Therapeutic Advances in Eosinophilic Granulomatosis with Polyangiitis

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KEYWORDS

• EGPA • Churg-Strauss • Eosinophilia • Anti-IL-5 • ANCA-associated vasculitis • Therapeutics • Mepolizumab

KEY POINTS

- Eosinophilic granulomatosis with polyangiitis (EGPA) is an eosinophilic vasculitis that affects a variety of organ systems.
- Because of its complexity, EGPA often requires a multi-disciplinary approach for both diagnosis and management and many specialties are called on to evaluate these patients at the time of diagnosis, during the course of disease, and/or to address clinical management questions.
- Historically, glucocorticoids and a variety of other immunosuppressants were used to abrogate the inflammation and tissue injury associated with EGPA.
- The goals of EGPA treatment are to induce remission, limit disease-related damage, prevent relapse, and ensure survival while minimizing treatment-related morbidity.
- The management of EGPA has evolved greatly during the last decade with the development of novel targeted therapeutics that have resulted in significantly improved outcomes for these patients including therapies that target B cells or modulate eosinophils; many more novel targeted therapies are emerging.

BACKGROUND

Eosinophilic granulomatosis with polyangiitis (EGPA) is an eosinophilic vasculitis that affects a variety of organ systems. Classically, EGPA histopathology is characterized by necrotizing vasculitis (most often of small vessels), extravascular granulomas, and infiltrative eosinophils (**Fig. 1**).[1] Although presentations may vary, the 2012 Chapel Hill

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Consensus Conference distinguished EGPA from other vasculitides by the presence of eosinophilic and granulomatous inflammation involving the respiratory tract accompanied by necrotizing vasculitis and by the association with asthma and eosinophilia.[2] Although EGPA is considered one of the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), only 30% to 40% of patients have a positive ANCA, most often with antimyeloperoxidase (MPO) antibodies.[3–5] Because of its complexity, EGPA often requires a multi-disciplinary approach for both diagnosis and management and many specialties are called on to evaluate these patients at the time of diagnosis, during the course of disease, and/or to address clinical management questions. Historically, glucocorticoids and a variety of other immunosuppressants were used to abrogate the inflammation and tissue injury associated with EGPA; however, the management of EGPA has evolved greatly during the last decade with the development of novel targeted therapeutics that have resulted in significantly improved outcomes for these patients.[6,7] This review gives an overview of the presentation of EGPA and the novel approaches toward treatments that have emerged in recent years.

EPIDEMIOLOGY

EGPA has an estimated incidence of 1 to 3 cases per million per year and a prevalence of 14 cases per million per year.[8] Thus, much of what we know about EGPA comes from diverse international cohorts. EGPA is the rarest form of AAV, and is likely underdiagnosed given its variegated clinical presentation, improvement with glucocorticoids, and similarities to severe asthma. There is no male or female predominance in adults with EGPA.[4,5] Although the average age of diagnosis is in the late 40s or early 50s, it often takes years to come to a formal diagnosis.[9] EGPA is quite rare in children but does occur in this age group and is often misdiagnosed, warranting thorough investigation of any child who presents with eosinophilia.

CAUSE

The cause of EGPA is unknown; however, it is suspected that both environmental and genetic factors play a role. Possible environmental triggers include allergens, infections, medications, and silica inhalation.[10–12] Some epidemiologic studies also suggest increased frequency at higher latitudes and more rural areas. An association between the development of EGPA and a variety of asthma therapies has long been

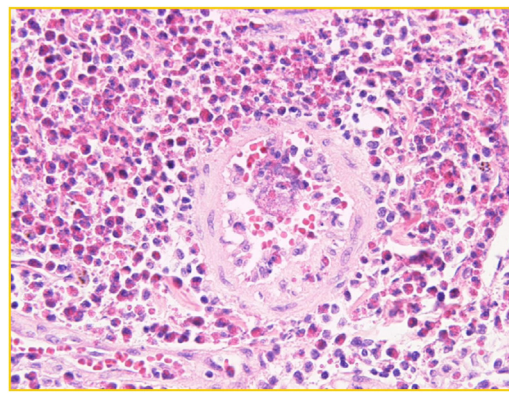

Fig. 1. Typical pathologic features of eosinophil tissue infiltration at the blood vessel wall with granulomata and evidence of eosinophilic vasculitis.

appreciated with cases reported in those taking inhaled glucocorticoids, leukotriene modifiers, and biologics including omalizumab and dupilumab.[13–16] Nonetheless, no causal link has been established and EGPA cases associated with these therapies have generally fallen into 2 categories—forme fruste EGPA, resulting from the withdrawal of systemic glucocorticoids that was masking the underlying eosinophilic vasculitis and coincidental cases of what was perceived to be worsening asthma treated with biologics or other therapies in lieu of administration of glucocorticoids for what was actually incipient EGPA. Genome wide association studies are currently ongoing but earlier genetic studies have implicated HLA-DRB1*07 and HLA-DRB4 as being associated with the development of EGPA.[17,18] ANCA negative subtypes have been associated with IL-10 polymorphisms.[19]

PATHOGENESIS

The pathophysiology of EGPA is complex, resulting in a significant immune dysregulation.[20] There is involvement of both T helper (Th)-1 and Th-2 cells, leading to the granulomatous pulmonary inflammation and the allergic and eosinophilic features, respectively. Additionally, decreased IL-10 levels in EGPA indicate reduced regulatory T-cells, whereas elevated immunoglobulin levels indicate dysregulated humoral immunity.[21–23] The hypereosinophilia in EGPA is most likely due to Th-2 cell or innate lymphoid cell (ILC2)-mediated upregulation of IL-5 predominantly, but also of IL-4 and IL-13.[24] Decreased eosinophil apoptosis can also play a role. Eosinophils are thought to be pathogenic by the release of toxic granular proteins locally in the tissue, including eosinophilic cationic protein, eosinophil derived neurotoxin (EDN), eosinophil peroxidase and major basic protein.[25–28] Deposition of these proteins can lead to local inflammation and damage to the blood vessel wall, resulting in vasculitis, hypercoagulability, and tissue damage, and to many of the features of asthma and chronic sinusitis that are seen in these patients. As IL-5 is involved in the maturation, proliferation, and activation of eosinophils, it has become a major target in EGPA management (see later discussion).[24] IL-4 is also implicated in EGPA pathophysiology because it is involved in B-cell mediated production of antibodies including ANCA, IgE and IgG4, all of which can be elevated in these patients.[29] ANCA is thought to bind to antigens present on the neutrophil, which then adheres to the blood vessel endothelium and migrates through the blood vessel wall, where they recruit other inflammatory cells to the site, causing local damage.[5]

