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REVIEW

A Review of Anti-IL-5 Therapies for Eosinophilic Granulomatosis with Polyangiitis

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ABSTRACT

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg–Strauss syndrome, is a systemic disorder characterized by asthma, eosinophilia, and vasculitis primarily affecting small vessels. Although this disease is classified as an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis along with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), observations suggest that eosinophils play a vital role in the pathophysiology of EGPA. Therefore, biopsy specimens derived from patients with EGPA demonstrated an increase in eosinophils within the vascular lumen and extravascular interstitium, especially in patients negative for ANCA. In addition, active secretion of eosinophil intracellular components by cytolysis and piecemeal degranulation occurs in the extravascular interstitium and bloodstream. Although the treatment for EGPA is described in the context of ANCA-associated vasculitis along with MPA and GPA, a therapeutic approach to suppress eosinophils is also considered. Monoclonal antibodies directed against interleukin-5 (IL-5) or its receptors are good therapeutic agents because IL-5 plays an important role in eosinophil growth, activation, and survival. Currently, mepolizumab (Nucala), reslizumab (Cinqair), and benralizumab (Fasenra) have been studied for use in patients with EGPA. These monoclonal antibodies were initially approved for use in patients with severe eosinophilic asthma. Mepolizumab is now approved for treating EGPA following the success of phase 3 randomized controlled trial. Therefore, further studies are needed to clarify long-term safety and efficacy of anti-IL-5 agents and establish indications of individual therapeutic agents tailored to individual conditions of patients with EGPA.

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Key Summary Points

Eosinophilic granulomatosis with polyangiitis (EGPA) belongs to the spectrum of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis along with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA).

Accumulating evidence suggests that eosinophils also play an important role in the pathophysiology of EGPA.

Although EGPA's treatment has been described in the context of ANCA-associated vasculitis along with MPA and GPA, a therapeutic strategy to suppress eosinophils has also been considered.

Monoclonal antibodies directed against IL-5 or its receptors are good candidate therapeutic agents because IL-5 plays a central and profound role in the growth, activation, and survival of eosinophils.

Currently, mepolizumab, reslizumab, and benralizumab have been developed as anti-IL-5 agents, and mepolizumab was approved for use in patients with EGPA.

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA), initially known as Churg–Strauss syndrome, is a type of inflammatory disease conventionally characterized by asthma, eosinophilia, and vasculitis predominantly affecting small vessels [1, 2]. According to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC2012), it is histologically defined as eosinophil-rich, necrotizing granulomatous inflammation often involving the respiratory tract and necrotizing vasculitis predominantly affecting small- to medium-sized vessels [1]. EGPA has been considered one of the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides along with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) [1, 3]. Although ANCA has been considered vital in the pathogenesis of vasculitis [2], the positivity rate of ANCA in sera from patients with EGPA is only 30–40% [4, 5]. This contrasts with MPA and GPA, in which about 80% of patients are positive for ANCA [6, 7]. As a result, at least two distinct mechanisms are now thought to be involved in the EGPA disease process: necrotizing vasculitis associated with ANCA and tissue damage associated with eosinophils (Fig. 1) [8, 9]. Although the conventional therapeutic strategy for EGPA is similar to that applied to MPA and GPA from the viewpoint of ANCA-associated vasculitis, the recent development of targeted therapies directed against the eosinophil-associated disease process provided additional therapeutic options. In particular, attention has been paid to interleukin-5 (IL-5), which is important for activating eosinophils. In 2017, a phase 3 clinical trial for EGPA showed that mepolizumab, a humanized monoclonal antibody against IL-5, was effective [10].

Therefore, in this study, we reviewed recent topics in the pathophysiology and treatment of EGPA, emphasizing the rationale for using anti-IL-5 therapies for this disease. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CHARACTERISTICS OF EGPA

EGPA is a systemic disease strongly associated with allergic diathesis, particularly asthma and eosinophilia [11]. The respiratory tract and other organs frequently involved are the peripheral nerve, lung, heart, kidney, and skin [8, 12]. The American College of Rheumatology (ACR) proposed the EGPA classification criteria in 1990 [13]. Following the ACR criteria, the

