissue destruction (Mueller et al., 2014; Müller et al., 2021). Each of these axes identifies distinct and biologically plausible targets for future biologic and targeted therapies (Müller et al., 2021).

Among the most translationally advanced pathways are C5a/C5aR, BAFF/APRIL/BCMA/TACI, and IL-6/IL-6R (Berti et al., 2019; D. R. W. Jayne et al., 2021; Mueller et al., 2014). The C5a/C5aR axis has already been clinically validated by avacopan, providing strong rationale for the further development of anti-C5a therapies or broader modulation of the alternative complement pathway, particularly in phenotypes characterized by prominent neutrophil activation (Brilland et al., 2020; D. R. W. Jayne et al., 2021). The BAFF/APRIL/BCMA/TACI pathway remains especially attractive in granulomatous disease, where persistent plasma-cell niches may sustain local autoreactivity despite depletion of circulating B cells (Mueller et al., 2014; Müller et al., 2021). The neutral outcome of belimumab trials does not negate the biological relevance of this pathway, but rather suggests that isolated BAFF blockade may be insufficient or introduced at a suboptimal stage of disease (D. Jayne et al., 2019; Mueller et al., 2014). Similarly, the IL-6/IL-6R axis appears particularly relevant in granulomatous and infiltrative phenotypes, as elevated IL-6 levels have been associated with PR3-ANCA positivity and granulomatous manifestations such as pulmonary nodules and cavitary lesions (Berti et al., 2019).

A second group of potential targets involves regulation of T-cell responses and T–B cell interactions (Martinez Valenzuela et al., 2019). The IL-21/Tfh/ICOS axis may play a critical role in maintaining mature B-cell responses, plasmablast differentiation, and persistent autoreactivity (Abdulahad et al., 2013). Increased IL-21 activity and imbalance between circulating T follicular helper (cTfh) cells and regulatory T cells represent some of the most consistent findings in translational studies of GPA (Abdulahad et al., 2013; Xu et al., 2019). The Th17/IL-23 pathway is also of considerable interest, particularly in relapsing disease in which conventional immunosuppression fails to achieve complete suppression of inflammation (Nogueira et al., 2010).

A third category of targets focuses on direct inhibition of local tissue-destructive programs (Müller et al., 2021). These include plasma-cell depletion through anti-CD38 therapies, modulation of NETosis and its regulators, and inhibition of the S100A8/S100A9–MMP-9 axis or fibroblast-driven MMP/IL-6/IL-8 signaling (Kesel et al., 2012; Ostendorf et al., 2023; Söderberg & Segelmark, 2016). Reports of successful daratumumab use in refractory AAV suggest that persistence of long-lived plasma cells may represent one mechanism underlying failure of anti-CD20 therapy (Ostendorf et al., 2023). Furthermore, evidence regarding NET-induced invasive monocytes and fibroblast-dependent tissue destruction indicates that suppression of ANCA-mediated inflammation alone may be insufficient in some orbital forms of GPA (Kesel et al., 2012; Müller et al., 2021).

Discussion and Conclusion

The most important conclusion emerging from current insights into immunopathogenesis is that ophthalmic manifestations of GPA do not represent a biologically uniform phenotype. Scleritis and peripheral ulcerative keratitis (PUK) appear to lie closer to the end of the disease spectrum dominated by ANCA-mediated neutrophilic inflammation, NET formation, endothelial injury, and microvascular damage (Byszewska et al., 2023; D. R. W. Jayne et al., 2021; Söderberg & Segelmark, 2016). In contrast, orbital masses, lacrimal drainage system involvement, and compressive optic neuropathy demonstrate a stronger granulomatous–stromal component, in which local plasma-cell niches, macrophages, multinucleated giant cells, invasive monocytes, and activated fibroblasts may be as important as circulating ANCA (Akiyama et al., 2019; Holle et al., 2013; Kesel et al., 2012; Mueller et al., 2014). From a therapeutic perspective, these observations strongly suggest that a "one-treatment-for-all" approach is conceptually inadequate (Müller et al., 2021).