A variety of biomarkers is under investigation for their potential role in disease monitoring and/or medication development. Possible markers of vasculitic activity include urinary-MCP-1 (correlates with renal disease activity and therapy response), urinary soluble-CD163 (correlates with necrotizing crescentic glomerulonephritis), serum and urinary soluble CD25, serum markers of the alternative complement pathway (correlates with disease activity in MPO-ANCA positive renal vasculitis), and markers of B-cell activation/repopulation.[30] Although potential markers of eosinophilic activity include IgG4, CCL26/Eotaxin-3, CL17/TARC, ECP, urinary EDN, and periostin, none has been shown to be more useful than absolute eosinophils in terms of predicting disease or response to the therapies.[30,31]

CLINICAL PRESENTATION

Patients typically develop EGPA during the course of many years and through 3 stages: prodromal, eosinophilic, and vasculitic.[32] The prodromal phase consists of allergic rhinitis, nasal polyposis, atopic disease, and asthma. Most often, this occurs in the second or third decades of life. During stage 2, or the eosinophilic phase,

patients develop peripheral blood eosinophilia and infiltration of eosinophils into organs such as the lung, heart, and gastrointestinal tract. Finally, the vasculitic phase includes necrotizing vasculitis of small- sized to medium-sized vessels and granulomatous inflammation that can affect multiple organ systems such as the lungs, nerves, heart, intestines, skin, and kidneys. Constitutional symptoms occur more frequently in this stage, including weight loss, fever, malaise, and fatigue. Although classically in succession, phases may overlap or occur in any order.[9,33–35]

Although EGPA is typically a multisystem disease, pulmonary manifestations are the most common clinical feature. More than 90% of patients have asthma that is often severe and poorly controlled on inhaled glucocorticoids. Less commonly, some patients may have pleural effusions, pulmonary nodules, or, rarely, diffuse alveolar hemorrhage. Skin disease, such as urticaria, palpable purpura, tender subcutaneous nodules, or hemorrhagic vasculitic lesions, are among the most common presenting findings leading to a diagnosis. Up to three-quarters of patients experience peripheral sensory or motor neuropathy, most often due to mononeuritis multiplex, which can be debilitating for patients, resulting in permanent nerve damage. The most life-threatening manifestation of EGPA is cardiac involvement, which may present as eosinophilic myocarditis, heart failure, pericarditis, valvulitis, coronary vasculitis, and/or rhythm abnormalities. Although it can be asymptomatic, cardiac disease often presents early and is more prevalent in patients who are ANCA-negative and have high eosinophil counts at diagnosis.[36] Eosinophilic gastroenteritis is also common and may present with abdominal pain, diarrhea, gastrointestinal bleeding, or colitis. As with other AAV, venous thromboembolism can be prevalent and a cause of significant morbidity. Additional features seen commonly in EGPA include upper airway, sinus, and ear disease; ophthalmologic complications; hypertension; renal disease; lymphadenopathy; myalgias/myositis; and arthralgias/arthritis (**Table 1**).[9,20,35,37] ANCA-positive patients experience more glomerulonephritis, diffuse alveolar hemorrhage, ENT manifestations, palpable purpura, peripheral nerve pathologic condition, and are more likely to have vasculitis present on biopsy.[4,5,9]

EVALUATION OF SUSPECTED EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

Evaluation of EGPA requires a thorough history and physical examination accompanied by laboratory and imaging tests. There is no single test to diagnose EGPA, although histopathology from a tissue sample is most specific.[9,38] Common laboratory findings include peripheral eosinophilia, elevated immunoglobulin E, positive rheumatoid factor, low-positive antinuclear antigen antibody, positive-anti-MPO antibody, and elevated C-reactive protein and erythrocyte sedimentation rates. Although peripheral eosinophilia is generally defined as greater than the upper limit of normal cells (roughly 500 cells/μL) or greater than 10% of the total leukocyte count, eosinophil counts greater or equal to 1500 cells/μL should raise suspicion for a hypereosinophilic syndrome such as EGPA. It is important to note that eosinophils respond rapidly to glucocorticoids and thus could be falsely diminished if checked after treatment. In this case, eosinophils may still be present in tissue. As discussed, ANCA are present in roughly 40% of patients with EGPA, almost all against MPO.

Imaging should be directed by the presenting signs and symptoms, although additional screening is often warranted once the diagnosis is confirmed. Patients typically undergo chest radiography followed by high-resolution chest computed tomography (CT), which often demonstrates ground glass opacities and nodular densities or fleeting pulmonary infiltrates.[39] When pulmonary infiltrates are present, bronchoalveolar lavage may be performed, which can be useful in demonstrating elevated

Table 1
Clinical manifestations of eosinophilic granulomatosis with polyangiitis[9,20,35,37,99,100]