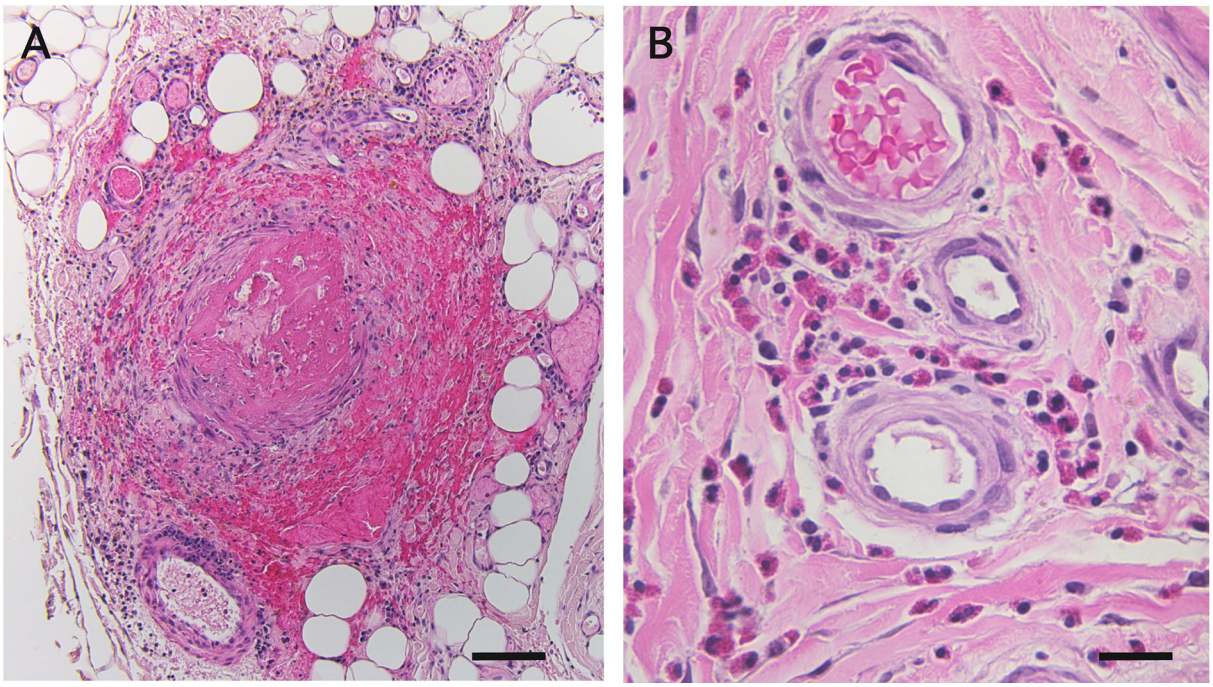

Fig. 1 Representative photographs taken from patients with eosinophilic granulomatosis with polyangiitis. Cross sections of sural nerve biopsy specimens. **a** Fibrinoid necrosis of the epineurial vessel is detected, particularly in patients positive for anti-neutrophil cytoplasmic antibodies. **b** Eosinophil infiltration into the epineurium's extravascular space is observed, suggesting that eosinophils also participate in the mechanisms of tissue damage. Hematoxylin and eosin staining. Scale bars = 100 µm (**a**) and 20 µm (**b**)

presence of four or more of the following six criteria yielded a sensitivity of 85% and a specificity of 99.7%: asthma, eosinophilia, peripheral neuropathy, pulmonary infiltrates, paranasal abnormality, and biopsy containing a blood vessel with extravascular eosinophils [13]. Although the concept of ANCA-associated vasculitis developed later [14], the positivity rate for ANCA in patients with EGPA is not high, constituting only 30–40% of patients, as described earlier [4, 5]. As a result of the presence of IgG autoantibodies directed against myeloperoxidase (MPO-ANCA) and proteinase 3 (PR3-ANCA), ANCA is classified as perinuclear (p-ANCA) or cytoplasmic (c-ANCA) on the basis of immunofluorescence staining patterns of neutrophils [15]. p-ANCA/MPO-ANCA are detected in patients with EGPA and MPA [8, 16], while c-ANCA/PR3-ANCA are associated with GPA [17], and the diagnosis of EGPA becomes less likely when c-ANCA/PR3-ANCA are detected [11]. Furthermore, many studies have shown differences in the clinical characteristics of patients with EGPA, depending on their ANCA status [4, 5, 8, 18, 19]. These studies indicate that patients with ANCA-negative EGPA have a higher frequency of cardiac lesions and a lower frequency of ear, nose, and throat symptoms, peripheral nerve, and renal involvement than those with ANCA-positive EGPA. A genome-wide association study also supported that this disease comprises two distinct syndromes [20]. Following this study, patients with ANCA-positive EGPA were significantly related to the HLA class II DQ haplotype common to patients with MPA, while those with ANCA-negative EGPA were related to the GP33 and IL5/IRF1 loci, indicating a possible mucosal/barrier dysfunction.