Current treatment standards for severe GPA, including vision-threatening ocular disease, continue to rely on rapid suppression of systemic inflammation, typically with glucocorticoids combined with rituximab or cyclophosphamide (Hellmich et al., 2024; Stone et al., 2010). However, systemic disease control alone does not guarantee reversibility of ophthalmic damage. This is particularly evident in orbital disease, where the interval between symptom onset and treatment initiation may be more important than the specific immunosuppressive regimen itself. Once fibrosis and compressive tissue remodeling become established, anatomical recovery is frequently incomplete (Holle et al., 2013; Ismailova et al., 2018). These observations support the concept of earlier and more aggressive targeted therapy in orbital and corneoscleral phenotypes (Ebrahimiadib et al., 2016; Holle et al., 2013).

From a translational perspective, the concept of "layered therapy" appears particularly compelling. In a practical model, patients with active scleritis or PUK may derive the greatest benefit from anti-CD20 therapy combined with C5aR blockade, whereas patients with orbital masses, bone erosion, and chronic infiltrative disease may require additional targeting of IL-6, CD38, or BAFF/APRIL/BCMA-related pathways (Berti et al., 2019; D. R. W. Jayne et al., 2021; Mueller et al., 2014; Ostendorf et al., 2023; Stone et al., 2010). Although this strategy currently remains hypothetical, it is strongly supported by emerging immunobiological evidence (Müller et al., 2021).

Several important limitations and unanswered questions remain. The most significant evidence gap is the absence of randomized controlled trials specifically designed with ophthalmic endpoints. Most currently available ocular data derive from case reports, retrospective studies, and published case series, increasing the risk of selection bias and overestimation of treatment efficacy (Dammacco et al., 2023; Sfiniadaki et al., 2019). A second limitation concerns tissue-specific biology, as most mechanistic data originate from studies of sinonasal mucosa, upper respiratory tract lesions, or renal tissue rather than directly from the sclera, cornea, or orbit (Mueller et al., 2014; Voswinkel et al., 2006; Zhao et al., 2012). Third, validated biomarkers capable of distinguishing predominantly vasculitic disease from granulomatous–destructive phenotypes are still lacking, limiting the possibility of truly individualized therapy (Müller et al., 2021). Finally, this review was based primarily on PubMed-indexed literature; although additional regional publications exist, relatively few contemporary high-quality Polish-language studies specifically address the immunopathogenesis of ophthalmic GPA.

Several practical conclusions can nevertheless be drawn. First, ophthalmic GPA likely represents at least two overlapping immunophenotypes: an ANCA/neutrophil-driven phenotype and a granulomatous–stromal phenotype, which should be approached differently from a therapeutic standpoint (Byszewska et al., 2023; Holle et al., 2013). Second, rituximab remains the biologic agent of first choice, although it does not fully address orbital disease and tissue-destructive manifestations (Holle et al., 2013; Stone et al., 2010). Third, the C5a/C5aR, BAFF/APRIL/BCMA, CD38, IL-6/IL-6R, IL-21/Tfh, and Th17/IL-23 pathways currently represent the most biologically plausible targets for future therapies, with combination strategies targeting multiple pathogenic layers likely to provide the greatest benefit (Abdulahad et al., 2013; Berti et al., 2019; D. R. W. Jayne et al., 2021; Mueller et al., 2014; Nogueira et al., 2010; Ostendorf et al., 2023). Finally, future clinical studies should distinguish scleral/corneal endpoints from orbital endpoints, as these phenotypes are not immunobiologically equivalent (Holle et al., 2013; Sfiniadaki et al., 2019).