Cardiovascular • Heart failure (41%) • Eosinophilic myocarditis (16%) • Cardiomyopathy (16%) • Pericarditis (10%–15%) • Valvulitis • Coronary vasculitis • Rhythm abnormalities	Musculoskeletal • Arthralgia/arthritis (30%–40%) • Myalgia/myositis (26%–39%)
Constitutional • Fatigue (72%) • Weight loss (30%–50%) • Fever (39%) • Lymphadenopathy (30%–40%)	Neurologic • Neuropathy (55%–72%) ◦ Sensory neuropathy (51%) ◦ Mononeuritis multiplex (33%–46%) • Cranial nerve palsies (3%) • Stroke (1%)
Mucocutaneous • Palpable purpura (23%–25%) • Urticaria (10%) • Tender subcutaneous nodules (7%–10%) • Ulcerations (4%) • angrene (1%–4%) • Hemorrhagic vasculitic lesions • Nasal or oral ulcers	Ocular (7%) • Ischemic optic neuropathy • Central retinal artery or vein occlusion • Conjunctival nodules • Orbital myositis • Scleritis/episcleritis
Ear, nose, and throat • Recurrent sinusitis (77%) • Nasal polyposis (50%) • Allergic rhinitis (17%) • Sensorineural hearing loss • Serous otitis media	Pulmonary • Asthma, often severe (93%) • Pulmonary infiltrates (39%–58%) • Pleural effusion (9%–10%) • Pulmonary nodules (5%–12%) • Diffuse alveolar hemorrhage (4%–6%)
astrointestina l • Abdominal pain (59%) • Eosinophilic gastroenteritis (4%) • Ischemic bowel (2%) Hematologic • Hypereosinophilia (all[a]) • Venous thromboembolism (8%)	Renal • Hypertension (10%–30%) • Proteinuria (6%–13%) • lomerulonephritis (8%) • Hematuria (8%) • Elevated creatinine (4%–5%)

[a] Hypereosinophilia may not be present if pretreated with glucocorticoids

eosinophil levels, to look for alveolar hemorrhage, and to rule out infection. Spirometry will likely show airflow obstruction. Sinus CT may demonstrate mucosal thickening and/or evidence of nasal or sinus polyps.

All patients suspected of having EGPA should receive an electrocardiogram and undergo echocardiography. Patients who have a reduced ejection fraction should undergo cardiac MRI assessing for valvular or mural thrombi and wall motion abnormalities.[40–44] Additional cardiac testing may include N-terminal-pro B-type natriuretic peptide, and troponin measurement. Cardiac fluorodeoxyglucose-positron emission tomography may be considered to assess for fibrosis versus inflammation.

Although a diagnosis of EGPA can often be made based on clinical history and supportive laboratory findings, ultimately, a tissue biopsy may be required for diagnosis. The most easily accessible affected tissue is often the best choice (skin, kidney, and so forth) although lung and endomyocardial biopsies may be necessary.

Nerve conduction studies and electromyograms can help characterize neuropathy due to EGPA.

CLASSIFICATION AND DIAGNOSIS

A variety of classification criteria exist for EGPA including the 1984 Lanham Diagnostic Criteria, 1990 American College of Rheumatology (ACR) Classification Criteria, 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides definition, 2015 European Respiratory Society's EGPA Consensus Task Force Criteria, and 2022 ACR/European Alliance Of Associations For Rheumatology Classification Criteria (**Box 1**).[2,3,32,45,46] Although these criteria help distinguish different vasculitides or facilitate inclusion of patients into clinical trials, diagnostic criteria are limited. Although it is generally not difficult to distinguish EGPA from other vasculitides such as granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) because of the presence of eosinophilia and asthma in EGPA and by the relative absence of ANCA in EGPA, it can be challenging to distinguish EGPA from the idiopathic hypereosinophilic syndrome (HES) and chronic eosinophilic pneumonia. Like EGPA, HES is characterized by high blood/tissue eosinophils, and can present with pulmonary infiltrates and multisystem involvement. One way to distinguish EGPA from HES is by the greater likelihood of asthma and the presence of ANCA or vasculitic disease features in EGPA or by the identification of specific myeloproliferative or lymphoproliferative features in HES. Although chronic eosinophilic pneumonia is also associated with asthma, eosinophilia, sinusitis and pulmonary infiltrates, it generally lacks the extrapulmonary manifestations seen in EGPA, and is not associated with ANCA or vasculitis.[47–49]

In any patient with eosinophilia, it is critical to take a good history. Drug reactions are among the most common causes of eosinophilia in North America and need to be excluded. Worldwide, parasites are the most common cause of hypereosinophilia so testing for ova and parasites should be considered in patients with a suggestive history or those coming from Africa, South America, or South East Asia. Strongyloides in particular should be excluded because treatment with glucocorticoids in these patients can result in systemic strongyloidiasis, which can be fatal.[50] Malignancies, especially leukemia and lymphoma, should also be excluded as should solid tumors that can also present with eosinophilia and systemic manifestations. Other diagnoses to consider include aspirin-exacerbated respiratory disease and allergic bronchopulmonary aspergillosis.

MANAGEMENT

Because of the rarity of EGPA, there have been very few randomized trials with most published experience being based on small open-label prospective studies, retrospective cohort studies and case series. The lack of randomized trials has led to the use of a wide range of different treatment approaches for EGPA. Some of the treatments used were derived from studies in other vasculitides or trials evaluating asthma. In Duobelt and colleagues' study of 354 adult patients with EGPA from 2003 to 2019, 42% received cyclophosphamide (CYC), 52% received azathioprine (AZA), 9% received mycophenolate mofetil (MMF), 9% received mepolizumab, and 10.5% received rituximab at some point during their disease course, highlighting the diversity of treatments that have been used in EGPA. Glucocorticoid dosing lasted a median of 12 months (interquartile range = 9) with only 12.6% able to discontinue systemic glucocorticoids and immunosuppressive agents for more than 2 years and 40.8% able to discontinue glucocorticoid therapy alone for more than 2 years. The length of time between diagnosis and the last follow-up visit in this study was 7.0 ($\pm$6.2) years.[37]

Box 1
Criteria and nomenclature for eosinophilic granulomatosis with polyangiitis[2,3,32,45,46]

1984 Lanham Diagnostic Criteria
All 3 of the following:
- Asthma
- Peripheral eosinophilia greater than 1.5 × 10^6/cc
- Systemic vasculitis involving 2 or more extrapulmonary organs

1990 American College of Rheumatology Classification Criteria
At least 4 of the following:
- Asthma
- Eosinophilia greater than 10%
- Neuropathy, mono or poly
- Pulmonary infiltrates, nonfixed
- Paranasal sinus abnormality
- Extravascular eosinophils

2012 Revised International Chapel Hill Consensus Conference Definition
- Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent in EP A when glomerulonephritis is present.