The ACR/European Alliance of Associations for Rheumatology (EULAR) created new EPGA classification criteria in 2022 [11]. Clinical,

laboratory, and biopsy findings were scored using the following ACR/EULAR criteria: obstructive airway disease (+ 3), nasal polyps (+ 3), mononeuritis multiplex (+ 1), blood eosinophil count $\geq 1 \times 10^9$/L (+ 5), extravascular eosinophilic predominant inflammation (+ 2), a positive test for c-ANCA/PR3-ANCA (− 3), and hematuria (− 1). In addition, after exclusion of diseases mimicking vasculitis, patients diagnosed with small- and medium-vessel vasculitis could be classified as having EGPA if their cumulative score was six or higher, with a sensitivity of 85% and a specificity of 99% [11].

Furthermore, the outcomes of epidemiological studies differ, depending on the diagnostic criteria and disease awareness. The incidence of EGPA ranges from 0.5 to 4.2 per million population, with a prevalence of 2–8 per million [21–24].

PATHOPHYSIOLOGY

From the Viewpoint of ANCA-Associated Vasculitis

As previously stated, EGPA is currently classified as an ANCA-associated vasculitis, in which ANCA plays a crucial role in vasculitis mechanisms [1, 2]. Passive transfer of anti-MPO IgG to mice resulted in pauci-immune necrotizing glomerulonephritis similar to that seen in patients with ANCA-associated vasculitis [25]. The immunization of rats using human MPO led to the production of anti-MPO antibodies to rat leukocytes and enhanced the interaction between leukocytes and vascular endothelial cells [26]. During the development of vasculitis, neutrophil degranulation and production of toxic species, including reactive oxygen species, induced by ANCA seem to play a significant role [27]. Furthermore, even long chromatin neutrophil fibers are suggested to extrude into the extracellular space along with other intracellular components, forming neutrophil extracellular traps [28]. This phenomenon is called NETosis because it is an active cell death mechanism distinct from necrosis and apoptosis [29]. Although NETosis was formally regarded as an innate defense mechanism against bacteria [28], subsequent studies suggested that this phenomenon involved various diseases, including ANCA-associated vasculitis [30–32].

Recently, studies using nerve biopsy specimens obtained from patients with ANCA-associated vasculitis, including those with EGPA, morphologically backed the process of vasculitis mediated by neutrophils [8, 16, 33, 34]. According to a study comparing pathological features of ANCA-associated vasculitis to those of nonsystemic vasculitic neuropathy, in which complements but not ANCA play a vital role in the mechanisms of vasculitis, neutrophil adhesion to vascular endothelial cells was more frequently found in patients with ANCA-associated vasculitis than in those with nonsystemic vasculitic neuropathy [16]. An electron microscopy study indicated that some neutrophils penetrated the endothelial cell layer and migrated out of the vessels [34]. In addition, some neutrophils migrating from the vessels lost part of their plasma membrane and released cytoplasmic granules extracellularly (i.e., degranulation). Furthermore, decondensation of nuclear chromatin and obscuration of the nuclear envelope that seemed to allow the release of chromatin into the extracellular space were observed, demonstrating the occurrence of NETosis in patients with ANCA-associated vasculitis [34].

From the Viewpoint of Eosinophil-Associated Disease

Although EGPA has been classified as ANCA-associated vasculitis, tissue damage caused by eosinophils is also involved in the disease's tissue damage process. Eosinophils have multiple functions, including maintaining homeostasis, host defense against infectious agents, immunomodulation through Th1/Th2 balance regulation, and anti-inflammatory and anti-tumor effects [35, 36]. In addition, eosinophils have been linked to the pathogenesis of eosinophilia-associated diseases other than EGPA, such as eosinophilic asthma and hypereosinophilic syndrome [35]. Eosinophils are a

source of various mediators, including granule-associated proteins, cytokines, chemokines, growth factors, lipid mediators, and adhesion molecules [36]. These mediators are selectively secreted into the extracellular space in response to external stimuli and modulate inflammatory conditions and tissue injury [37].