REFERENCES

1. Abdulahad, W. H., Lepse, N., Stegeman, C. A., Huitema, M. G., Doornbos-van der Meer, B., Tadema, H., Rutgers, A., Limburg, P. C., Kallenberg, C. G. M., & Heeringa, P. (2013). Increased frequency of circulating IL-21 producing Th-cells in patients with granulomatosis with polyangiitis (GPA). *Arthritis Research & Therapy, 15*(3), Article R70. https://doi.org/10.1186/ar4247
2. Akiyama, M., Zeisbrich, M., Ibrahim, N., Ohtsuki, S., Berry, G. J., Hwang, P. H., Goronzy, J. J., & Weyand, C. M. (2019). Neutrophil extracellular traps induce tissue-invasive monocytes in granulomatosis with polyangiitis. *Frontiers in Immunology, 10*, Article 2617. https://doi.org/10.3389/fimmu.2019.02617
3. Berti, A., Cavalli, G., Campochiaro, C., Guglielmi, B., Baldissera, E., Cappio, S., Sabbadini, M. G., Doglioni, C., & Dagna, L. (2015). Interleukin-6 in ANCA-associated vasculitis: Rationale for successful treatment with tocilizumab. *Seminars in Arthritis and Rheumatism, 45*(1), 48–54. https://doi.org/10.1016/j.semarthrit.2015.02.002
4. Berti, A., Warner, R., Johnson, K., Cornec, D., Schroeder, D. R., Kabat, B. F., Langford, C. A., Kallenberg, C. G. M., Seo, P., Spiera, R. F., St. Clair, E. W., Fervenza, F. C., Stone, J. H., Monach, P. A., Specks, U., Merkel, P. A., & RAVE-ITN Research Group. (2019). The association of serum interleukin-6 levels with clinical outcomes in antineutrophil cytoplasmic antibody-associated vasculitis. *Journal of Autoimmunity, 105*, Article 102302. https://doi.org/10.1016/j.jaut.2019.07.001
5. Brilland, B., Garnier, A.-S., Chevailler, A., Jeannin, P., Subra, J.-F., & Augusto, J.-F. (2020). Complement alternative pathway in ANCA-associated vasculitis: Two decades from bench to bedside. *Autoimmunity Reviews, 19*(1), Article 102424. https://doi.org/10.1016/j.autrev.2019.102424
6. Byszewska, A., Skrzypiec, I., Rymarz, A., Niemczyk, S., & Rękas, M. (2023). Ocular involvement of granulomatosis with polyangiitis. *Journal of Clinical Medicine, 12*(13), Article 4448. https://doi.org/10.3390/jcm12134448
7. Clément, M., Néel, A., Toulgoat, F., Weber, M., Godmer, P., Hutin, P., Hamidou, M., & Lebranchu, P. (2021). Inflammatory optic neuropathy in granulomatosis with polyangiitis can mimick isolated idiopathic optic neuritis. *European Journal of Ophthalmology, 31*(1), 245–251. https://doi.org/10.1177/1120672119889008
8. Csernok, E., Trabandt, A., Müller, A., Wang, G. C., Moosig, F., Paulsen, J., Schnabel, A., & Gross, W. L. (1999). Cytokine profiles in Wegener's granulomatosis: Predominance of type 1 (Th1) in the granulomatous inflammation. *Arthritis and Rheumatism, 42*(4), 742–750. https://doi.org/10.1002/1529-0131(199904)42:4%3C742::AID-ANR18%3E3.0.CO;2-I