2015 European Respiratory Task Force Diagnostic Criteria
History or presence of asthma plus eosinophilia (>1.0 × 10^9/L and/or > 10% of leukocytes)
And 2 of the following:
- A biopsy showing histopathological evidence of eosinophilic vasculitis
- Perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation
- Neuropathy, mono or poly (motor deficit or nerve conduction abnormality) Pulmonary infiltrates, non-fixed
- Sino-nasal abnormality
- Cardiomyopathy (established by echocardiography or MRI)
- lomerulone phritis (hematuria, red cell casts, proteinuria)
- Alveolar hemorrhage (by bronchoalveolar lavage)
- Palpable purpura
- Positive test for ANCA (anti-MPO or anti-PR3)

2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria
- Only applies if the patient has already been diagnosed with small-vessel or medium-vessel vasculitis and alternative diagnoses mimicking vasculitis have been excluded.

Total Score ≥ 6
Clinical Criteria
- Obstructive airway disease (+3 points)
- Nasal polyps (+3 points)
- Mononeuritis multiplex (+1 points)

Laboratory and Biopsy Criteria
- Blood eosinophil count >/ = 1 × 10^9/L (+5 points)
- Extravascular eosinophilic-predominant inflammation on biopsy (+2 points)
- Positive test for cytoplasmic antineutrophil cytoplasmic antibodies or anti-PR3 (−3 points)
- Hematuria (−1 points)

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; PR3, proteinase 3; MPO, myeloperoxidase.

Although EGPA treatment guidelines have been published by several groups and are useful in framing management approaches based on the published literature, they need to be viewed within the context of the individual patient.[46,51] Nonetheless, it is well established that the goals of treatment of EGPA are to induce remission, limit

disease-related damage, prevent relapse, and ensure survival while minimizing treatment-related morbidity. Treatment is considered to have 2 phases: induction (when active disease is put into remission) and maintenance.

Remission Induction

The goal of induction of remission is to get active disease under control, whether at the time of diagnosis or recurrence of active disease, and to prevent organ damage from occurring. The approach to remission induction is based on whether the patient has mild-to-moderate disease or organ-threatening or life-threatening manifestations. The 1996 Five-Factor Score (FFS) may be used to assess disease severity and consists of 5 items: myocardial involvement, gastrointestinal disease (bleeding, perforation, infarction, or pancreatitis), renal insufficiency (plasma creatinine concentration greater than 1.6 mg/dL [141 μmol/L]), proteinuria (>1 g/d), and central nervous system involvement. All items are associated with a poor prognosis and are worth 1 point.[52] A revised FFS published in 2011 replaced proteinuria and central nervous system involvement with age greater than 65 years and the absence of ENT manifestations. Additionally, renal insufficiency was altered to signify a stabilized peak creatinine of 1.7 mg/dL (150 μmol/L). Still, prognostic studies based on FFS used the 1996 version.[53]

Organ-threatening or life-threatening disease

Patients who have organ or life-threatening disease should be treated with high dose glucocorticoids (500–1000 mg IV methylprednisolone daily for 3–5 days) and either CYC or rituximab. In addition to the factors within the FFS, diffuse alveolar hemorrhage, glomerulonephritis, cerebral vasculitis, vision threatening ocular disease, and significant mononeuritis multiplex also warrant more aggressive agents.

CYC is an alkylating neoplastic agent. Efficacy for CYC use in EGPA was explored in a 2001 meta-analysis by Gayraud and colleagues of patients with EGPA, MPA, and polyarteritis nodosa, in which 215 patients received glucocorticoids alone or glucocorticoids plus CYC. Although survival was similar between groups overall and for those with FFS scores of 0 and 1, the patients with an FFS score of 2 or greater experienced significantly greater survival with the combination of glucocorticoids plus CYC compared with those who received glucocorticoids alone ($P = .04$).[54] An earlier study in 1996, demonstrated a lower mortality rate in patients with EGPA and an FFS of 1 with the addition of CYC. Dosing for CYC is based off of treatment of GPA and includes daily dosing (1.5–2 mg/kg daily oral CYC for 3–6 months) and intermittent dosing (15 mg/kg given intravenously CYC every 2 weeks for 3 doses followed by every 3 weeks for at least 3 doses). The duration of therapy is typically 3 to 6 months followed by treatment with a conventional immunosuppressive agent such as AZA, methotrexate (MTX), or MMF based on GPA studies. Although CYC is often preferred in patients with cardiomyopathy, it can cause significant toxicity including increased risk of infections, cytopenias, malignancy, infertility, and hemorrhagic cystitis.

Rituximab, an anti-CD20 monoclonal antibody against B cells, is also used in severe EGPA based on compelling case series and rigorous studies in GPA and MPA.[55,56] A 2021 systematic review of 368 patients with EGPA demonstrated more than 80% of patients reached complete or partial remission with rituximab therapy.[57] Similar results were seen in a 2014 international study of 41 patients with EGPA demonstrating the ability to achieve remission or a partial response to therapy (83% by 6 months, 88% by 12 months) and taper glucocorticoids with rituximab therapy. Notably, those with a positive ANCA had a higher rate of remission at 12 months.[58] A 2020 retrospective analysis also demonstrated improved asthma control in EGPA and decreased glucocorticoid use.[59] A study by Wang and colleagues showed reduced eosinophils

and improved cardiac dysfunction in patients with ANCA-negative EGPA-related myocarditis who received rituximab.[60] Finally, Teixeria and colleagues found that asthma and ear, nose, and throat relapse rates remained high despite decreased glucocorticoid use in EGPA patients who received rituximab due to refractory disease or contraindicated CYC use. Those with ANCA-positivity reached remission more quickly and experienced a longer relapse-free survival.[61] Further studies on rituximab use in EGPA are currently underway.

