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Advances in the Therapy of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in 2025

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Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic vasculitis affecting small to medium-sized vessels, characterized by asthma, eosinophilia, and inflammation. Recent advances in the understanding of EGPA pathogenesis have facilitated the development of targeted therapies, particularly biologics, aimed at improving disease control and reducing treatment-associated toxicity. This review discusses the current therapeutic landscape for EGPA in 2025, highlighting key clinical trials, real-world data, and future directions.

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a multisystem disorder with a heterogeneous clinical presentation, typically affecting the respiratory system (all patients), peripheral nerves (up to 60% of patients), and skin (40–60% of patients). Cardiac involvement is rarer (up to 25% of patients) but carries a poor prognostic value. Although EGPA is one of the 3 antineutrophil cytoplasm antibodies (ANCA)-associated vasculitides (along with granulomatosis with polyangiitis and microscopic polyangiitis), only 30–40% of patients with EGPA are ANCA positive (mostly with MPO-ANCA).[1]

The disease's rarity (annual incidence of 1–2 per million in North America or Europe) complicates the development of standardized treatments. Historically, glucocorticoids (GC) and conventional immunosuppressants such as cyclophosphamide and azathioprine formed the cornerstone of treatment, selected based on disease severity.[2,3] However, the limited efficacy and significant morbidity associated with these therapies have necessitated the exploration of other, safer and more targeted approaches.[4]

Recent insights into EGPA's immunopathology, particularly the roles of interleukin-5 (IL5) and eosinophils, in parallel with advancing research on eosinophilic asthma, have paved the way for biologics such as mepolizumab and benralizumab. Rituximab has emerged over the past 20 years as a major treatment for granulomatosis with polyangiitis and microscopic polyangiitis, and it has more recently been investigated for use in EGPA. This article reviews the current evidence on these therapies and their integration into clinical practice.

Pathogenesis and Cytokine Driven Therapeutics

1. ***Mepolizumab:*** Mepolizumab, a humanized anti-IL5 monoclonal antibody, was the first biologic approved for EGPA. The pivotal MIRRA trial demonstrated that mepolizumab (300 mg subcutaneously, every 4 weeks) significantly increased remission rates compared to placebo (32% vs 3%, respectively), and reduced GC use and dependence.[4] Follow-up studies have confirmed its efficacy in maintaining long-term remission, especially in ANCA-negative patients.[5-8] However, its efficacy for acute, more severe manifestations of EGPA, such as cardiomyopathy or mononeuritis multiplex, remains unknown.

2. ***Benralizumab:*** Benralizumab, which targets the IL5 receptor α, blocks the IL5 pathway, and induces eosinophil apoptosis through antibody-dependent cellular cytotoxicity. It has recently been approved by the FDA for the treatment of EGPA. A few trials showed good results in patients with refractory or GC-dependent EGPA.[9] The recent results of the head-to-head comparative MANDARA trial showed similar efficacy in the rate of remission at week 52 for benralizumab (30 mg subcutaneously, every 4 weeks) or mepolizumab (59% vs 56%, respectively). In addition, slightly more EGPA patients achieved a GC-free remission at week 52 with benralizumab (a secondary endpoint; 41% vs 26% with mepolizumab).
3. ***Dupilumab:*** Dupilumab, an anti-IL4 and IL13 monoclonal antibody, has gained attention for EGPA patients based on its efficacy in treating eosinophilic asthma and atopic comorbidities.[10] Early-phase trials suggest that dupilumab may reduce asthma exacerbations and eosinophil tissue infiltration, although its vasculitis-modifying effects remain under investigation.

Rituximab, Conventional Therapies and Their Role in 2025

Despite the rise of the latter anti-IL5 (and other anticytokine) biologics, conventional therapies remain relevant for relapsing, severe, and/or organ-threatening disease. To date, treatment choices are mostly based on disease severity and patient clinical characteristics (**Figure 1**). ANCA-positive and ANCA-negative patients are treated similarly, and independently of the precise level of their eosinophil count at the time of a flare or their genetic background. Patients with cardiac, severe renal, gastro-intestinal, and/or central nervous system involvement(s) require the most aggressive treatment. Patients with progressing and/or severe neuropathic, ocular, or gangrenous skin involvement should also receive intensive treatment. In 2025, intense or aggressive approaches remain based on high-dose GC and immunosuppressants, mostly cyclophosphamide.[11] Rituximab can be considered as an alternative to cyclophosphamide in some cases, but there is still limited data to confirm its equivalence in all situations. Patients with less severe EGPA can initially be treated with GC alone. However, the early addition of mepolizumab or benralizumab can be considered, because up to 80% of these patients will likely develop GC-dependent asthma or sinonasal polyposis.