9. Dammacco, R., Biswas, J., Earatt, A., Lisch, W., Zito, F., Rubini, G., Manno, C., Cicco, S., Alessio, G., & Dammacco, F. (2023). The eye is a common site of granulomatosis with polyangiitis: A collaborative study. *BMC Ophthalmology, 23*, Article 26. https://doi.org/10.1186/s12886-022-02743-x
10. Ebrahimiadib, N., Modjtahedi, B. S., Roohipoor, R., Anesi, S. D., & Foster, C. S. (2016). Successful treatment strategies in granulomatosis with polyangiitis-associated peripheral ulcerative keratitis. *Cornea, 35*(11), 1459–1465. https://doi.org/10.1097/ICO.0000000000000919
11. Garg, J., & Frishman, W. H. (2023). Avacopan: A new adjunctive therapy for antineutrophil cytoplasmic antibody-associated vasculitis. *Cardiology in Review, 31*(1), 3–6. https://doi.org/10.1097/CRD.0000000000000496
12. Gheita, T. A., & Abd El Latif, E. M. (2019). Relationship of ocular presentation in granulomatosis with polyangiitis to autoantibodies and disease activity. *Zeitschrift für Rheumatologie, 78*(3), 281–286. https://doi.org/10.1007/s00393-018-0495-5
13. Guillevin, L., Pagnoux, C., Karras, A., Khouatra, C., Aumaître, O., Cohen, P., Maurier, F., Decaux, O., Ninet, J., Gobert, P., Quémeneur, T., Blanchard-Delaunay, C., Godmer, P., Puéchal, X., Carron, P.-L., Hatron, P.-Y., Limal, N., Hamidou, M., Ducret, M., . . . French Vasculitis Study Group. (2014). Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *The New England Journal of Medicine, 371*(19), 1771–1780. https://doi.org/10.1056/NEJMoa1404231
14. Hassanpour, K., ElSheikh, R. H., Arabi, A., Frank, C. R., Elhusseiny, A. M., Eleiwa, T. K., Arami, S., Djalilian, A. R., & Kheirkhah, A. (2022). Peripheral ulcerative keratitis: A review. *Journal of Ophthalmic & Vision Research, 17*(2), 252–275. https://doi.org/10.18502/jovr.v17i2.10797
15. Hellmich, B., Sanchez-Alamo, B., Schirmer, J. H., Berti, A., Blockmans, D., Cid, M. C., Holle, J. U., Hollinger, N., Karadag, O., Kronbichler, A., Little, M. A., Luqmani, R. A., Mahr, A., Merkel, P. A., Mohammad, A. J., Monti, S., Mukhtyar, C. B., Musial, J., Price-Kuehne, F., . . . Jayne, D. (2024). EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Annals of the Rheumatic Diseases, 83*(1), 30–47. https://doi.org/10.1136/ard-2022-223764
16. Holle, J. U., Voigt, C., Both, M., Holl-Ulrich, K., Nölle, B., Laudien, M., Moosig, F., & Gross, W. L. (2013). Orbital masses in granulomatosis with polyangiitis are associated with a refractory course and a high burden of local damage. *Rheumatology, 52*(5), 875–882. https://doi.org/10.1093/rheumatology/kes382
17. Ismailova, D. S., Abramova, J. V., Novikov, P. I., & Grusha, Y. O. (2018). Clinical features of different orbital manifestations of granulomatosis with polyangiitis. *Graefe's Archive for Clinical and Experimental Ophthalmology, 256*(9), 1751–1756. https://doi.org/10.1007/s00417-018-4014-9