Dosing in adults with EGPA is 375 mg/m^2 IV rituximab every week for 4 weeks or 1000 mg IV for 2 doses given 2 weeks apart. Rituximab may be more useful in cases with a positive ANCA, active glomerulonephritis, or if there are concerns about CYC side effects. Possible side effects of rituximab include increased risk of infection, infusion reactions, lack of response to vaccines, hypogammaglobulinemia, progressive multifocal leukoencephalopathy, delayed onset neutropenia, and refractory B cell depletion.

Mild-to-moderate disease

For selected patients with mild-to-moderate disease, initial treatment with systemic glucocorticoids alone may be sufficient for patients with an FFS score of 0 or 1. This is based on results of randomized trial results showing high remission and high 5-year survival rates (93% and 97%, respectively) on glucocorticoids alone in patients with an FFS of 0. The relative treatment failures, relapse rate, or glucocorticoids use when on glucocorticoids alone did not change with the addition of AZA.[62,63] Still, although glucocorticoids remain extremely effective in reducing eosinophilia, they can cause significant side effects, even in the short term. Side effects may include infection, cataracts, glaucoma, osteoporosis, avascular necrosis, hypertension, cardiovascular disease, metabolic disease, and depression. It is important to taper glucocorticoids as able while recognizing that disease often recurs with lower doses. For this reason, additional glucocorticoid-sparing agents are often added alongside glucocorticoids from the start even in mild-to-moderate disease. Initial doses of oral prednisone range from 0.5 to 1 mg/kg/d (max 80 mg/d).

Refractory disease

Although glucocorticoids and CYC or rituximab are generally effective in terms of achieving disease control, some patients continue to have refractory disease despite these treatments. Refractory vasculitic disease is uncommon and should prompt a careful examination for whether what is being considered refractory disease is actually disease-related damage or from other causes such as infection or medication side effects. True refractory disease is most often due to persistent asthma and sinus disease. For these patients, adding an additional conventional immunosuppressive agent alongside glucocorticoids should be considered, with a goal of achieving remission and/or lessening glucocorticoid exposure. Historically, refractory disease has been treated with the addition of MTX, AZA, MMF, interferon alpha, intravenous immunoglobulin, imatinib, and plasma exchange without lot of data and with variable success.[64,65] More recently, anti-IL-5 therapies such as mepolizumab have been noted to be effective in predominantly eosinophilic patients with EGPA. Many of these medications are described in more detail below.

Remission Maintenance

The goals of remission maintenance are to prevent relapses and to facilitate the withdrawal of glucocorticoids and other toxic immunomodulators. In one series observed between 2003 and 2019, 50% of patients were reported to have at least 1 relapse, which was characterized by active asthma only (17%), ear/nose/throat (ENT) only

(21%), active asthma and ENT (18%), other lung disease (14%), cardiac (9%), skin manifestations (8%), and/or neuropathy (18%).[37] Relapses, which often manifest as asthma exacerbations or bouts of sinusitis with or without eosinophilia, typically require additional systemic glucocorticoids and additional therapies to optimize control (such as bronchodilators, inhaled glucocorticoids, and nasal glucocorticoids). However, vasculitic flares can also occur and be life-threatening. Vasculitic relapses should be managed with a remission-induction regimen based on disease severity as previously discussed.

Although many providers attempt to taper off of glucocorticoids first before initiating additional therapies in nonsevere EGPA, the approach to maintaining remission depends on a patient's disease severity at presentation and their induction therapy regimen. If CYC was used for induction, patients may receive AZA or other antimetabolites afterward. In GPA and MPA, rituximab has been used for remission maintenance after CYC but there has been less experience with this approach in EGPA. Newer practices may involve initiation of anti-IL-5 therapies in this scenario as well. Additionally, if used to induce remission, anti-IL-5 therapies are continued for maintenance. If rituximab is used for induction therapy, it may be continued every 6 months as maintenance therapy (500–1000 mg IV for adults).

Antimetabolites

Although a mainstay of treatment in the past, antimetabolites such as AZA, MTX, and MMF are used less often now as first-line therapies in EGPA.

AZA is a purine analog that disrupts RNA and DNA synthesis by interfering with purine synthesis. It is the most common antimetabolite used for management of EGPA in both remission induction and maintenance. In trials in GPA and MPA, there was no difference in relapse rates between AZA and oral daily CYC when used for remission maintenance and AZA reduced relapse rates and improved renal survival when continued beyond 18 to 24 months to 48 months.[66,67] However, a trial in GPA and MPA comparing AZA to rituximab for remission maintenance showed that rituximab was superior to AZA in preventing major relapses at 28 months.[68] In EGPA, AZA-induced remission in half of patients with an FFS of 0 and treatment failure or relapse while the addition of AZA to glucocorticoids in a double-blind 2017 trial study did not reduce treatment failures, relapse rate, or glucocorticoids use at 24 months.[62,63] Testing for thiopurine methyltransferase (TPMT) enzyme activity via both genotype and phenotype testing will assist in determining the most appropriate dose for individual patients with AZA being contraindicated in patients who have complete deficiency of TPMT or a homozygous TPMT mutation pattern. AZA is typically initiated at 50 mg/d while awaiting TPMT testing with a goal dose of 2 mg/kg/d (max 200 mg/d) if TPMT enzyme activity is normal. Potential side effects of AZA include increased infections, cytopenias, gastrointestinal upset, hepatotoxicity, and hypersensitivity.

MTX is an antimetabolite that inhibits dihydrofolate reductase and therefore inhibits DNA, RNA, thymidylate, and protein synthesis. It may be given orally or via subcutaneous injection. A 2004 open-label study found that 12 out of 23 patients with non–life-threatening EGPA maintained remission on MTX and glucocorticoids alone and allowed for a 53% reduction in glucocorticoids; however, relapses were frequent.[69] A trial in GPA and MPA comparing MTX to AZA for remission maintenance showed similar adverse event rates and relapse rates.[70] Typical dosing begins at 15 mg/wk by mouth or as a subcutaneous injection, with gradual increases up to 20 or 25 mg/wk if tolerated. Possible adverse effects of MTX include increased infections, nausea/vomiting, cytopenias, liver toxicity, teratogenicity, and MTX pneumonitis.

