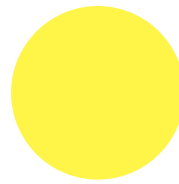


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ANCA-ASSOCIATED VASCULITIS FOR THE ALLERGIST AND IMMUNOLOGIST: A CLINICAL UPDATE

Introduction

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are a group of multisystemic, relapsing, autoimmune diseases that include eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA). While rare, with incidences between

1 and 25 per 100,000 individuals/year, these are diagnoses that should not be missed, as unrecognized, they are associated with significant morbidity and mortality.¹ Despite their infrequency, international collaborative research has resulted in multiple new therapeutic strategies across all three diseases.

Sinusitis in ANCA-associated Vasculitis

Sixty to sixty-five percent of patients with EGPA or GPA initially present with sinus symptoms.^{2,3} EGPA typically presents with years of difficult-to-control, eosinophilic, polypotic rhinosinusitis with nasal polyposis and asthma, often requiring regular oral glucocorticoids in addition to conventional therapy to maintain disease control. Over time, blood eosinophilia becomes apparent, extra-sinopulmonary manifestations (e.g., eosinophilic pneumonia) often occur, and the disease evolves into EGPA with the emergence of vasculitic features that can include cardiomyopathy, gastrointestinal (GI) involvement, vasculitic skin lesions, and/or neuropathy.¹ Given that symptoms can be common to severe eosinophilic sinopulmonary disease, hypereosinophilic syndromes, and EGPA, it can be difficult to confirm the diagnosis if there are no overt vasculitic findings.⁴ The 2022 classification criteria for ANCA-associated vasculitides (AAVs) have assisted in this process but require a vasculitis syndrome to first be diagnosed *before* considering EGPA-specific manifestations, and thus only provides limited inroads to this dilemma.⁵ In addition to vasculitic manifestations, profound blood eosinophilia and serum ANCA (typically to myeloperoxidase) can help differentiate EGPA from other diseases.⁶ Recently, sputum ANCA have demonstrated potential in detecting severe airway disease that is evolving into EGPA.⁷

GPA tends to present more acutely over weeks to months. It can initially manifest as rhinosinusitis (with episcleritis/conjunctivitis that mimics allergic disease in 10% of patients), but is often associated with bloody or purulent discharge suggesting infection that is refractory to antibiotics. As the disease progresses, up to 60% of patients will show tell-tale sinus bony destruction, septal perforation, and neo-osteogenesis on imaging.⁸ Systemic manifestations that indicate a diagnosis of GPA includes diffuse alveolar hemorrhage and/or nodular lung disease; hematuria and glomerulonephritis; leukocytoclastic vasculitis; and mononeuritis multiplex.¹ ANCA are seen in 90% of cases of GPA and are typically reactive to serine protease 3 (PR3). In addition to GPA, several other rheumatic diagnoses to consider based on the presence of erosive sinus disease are drug-induced vasculitis, cocaine-induced midline destructive lesions, IgG4-related disease, and relapsing polychondritis.

Updates in the Treatment of GPA and EGPA

The recent publication of the 2021 American College of Rheumatology guidelines for the management of AAV has consolidated treatment approaches.⁹

EGPA

As a disease with overlap of eosinophilic, allergic and vasculitic pathologies, the treatment for EGPA is varied and influenced by the underlying manifestations. Treatment for vasculitic manifestations of EGPA is often stratified by the five-factor score.¹⁰ Patients with a score of zero, including those with refractory sinus symptoms but relatively mild vasculitis, can be treated with azathioprine or methotrexate; those with a score of one or greater can be treated with cyclophosphamide (followed by azathioprine) or, as suggested by forthcoming data from the REOVAS trial, potentially rituximab as well.^{9,11} Vasculitic manifestations of EGPA are often responsive to therapy; the eosinophilic and sinopulmonary components have been more difficult to control with these agents and may require chronic, high-dose oral glucocorticoids.¹² This has changed, however, since the realization of the utility of anti-interleukin-5 (IL-5) agents in treating refractory sinopulmonary EGPA. The MIRRA trial demonstrated the efficacy of high-dose mepolizumab (300 mg subcutaneously every four weeks) to control disease and minimize glucocorticoid use in patients with EGPA; 28% of patients on mepolizumab achieved remission on 4 mg of prednisone per day or less at 52 weeks vs 3% of those taking placebo.¹³ There were, however, few patients with true vasculitic manifestations; therefore, the use of mepolizumab for manifestations including cardiomyopathy and glomerulonephritis is not clear. Due to access issues, the conventional dose of 100 mg every four weeks has also been tried with some success, however, many patients do not achieve sufficient control with this dose and require either a switch to another anti-IL-5 agent or dose escalation of mepolizumab, with ongoing trials of alternative dosing strategies and agents.¹⁴