18. Jayne, D., Blockmans, D., Luqmani, R., Moiseev, S., Ji, B., Green, Y., Hall, L., Roth, D., Henderson, R. B., Merkel, P. A., & BREVAS Study Collaborators. (2019). Efficacy and safety of belimumab and azathioprine for maintenance of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized controlled study. *Arthritis & Rheumatology, 71*(6), 952–963. https://doi.org/10.1002/art.40802
19. Jayne, D. R. W., Merkel, P. A., Schall, T. J., Bekker, P., & ADVOCATE Study Group. (2021). Avacopan for the treatment of ANCA-associated vasculitis. *The New England Journal of Medicine, 384*(7), 599–609. https://doi.org/10.1056/NEJMoa2023386
20. Jones, R. B., Tervaert, J. W. C., Hauser, T., Luqmani, R., Morgan, M. D., Peh, C. A., Savage, C. O., Segelmark, M., Tesar, V., van Paassen, P., Walsh, D., Walsh, M., Westman, K., Jayne, D. R. W., & European Vasculitis Study Group. (2010). Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *The New England Journal of Medicine, 363*(3), 211–220. https://doi.org/10.1056/NEJMoa0909169
21. Kesel, N., Köhler, D., Herich, L., Laudien, M., Holl-Ulrich, K., Jüngel, A., Neidhart, M., Gay, S., Gay, R. E., Csernok, E., Lamprecht, P., Gross, W. L., Schumacher, U., & Ullrich, S. (2012). Cartilage destruction in granulomatosis with polyangiitis (Wegener's granulomatosis) is mediated by human fibroblasts after transplantation into immunodeficient mice. *The American Journal of Pathology, 180*(5), 2144–2155. https://doi.org/10.1016/j.ajpath.2012.01.021
22. Lamprecht, P., Kumanovics, G., Mueller, A., Csernok, E., Komocsi, A., Trabandt, A., Gross, W. L., & Schnabel, A. (2002). Elevated monocytic IL-12 and TNF-alpha production in Wegener's granulomatosis is normalized by cyclophosphamide and corticosteroid therapy. *Clinical and Experimental Immunology, 128*(1), 181–186. https://doi.org/10.1046/j.1365-2249.2002.01801.x
23. Lamprecht, P., Voswinkel, J., Lilienthal, T., Nolle, B., Heller, M., Gross, W. L., & Gause, A. (2002). Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology, 41*(11), 1303–1307. https://doi.org/10.1093/rheumatology/41.11.1303
24. Langford, C. A., Khalidi, N., Springer, J., Friedman, M., Hellmich, B., Pagnoux, C., Dehghan, N., Gewurz-Singer, O., Koening, C. L., Lin, Y. C., Monach, P. A., Moreland, L. W., Fifi-Mah, A., Flossmann, O., Forbess, L. J., Lanyon, P., Molloy, E., Specks, U., Spiera, R., . . . Vasculitis Clinical Research Consortium and the European Vasculitis Society. (2025). A randomized, double-blind, placebo-controlled trial of abatacept for the treatment of relapsing, nonsevere granulomatosis with polyangiitis. *Arthritis & Rheumatology, 77*(12), 1739–1748. https://doi.org/10.1002/art.43272
25. Langford, C. A., Monach, P. A., Specks, U., Seo, P., Cuthbertson, D., McAlear, C. A., Ytterberg, S. R., Hoffman, G. S., Krischer, J. P., Merkel, P. A., & Vasculitis Clinical Research Consortium. (2014). An open-label trial of abatacept (CTLA4-Ig) in non-severe relapsing granulomatosis with polyangiitis (Wegener's). *Annals of the Rheumatic Diseases, 73*(7), 1376–1379. https://doi.org/10.1136/annrheumdis-2013-204164