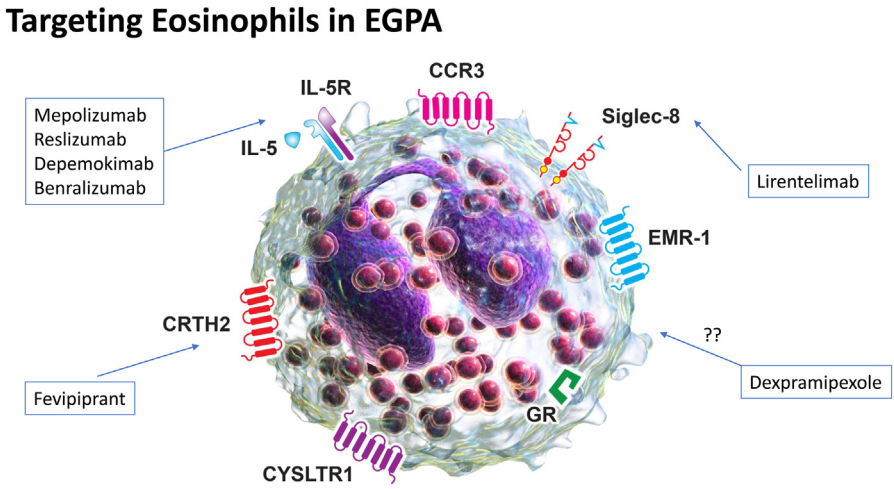

Fig. 2. There are many potential targets in EP A but given the role of eosinophils in EP A pathophysiology, targeting the eosinophil is a rational approach. Mepolizumab binds IL-5 and is the first therapy approved for EP A management. Other therapies that target IL5 or its receptor include reslizumab, depemokimab, and benralizumab. Lirentelimab binds siglec 8 and fevipiprant binds the prostaglandin D2 receptor CRTH2; both can potentially block eosinophil activity. Dexpramipexole blocks eosinophil activity through an unknown mechanism. Upstream targeting of eosinophil production may be achieved by blocking TSLP with tezepelumab or IL-33 with itepekimab and eosinophil trafficking may be impeded by blocking IL-4/IL-13 with dupilumab. (*Adapted from* Wechsler ME, Fulkerson PC, Bochner BS, et al. Novel targeted therapies for eosinophilic disorders. J Allergy Clin Immunol. 2012;130(3):563-571.)

MMF is an antimetabolite that, once taken orally and converted to inosine-5'-monophosphate dehydrogenase, inhibits purine synthesis and therefore DNA replication in B cells and T cells. There are limited data on the use of MMF in patients with EGPA apart from case reports and a recent retrospective study.[71,72] In remission maintenance studies in GPA and MPA, there were more relapses seen with MMF compared with AZA.[73] MMF is dosed at 750 to 1500 mg by mouth twice daily, usually during a couple weeks to alleviate gastrointestinal upset. Along with gastrointestinal symptoms, possible adverse effects of MMF include increased infections, cytopenias, teratogenicity, and malignancy.

Interleukin-5 inhibitors

During the last 7 years, there has been an emergence of a new class of therapies targeting interleukin-5 (IL-5; **Fig. 2**).[74] IL-5 is a cytokine that specifically affects eosinophil maturation, proliferation, activation, migration to blood and tissues, and survival. Thus, by interrupting IL-5 signaling, the number of eosinophils in blood and tissue may be greatly reduced. Although this could potentially put individuals at increased risk of parasitic infection, there have been no reports of such cases. Side effects can include injection site reactions, hypersensitivity, and a possible increased risk for Herpes zoster. The most prominent anti-IL-5 therapy is mepolizumab, an anti-IL-5 monoclonal antibody targeting peripheral eosinophils, which is administered as a subcutaneous injection. Mepolizumab was first approved by the United States Food and Drug Administration (FDA) in 2015 at a dose of 100 mg/mo for use in patients 12 years and older with severe eosinophilic asthma (and later for children aged 6–12 years in

2019) because it significantly reduced asthma exacerbations and hospitalizations. In 2017, mepolizumab gained FDA approval to treat adults with EGPA because of a multicenter, double-blind, parallel-group, phase 3 trial that assigned patients with relapsing or refractory EGPA to receive 300 mg of mepolizumab or placebo every 4 weeks for 52 weeks.[75] Patients had already received treatment for at least 4 weeks and were on stable doses of glucocorticoids and standard of care therapies. The results demonstrated a significantly greater number of weeks of remission in the mepolizumab group than the placebo group (28% vs 3% accrued >24 weeks). More than half of patients on mepolizumab achieved remission, and the mepolizumab treated group had a decreased annualized relapse rate versus placebo (1.14 compared to 2.27). Significantly more patients on mepolizumab reached the daily low-dose glucocorticoid average compared with the placebo group (44% vs 7%) and mepolizumab treated patients achieved a 50% reduction in prednisone dosing by the end of the study compared with placebo.[76] As both groups had similar safety profiles in this first randomized controlled trial completed in EGPA, mepolizumab became the first drug approved by the FDA for EGPA.

Notably, the dose for severe eosinophilic asthma is 100 mg every 4 weeks as opposed to the 300 mg for EGPA striking debate as to whether a lower dose could be effective in patients with EGPA. Bettiol and colleagues compared the effectiveness of these doses in 191 patients with EGPA: 158 received 100 mg mepolizumab every 4 weeks, while 33 received mepolizumab 300 mg every 4 weeks. There were no significant differences observed in their Birmingham vasculitis activity score, prednisone dose, or eosinophil counts between 3 and 24 months.[77] Although this study suggests similar efficacy, others question whether the higher doses are needed for extrapulmonary and/or vasculitic manifestations. Additional anti-IL-5 agents have also showed promise and are discussed further below. Because patients with both severe disease and new onset disease were excluded from the mepolizumab trial, its efficacy in these settings is unknown; EGPA patients with new onset organ-threatening or life-threatening disease should receive a remission induction regimen with CYC or rituximab and glucocorticoids as previously described.