The long-term use of cyclophosphamide is limited by its significant adverse effects, including infertility and secondary malignancies.[12] Methotrexate and azathioprine are widely used as GC-sparing agents in general, and for maintenance therapy in EGPA, following cyclophosphamide-based induction in severe cases.[13] Although they are safer than cyclophosphamide in general, their efficacy remains limited, and neither methotrexate, azathioprine nor mycophenolate mofetil have been rigorously studied in EGPA. Only 1 randomized controlled trial was conducted with azathioprine for induction in non-severe EGPA, comparing it to a placebo and in combination with GC. The trial showed no added benefit from azathioprine.

Rituximab, primarily used in ANCA-associated vasculitis, has shown promise in small EGPA cohorts, particularly in ANCA-positive patients.[14] A recent trial (REOVAS) showed that rituximab-based induction is not superior to GC alone for non-severe EGPA, nor to GC and cyclophosphamide for severe EGPA. While rituximab may be a probable alternative to cyclophosphamide for severe EGPA, this has not been fully demonstrated. In addition, the appropriate course of action after remission is achieved with rituximab-based regimens remains uncertain. Repeat rituximab infusions (every 6 months) are now the standard of care for maintenance in granulomatosis with polyangiitis and microscopic polyangiitis; however, this approach has not been proven effective for EGPA. A study is ongoing (in France) to compare azathioprine and rituximab in patients with EGPA who have achieved remission with GC and cyclophosphamide (or rituximab, for some). Mepolizumab for maintenance after rituximab-based induction has also been investigated in small case series.

Glucocorticoid-Sparing Strategies

Previous studies, conducted prior to the era of biologics, have shown that up to 80% of patients with EGPA can achieve remission of the "vasculitic", non-asthma, non-ear nose throat (ENT) manifestations.[15] However, these patients will remain GC-dependent, averaging 10–12 mg/day of