26. Lyons, P. A., Rayner, T. F., Trivedi, S., Holle, J. U., Watts, R. A., Jayne, D. R. W., Baslund, B., Brenchley, P., Bruchfeld, A., Chaudhry, A. N., Cohen Tervaert, J. W., Deloukas, P., Feighery, C., Gross, W. L., Guillevin, L., Gunnarsson, I., Harper, L., Hrušková, Z., Little, M. A., . . . Smith, K. G. C. (2012). Genetically distinct subsets within ANCA-associated vasculitis. *The New England Journal of Medicine, 367*(3), 214–223. https://doi.org/10.1056/NEJMoa1108735
27. Martinez Valenzuela, L., Bordignon Draibe, J., Fulladosa Oliveras, X., Bestard Matamoros, O., Cruzado Garrit, J. M., & Torras Ambrós, J. (2019). T-lymphocyte in ANCA-associated vasculitis: What do we know? A pathophysiological and therapeutic approach. *Clinical Kidney Journal, 12*(4), 503–511. https://doi.org/10.1093/ckj/sfz029
28. Mohanan-Earatt, A., & Biswas, J. (2023). Clinical profile and management of granulomatosis with polyangiitis-associated scleritis from a tertiary care hospital in South India. *Indian Journal of Ophthalmology, 71*(1), 146–152. https://doi.org/10.4103/ijo.IJO_1411_22
29. Mueller, A., Brieske, C., Schinke, S., Csernok, E., Gross, W. L., Hasselbacher, K., Voswinkel, J., & Holl-Ulrich, K. (2014). Plasma cells within granulomatous inflammation display signs pointing to autoreactivity and destruction in granulomatosis with polyangiitis. *Arthritis Research & Therapy, 16*(1), Article R55. https://doi.org/10.1186/ar4490
30. Müller, A., Krause, B., Kerstein-Stähle, A., Comdühr, S., Klapa, S., Ullrich, S., Holl-Ulrich, K., & Lamprecht, P. (2021). Granulomatous inflammation in ANCA-associated vasculitis. *International Journal of Molecular Sciences, 22*(12), Article 6474. https://doi.org/10.3390/ijms22126474
31. Nogueira, E., Hamour, S., Sawant, D., Henderson, S., Mansfield, N., Chavele, K.-M., Pusey, C. D., & Salama, A. D. (2010). Serum IL-17 and IL-23 levels and autoantigen-specific Th17 cells are elevated in patients with ANCA-associated vasculitis. *Nephrology Dialysis Transplantation, 25*(7), 2209–2217. https://doi.org/10.1093/ndt/gfp783
32. Ostendorf, L., Burns, M., Wagner, D. L., Enghard, P., Amann, K., Mei, H., Eckardt, K.-U., Seelow, E., & Schreiber, A. (2023). Daratumumab for the treatment of refractory ANCA-associated vasculitis. *RMD Open, 9*(1), Article e002742. https://doi.org/10.1136/rmdopen-2022-002742
33. Pruchniak, M. P., Ostafin, M., Wachowska, M., Jakubaszek, M., Kwiatkowska, B., Olesinska, M., Zycinska, K., & Demkow, U. (2019). Neutrophil extracellular traps generation and degradation in patients with granulomatosis with polyangiitis and systemic lupus erythematosus. *Autoimmunity, 52*(3), 126–135. https://doi.org/10.1080/08916934.2019.1631812