Therapies Under Active Investigation

Additional anti-IL-5 therapies that have been approved for eosinophilic asthma are currently under investigation for use in EGPA. In 2016, the monoclonal antibody against IL-5, reslizumab, was FDA approved for use in severe eosinophilic asthma in adults. In 2018, Kent and colleagues reported on 9 patients with treatment-refractory, glucocorticoid-dependent EGPA with severe eosinophilic asthma and extrapulmonary involvement treated with 3 mg/kg IV reslizumab every 4 weeks for 48 weeks. All patients tolerated more than a 50% reduction in glucocorticoid dose without deterioration in disease control as well as improved patient-reported outcomes.[78] Manka and colleagues assessed the safety and efficacy of reslizumab in an open-label study of 10 adults with EGPA and found it to be both safe and effective.[79]

A third anti-IL-5 agent, benralizumab, gained FDA-approval in 2017 for severe eosinophilic asthma in patients aged older than 12 years due to significant reductions in asthma exacerbations and glucocorticoid use and a strong safety profile. Benralizumab is an anti-IL-5 receptor-alpha monoclonal antibody that affects both peripheral and tissue eosinophils through antibody-dependent cell-mediated cytotoxicity. It is administered in asthma as a 30-mg subcutaneous injection every 4 weeks for 3 doses followed by every 8 weeks. In 2018, benralizumab was deemed an orphan drug by the FDA for treatment of EGPA. In 2020, a prospective 40-week open-label pilot study of benralizumab in 10 adults with EGPA showed that benralizumab allowed for a greater

than 50% reduction in oral glucocorticoid use and fewer EGPA exacerbations. A Phase 3, randomized, double blind multicenter clinical trial is currently underway to examine the efficacy and safety of monthly benralizumab versus mepolizumab in patients with relapsing or refractory EGPA.[80]

Depemokimab is a novel experimental long-acting anti-IL-5 therapy that can be administered every 6 months. It lowers eosinophil counts and is currently being evaluated in a phase 3 study in comparison to mepolizumab in both eosinophilic asthma as well as in relapsing and refractory EGPA.[81]

Possible Future Investigational Targets

With the development of so many novel biologic agents in the last decade for more common diseases such as asthma, it is not surprising that several new therapies could be on the horizon to investigate in EGPA based on their mechanism of action (see **Fig. 2**). To date, there remains no information on their efficacy and safety in this setting such that these should not be used in the clinical care of patients with EGPA.

- Although anti-IL-4/IL-13 therapy with dupilumab may prevent eosinophilic trafficking from blood into tissue, and has been approved for eosinophilic asthma, chronic rhinosinusitis, eosinophilic esophagitis and atopic dermatitis, concerns regarding increasing eosinophil counts and rare systemic eosinophilic manifestations have precluded its being studied in EGPA and thus a role in this disease is unknown.[82]
- Targeting of epithelial cytokines known as alarmins that are upstream to Th2 and ILC2 mediated cytokines such as IL4, IL5, and IL13 has been a strategy used in severe asthma with good success. Tezepelumab is an antithymic stromal lymphopoietin (TSLP) monoclonal antibody approved by the FDA for severe asthma in 2021. Because it lowers eosinophil counts, IgE and exhaled nitric oxide, it may be an effective strategy worth studying in EGPA.[83] Anti-IL33 targeted therapies such as itepekimab and astegolimab also work upstream, preventing IL33 from activating ILC2 cells from producing IL5. Anti-IL33 therapies are showing promise in both asthma and chronic obstructive pulmonary disease and therefore could be an attractive target to explore in EGPA as well.[84,85]
- Dexpramipexole is an oral investigational therapy first developed as a treatment of amyotrophic lateral sclerosis (ALS). Although it failed to meet its primary end point in ALS, dexpramipexole was observed to produce a significant and targeted depletion of eosinophils in the blood of ALS patients, making it a potential oral option for future investigation in EGPA, and in asthma, for which it is being actively studied.[86,87]
- Another eosinophil targeted therapy is lirentelimab, an anti-Siglec-8 antibody that depletes eosinophils and inhibits mast cells and that has shown potential in animal models and humans as a treatment of eosinophilic gastritis and duodenitis.[88] This oral therapy could also be an attractive option to study in patients with EGPA.
- Based on the complexity of EGPA pathophysiology, there is a strong rationale to target a variety of type 2 and nontype 2 cytokines and mediators in EGPA. Although chemokine receptor antagonists that bind CCR3 or therapies that target prostaglandins (CRTH2 antagonists such as fevipiprant) have not been shown to be effective in asthma, there still remains potential that these drugs, and others that target EMR1 or the cysteinyl leukotriene receptors, could be beneficial in EGPA, warranting further study.
- Avacopan, an oral anti-C5a receptor antagonist, is indicated as an adjunctive treatment of adults with severe GPA and MPA in combination with standard

therapy. It was safe and well tolerated in comparison to glucocorticoids.[89] Although EGPA is also considered to be within the family of AAV, there have been no data to date with the use of avacopan in EGPA.

MONITORING AND PROPHYLAXIS

Patients with EGPA require close monitoring for disease activity and medication safety. Ideally, patients will acquire a multidisciplinary team of providers most relevant to their needs, including (but not limited to) a pulmonologist, rheumatologist, allergy/immunologist, otolaryngologist, cardiologist, dermatologist, gastroenterologist, neurologist, and/or mental health professional. We recommend visits every 2 to 4 weeks for the first 3 months spaced out to 3-month intervals once disease control is obtained. Laboratory monitoring should include a complete blood cell count with differential (including eosinophils), complete chemistries, ESR and/or CRP, and urinalysis at an interval based on the disease activity status and medication. Immunoglobulin E monitoring may be useful in selected patients. Patients should undergo frequent pulmonary function testing. We also recommend vaccinating all patients against pneumococcal pneumonia, influenza, and SARS-CoV-2 according to published guidelines as well as providing any other nonlive vaccines recommended by current published guidelines for immunosuppressed hosts. Recombinant zoster (shingles) vaccine, for instance, is appropriate for patients receiving mepolizumab while prophylaxis against Pneumocystis jiroveci is recommended to patients on high doses of glucocorticoids in combination with additional immunosuppressive therapies. Prophylaxis against osteoporosis should be implemented and monitoring should be done annually with bone densitometry in patients on systemic glucocorticoids.