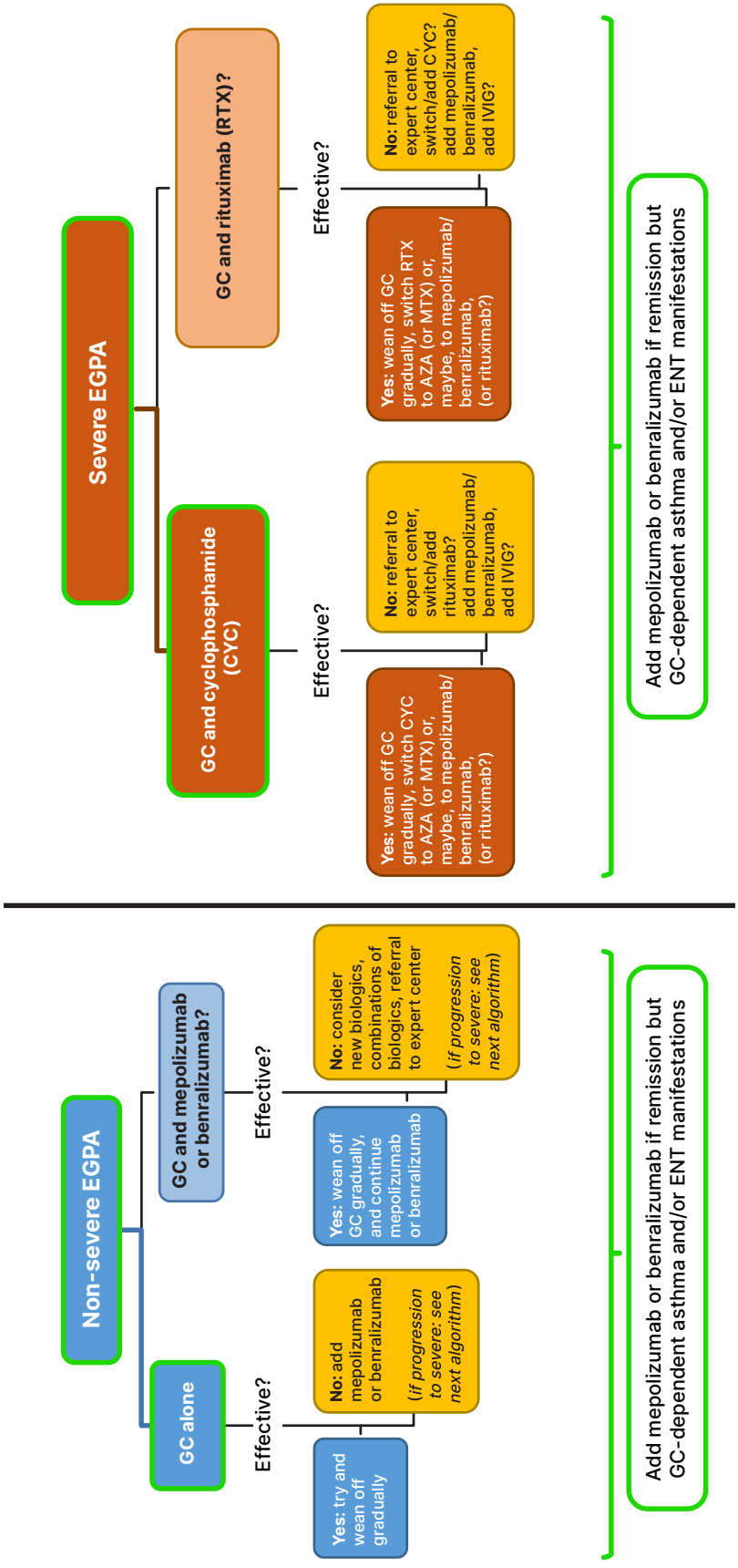

Figure 1. AZA: (oral) azathioprine (1.5-2 mg/kg/day); **CYC:** cyclophosphamide (oral 2 mg/kd/day, or IV pulses of 15 mg/kg at days 1, 15, 30 and then every 3 weeks for 3-9 months; dose adjusted to age and renal function); **ENT:** ear, nose, throat; GC: glucocorticoids (usually, and initially, prednisone 0.5-1 mg/kg/day, not exceeding 80 mg/day for 2 to 4 weeks, and then gradually tapered every 2 weeks; can be preceded by methylprednisolone IV pulses for severe forms 500-1000 mg/day for 1-3 days); *courtesy of Jason K. Lee, MD and Christian Pagnoux, MD.*

Abbreviations: IVIG: intravenous immunoglobulin; **MTX:** methotrexate (oral or subcutaneous, 20-25 mg/week); **RTX:** rituximab (1 g IV at day 1 and 15 for induction; 500 mg every 6 months if used for maintenance [scarce data to date on RTX for maintenance in EGPA]).

prednisone-equivalent, because of their asthma or ENT symptoms. Chronic GC use is associated with numerous complications, including osteoporosis, diabetes, coronary artery disease, and infections.[12] The advent of biologics has provided opportunities to minimize glucocorticoid exposure. Mepolizumab and benralizumab have been shown to substantially reduce prednisone requirements, with some patients achieving GC-free remission.[16] However, the MIRRA and MANDARA studies only enrolled patients at least 6 months after their EGPA diagnosis or after their last flare.[9] Earlier use of mepolizumab or benralizumab could likely decrease the rate of GC-dependency in EGPA or help earlier weaning off GC, but this requires further study. Personalized treatment plans should aim at balancing disease control and treatment toxicity.

Real-World Data and Long-Term Outcomes

While clinical trials provide critical insights, real-world data offers valuable perspectives on the effectiveness and safety of therapies. Registries and observational studies have thus far corroborated the efficacy of biologics in EGPA patient populations, including those with refractory disease.[16] Notably, the durability of remission and patient-reported outcomes, such as quality of life, have emerged as key metrics for evaluating therapeutic success.[7,17]

Whether these biologics should be administered for life or can be gradually discontinued after a few years needs to be studied. Trials in asthma have already begun to determine who can stop these treatments without experiencing an early relapse. The results from these studies and from other non-EGPA populations will likely guide future treatment approaches and/or studies for EGPA more specifically.

Future Directions

Emerging therapies targeting novel pathways, such as eosinophil trafficking and T-cell activation, hold promise for expanding treatment options. Anti-Siglec-8 monoclonal antibodies and Janus kinase (JAK) inhibitors are currently under investigation, with preliminary results indicating significant eosinophil suppression and potential efficacy in refractory EGPA.[18,19] Additionally, biomarker-driven approaches, including blood eosinophil counts, ANCA status, and possibly some genetic markers, may facilitate more precise patient stratification and therapy selection.

Conclusion

The therapeutic landscape for EGPA in 2025 reflects a paradigm shift toward personalized, pathogenesis-driven care. Biologics such as mepolizumab and benralizumab, now approved for EGPA, have transformed disease management by offering improved remission rates and reduced treatment toxicity. Ongoing research and real-world data will continue to refine these approaches, ensuring optimal outcomes for patients with this challenging disease.

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