34. Robson, J. C., Grayson, P. C., Ponte, C., Suppiah, R., Craven, A., Judge, A., Khalid, S., Hutchings, A., Watts, R. A., Merkel, P. A., Luqmani, R. A., & DCVAS Investigators. (2022). 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Annals of the Rheumatic Diseases, 81*(3), 315–320. https://doi.org/10.1136/annrheumdis-2021-221795
35. Salman, A.-R., Hur, M., Warrington, K. J., Garrity, J. A., Koster, M. J., Chodnicki, K. D., Tajfirouz, D. A., & Chen, J. J. (2024). Etiologies and outcomes of granulomatosis with polyangiitis-associated optic neuropathy: A case series and review of the literature. *Journal of Neuro-Ophthalmology, 45*(3), 333–337. https://doi.org/10.1097/WNO.0000000000002249
36. Schonberg, S., & Stokkermans, T. J. (2026). Episcleritis. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK534796/
37. Schreiber, A., Rousselle, A., Becker, J. U., von Mässenhausen, A., Linkermann, A., & Kettritz, R. (2017). Necroptosis controls NET generation and mediates complement activation, endothelial damage, and autoimmune vasculitis. *Proceedings of the National Academy of Sciences of the United States of America, 114*(45), E9618–E9625. https://doi.org/10.1073/pnas.1708247114
38. Sfiniadaki, E., Tsiara, I., Theodossiadis, P., & Chatziralli, I. (2019). Ocular manifestations of granulomatosis with polyangiitis: A review of the literature. *Ophthalmology and Therapy, 8*(2), 227–234. https://doi.org/10.1007/s40123-019-0176-8
39. Söderberg, D., & Segelmark, M. (2016). Neutrophil extracellular traps in ANCA-associated vasculitis. *Frontiers in Immunology, 7*, Article 256. https://doi.org/10.3389/fimmu.2016.00256
40. Stone, J. H., Holbrook, J. T., Marriott, M. A., Tibbs, A. K., Sejismundo, L. P., Min, Y.-I., Specks, U., Merkel, P. A., Spiera, R., Davis, J. C., St. Clair, E. W., McCune, W. J., Ytterberg, S. R., Allen, N. B., Hoffman, G. S., & Wegener's Granulomatosis Etanercept Trial Research Group. (2006). Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial. *Arthritis and Rheumatism, 54*(5), 1608–1618. https://doi.org/10.1002/art.21869
41. Stone, J. H., Merkel, P. A., Spiera, R., Seo, P., Langford, C. A., Hoffman, G. S., Kallenberg, C. G. M., St. Clair, E. W., Turkiewicz, A., Tchao, N. K., Webber, L., Ding, L., Sejismundo, L. P., Mieras, K., Weitzenkamp, D., Ikle, D., Seyfert-Margolis, V., Mueller, M., Brunetta, P., . . . RAVE-ITN Research Group. (2010). Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *The New England Journal of Medicine, 363*(3), 221–232. https://doi.org/10.1056/NEJMoa0909905
42. Tan, L. T., Davagnanam, I., Isa, H., Taylor, S. R., Rose, G. E., Verity, D. H., Pusey, C. D., & Lightman, S. (2014). Clinical and imaging features predictive of orbital granulomatosis with polyangiitis and the risk of systemic involvement. *Ophthalmology, 121*(6), 1304–1309. https://doi.org/10.1016/j.ophtha.2013.12.003
43. Tang, P.-F., Xu, L.-C., Hong, W.-T., & Shi, H.-Y. (2023). Successful treatment of granulomatosis with polyangiitis using tocilizumab combined with glucocorticoids: A case report. *World Journal of Clinical Cases, 11*(5), 1144–1151. https://doi.org/10.12998/wjcc.v11.i5.1144
44. Taylor, S. R. J., Salama, A. D., Joshi, L., Pusey, C. D., & Lightman, S. L. (2009). Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. *Arthritis and Rheumatism, 60*(5), 1540–1547. https://doi.org/10.1002/art.24454
45. Voswinkel, J., Mueller, A., Kraemer, J. A., Lamprecht, P., Herlyn, K., Holl-Ulrich, K., Feller, A. C., Pitann, S., Gause, A., & Gross, W. L. (2006). B lymphocyte maturation in Wegener's granulomatosis: A comparative analysis of VH genes from endonasal lesions. *Annals of the Rheumatic Diseases, 65*(7), 859–864. https://doi.org/10.1136/ard.2005.044909
46. Walulik, A., Łysak, K., Błaszkiewicz, M., Górecki, I., & Gomułka, K. (2023). The role of neutrophils in ANCA-associated vasculitis: The pathogenic role and diagnostic utility of autoantibodies. *International Journal of Molecular Sciences, 24*(24), Article 17217. https://doi.org/10.3390/ijms242417217
47. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. (2005). Etanercept plus standard therapy for Wegener's granulomatosis. *The New England Journal of Medicine, 352*(4), 351–361. https://doi.org/10.1056/NEJMoa041884
48. Xu, Y., Xu, H., Zhen, Y., Sang, X., Wu, H., Hu, C., Ma, Z., Yu, M., & Yi, H. (2019). Imbalance of circulatory T follicular helper and T follicular regulatory cells in patients with ANCA-associated vasculitis. *Mediators of Inflammation, 2019*, Article 8421479. https://doi.org/10.1155/2019/8421479
49. Zhao, Y., Odell, E., Choong, L. M., Barone, F., Fields, P., Wilkins, B., Tungekar, F. M., Patel, P., Sanderson, J. D., Sangle, S., D'Cruz, D., & Spencer, J. (2012). Granulomatosis with polyangiitis involves sustained mucosal inflammation that is rich in B-cell survival factors and autoantigen. *Rheumatology, 51*(9), 1580–1586. https://doi.org/10.1093/rheumatology/kes123