PROGNOSIS

EGPA carries significant risk of morbidity and potential mortality. Morbidity from EGPA may be related to the disease itself but also to toxicity from medications and the psychosocial burden of chronic disease. Although largely fatal initially, the use of glucocorticoids and other immunosuppressive therapies in patients with EGPA has improved mortality rates to roughly 10% with 5-year-survival rates of more than 90%.[9] Cardiac involvement represents the greatest cause of mortality.[7,9] Factors that attribute to a poor prognosis include age greater than or equal to 65 years old, renal failure, gastrointestinal bleeding, cerebral hemorrhage, and severe asthma.[9] Puechal and colleagues showed that the presence of anti-MPO antibodies at baseline is associated with shorter disease-free survival and higher risk of relapse, though overall survival rates were no different between groups, while Doubelt and colleagues did not find a difference in relapse or death rates based on ANCA status.[37,90] Infections in the setting of immunosuppressive therapies also contribute to mortality. Finally, a higher FFS (0 vs 1 vs 2) correlates with increasing 5-year mortality rates (9% vs 21% vs 40%), though anecdotally, many providers solely use these scores as a reminder of the most severe features of disease.[53]

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS IN CHILDREN

The incidence of all AAV in children is 0.45 to 6.4 cases per million children per year; as the smallest subset, EGPA is extremely rare in the pediatric age range.[91,92] Diagnosing EGPA in children is challenging, in part because classification and diagnostic criteria are based on adult patients. The mean age of onset in a systematic review of published pediatric EGPA cases was 12 years old with a male-to-female ratio of 0.74.[93]

Table 2
Current and emerging therapies in eosinophilic granulomatosis with polyangiitis

Class	Examples
Current Therapies	
Alkylating agent	Cyclophosphamide
Anti-CD20	Rituximab
Anti-IL-5	Mepolizumab[a]
Antimetabolite	Azathioprine
Antimetabolite	Methotrexate
Antimetabolite	Mycophenolate Mofetil
Therapies under active investigation	
Anti-IL-5	Depemokimab
Anti-IL-5	Benralizumab
Anti-IL-5	Reslizumab
Possible Future Investigational Targets	
Anti-EMR1	N/A
Anti-CRTH2	Fevipiprant
Anti-CCR3	N/A
Anticysteinyl leukotriene receptors	Montelukast
Anti-IL-4/IL-13	Dupilumab
Anti-interleukin 33	Astegolimab Itepekimab
Antithymic stromal lymphopoietin	Tezepelumab
Antisiglec-8	Lirentelimab
Small molecule	Dexpramipexole

Abbreviation: N/A, not applicable.
[a] Currently approved for use in adults with EP A by the FDA and European Commission.

Fewer than one-third of children with EGPA have positive ANCA antibodies, although when present, they are often directed at MPO.[6,7,93,94] Overall, EGPA in pediatrics is thought to be quite aggressive and often involves the heart and lungs.[6,7,95] A review of 47 published pediatric cases reported 13% mortality while relapse rates in 2 pediatric EGPA series were 46% and 64% during 12 to 18 months.[93,94]

Given its rarity, EGPA is greatly understudied in children, as is AAV in general, with no randomized controlled trials or observational studies involving children. Therefore, pediatric providers largely base their management principles from the adult strategies outlined above, considering that children metabolize medications differently and could be exposed to larger cumulative doses during their lifetime. Pediatric providers are especially interested in glucocorticoid-sparing therapies given the adverse effects of glucocorticoids on growth in childhood as well as their long-term sequalae.

In 2019, rituximab received FDA approval for GPA and MPA in children aged 2 years and older.[96] More recently, pediatric providers have been exploring the use of anti-IL-5 therapies such as mepolizumab and benralizumab in children with EGPA.[97,98] Although providers typically follow similar approaches to treatment in children with EGPA as described in this article, insurance approvals provide significant barriers given the lack of rigorous pediatric studies available. We encourage the medical community to report cases highlighting the clinical presentation, treatment, complications,

and outcomes of children with EGPA in order to increase pediatric patients' access to glucocorticoid-sparing agents.

FUTURE DIRECTIONS

The future is bright for the management of EGPA; however, collaborative multidisciplinary care and rigorous research must be prioritized to advance outcomes in this rare disease. The ability to conduct multicenter studies on EGPA as its own entity separate from other forms of vasculitis together with further investigation of the immunologic pathways involved in EGPA will allow for a greater focus on potential therapeutic targets unique to the disease. Identification of novel predictive and response biomarkers will be critical to advance the science and treatment of EGPA. In the meantime, expanding investigations of emerging therapies (**Table 2**) in EGPA will be critical to inform discussions with patients and their families regarding the risks and benefits of management decisions. Our community is also learning more about the ways in which EGPA presents and progresses in children and young adults and we hope to expand the toolbox of therapeutics available to pediatric patients. Ultimately, we aim to progress toward a more personalized approach to care for patients with EGPA, including best practices for ANCA-positive and ANCA-negative patients as well as organ-specific manifestations.

CLINICS CARE POINTS

- EP A can be a difficult diagnosis to establish. Consideration of EP A should be prompted by the constellation of allergic rhinitis, asthma, hypereosinophilia, and features of a systemic vasculitis although these features may not be present in sequence or at the same time.
- Patients receiving prednisone may not have hypereosinophilia and yet still have an underlying diagnosis of EP A because the eosinophil count will normalize with glucocorticoid treatment.
- Patients with organ-threatening or life-threatening vasculitic disease should be treated by clinicians with experience managing vasculitis; glucocorticoids combined with rituximab or CYC should be used in most severe patients while milder patients may be treated with glucocorticoids alone.
- Consider anti-IL-5 therapy with mepolizumab for patients with relapsing or refractory disease; it has been shown to reduce exacerbations and glucocorticoid dose by 50% or more.

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