Despite this success, there continues to be a population of patients who have refractory sinopulmonary disease. This is a large driver of patient frustration and morbidity; assessments of health-related quality of life (HRQOL) indicate that sinus symptoms are the most frustrating for patients with EGPA.¹² Dupilumab, effective in managing other asthma and sinus disease, has similarly been found to be effective as either alternative or adjunctive therapy to anti-IL5 agents. The drug itself, however, may be associated with an increased risk of EGPA in patients with isolated sinopulmonary disease and may unmask it in vulnerable patients.¹⁵ It is also important to note that while these drugs lower chronic oral glucocorticoid requirements for refractory EGPA patients, ongoing inhaled and/or intranasal therapy is often needed to achieve adequate disease

control. These parallel vasculitic and eosinophilic treatment strategies for EGPA, and the persistence of sinopulmonary disease, reinforce the heterogeneity of EGPA and the need to better understand both the disease pathogenesis and treatment options.⁴

GPA & MPA

The CYCLOPS, RITUXVAS and RAVE trials have ushered in the modern era of cyclophosphamide and rituximab as induction therapies for severe GPA and MPA. These agents achieve remission in over 90% of patients with these diseases.¹⁶ The MAINRITSAN series, and RITAZAREM and PEXIVAS trials for maintenance therapy have demonstrated that continued treatment with rituximab can also provide durable remission with relapse rates as low as 5% per year, and that we can treat patients with lower doses of glucocorticoids than previously used.¹⁶ Plasma exchange, long heralded as beneficial for diffuse alveolar hemorrhage, renal disease and mortality in AAV was found to have only some efficacy in acute, severe renal disease within the PEXIVAS trial and has shifted practice away from this intervention. Finally, the introduction of avacopan during the ADVOCATE trial has also helped realize the possibility of glucocorticoid-free treatments for AAV; however, its place in the therapeutic regimen is still being established.

In patients with non-severe disease including sinus involvement, methotrexate continues to be recommended. Sinus disease is, however, a source of impaired QOL; the disease is often refractory, requiring rituximab for effective treatment.^{17,18} These findings indicate that our current disease construct of severe or non-severe GPA or MPA is limited. Future treatment regimens explore the possibility of shifting from crude indices of severity to a risk-based approach that allows for optimal strategies based on the patient and their disease. Furthermore, fatigue and sinus disease are identified as the largest drivers of ongoing morbidity and represent an area of unmet need that also requires close follow up.

Immune Consequences of Long-term B-cell Depletion in AAV

The diminished humoral response induced by rituximab is important for disease control in AAV, but it is also associated with increased risk of infection and poor vaccine response. While this was a significant concern during the COVID-19 pandemic, it spurred research that quantified that rituximab is associated with a 65% decrease in the capacity to mount an effective COVID vaccine response, and that B-cell recovery takes more than a year to achieve for 60% of patients.¹⁹ As such, vaccinations should

ideally be timed to two-to-three weeks prior to re-administration of rituximab. Furthermore, vaccines should be delayed to at least one year (if safely possible) following completion of rituximab therapy.

A second consideration of long-term rituximab administration is irreversible humoral suppression causing hypogammaglobulinemia. This has been found to occur in approximately 15% of patients, and individuals who demonstrate hypogammaglobulinemia following their first dose of rituximab are at higher risk for it at a later point.²⁰ While this predisposes a patient to recurrent infections, antibodies may have variable functionality, and antibody replacement with intravenous (IV) or subcutaneous immunoglobulins is indicated only for those with multiple infections, who often have IgG levels below 3 g/L.⁹

Conclusion

Multiple advances have been made in the treatment of AAV that have significantly improved outcomes for patients with these rare but potentially devastating diagnoses, although EGPA treatment continues to be a challenge for many patients. As the disease landscape evolves, research has shifted its focus to finding the optimal balance between disease control and therapeutic toxicity, as well as addressing patient-important outcomes such as sinonasal disease and fatigue. As new therapies are adapted from multiple disciplines, ongoing collaboration will be required to continue to improve the standard of care in AAV.

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Financial Disclosures:

M.J.: None declared

N.K.: Roche, BMS, AbbVie, Otsuka, GSK, Astra Zeneca and Mallinckrodt and Sanofi

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