Recently, a study using nerve biopsy specimens obtained from patients with EGPA showed increased numbers of eosinophils within the vascular lumen and those in the endoneurial extravascular interstitium, particularly in patients negative with ANCA [8]. Electron microscopy examination indicated that

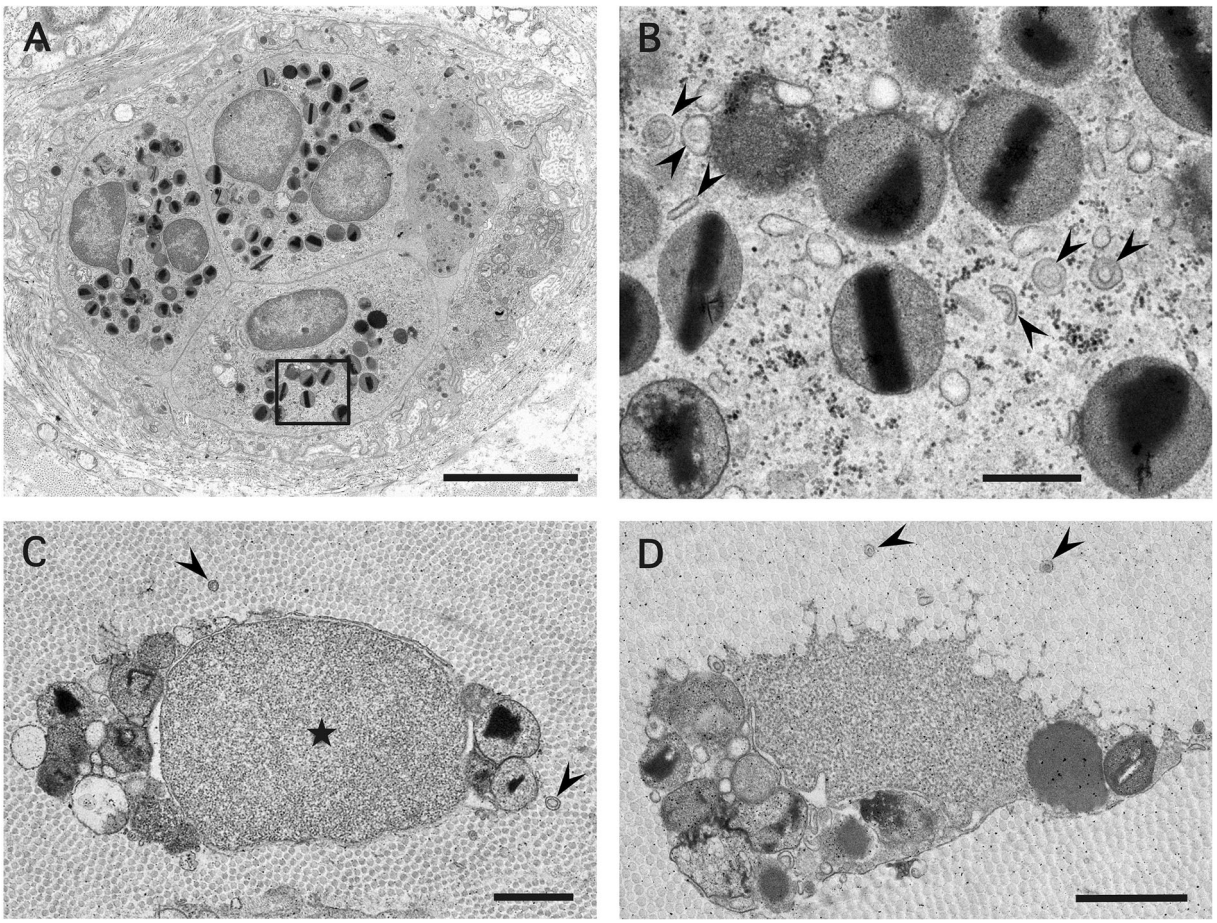

Fig. 2 Representative electron microscopy photographs of eosinophils. Cross sections of sural nerve biopsy specimens obtained from patients with eosinophilic granulomatosis with polyangiitis. **a** Eosinophils fill the vascular lumen in the endoneurium. A high-powered view of the box region in **a** is shown in **b**. **b** An eosinophil shows findings suggestive of piecemeal degranulation. Elongated, tubular, curved, or circular structures known as eosinophil sombrero vesicles are observed near specific granules. Arrowheads indicate representative eosinophil sombrero vesicles. **c** Cytolysis of eosinophils in the extravascular interstitium of the epineurium. The plasma membrane of this eosinophil was completely lost. The nucleus indicated by an asterisk lost the typical distinction between euchromatin and peripheral heterochromatin compared with eosinophils shown in **a**. Eosinophil sombrero vesicles are located in the extracellular space (arrowheads). **d** Spread of nuclear chromatin resulting from the loss of nuclear envelope, suggestive of the occurrence of eosinophil ETosis. Eosinophil sombrero vesicles are indicated by arrowheads. Samples prepared for transmission electron microscopy. Scale bars = 5 μm (**a**), 0.5 μm (**b**), and 1 μm (**c** and **d**)

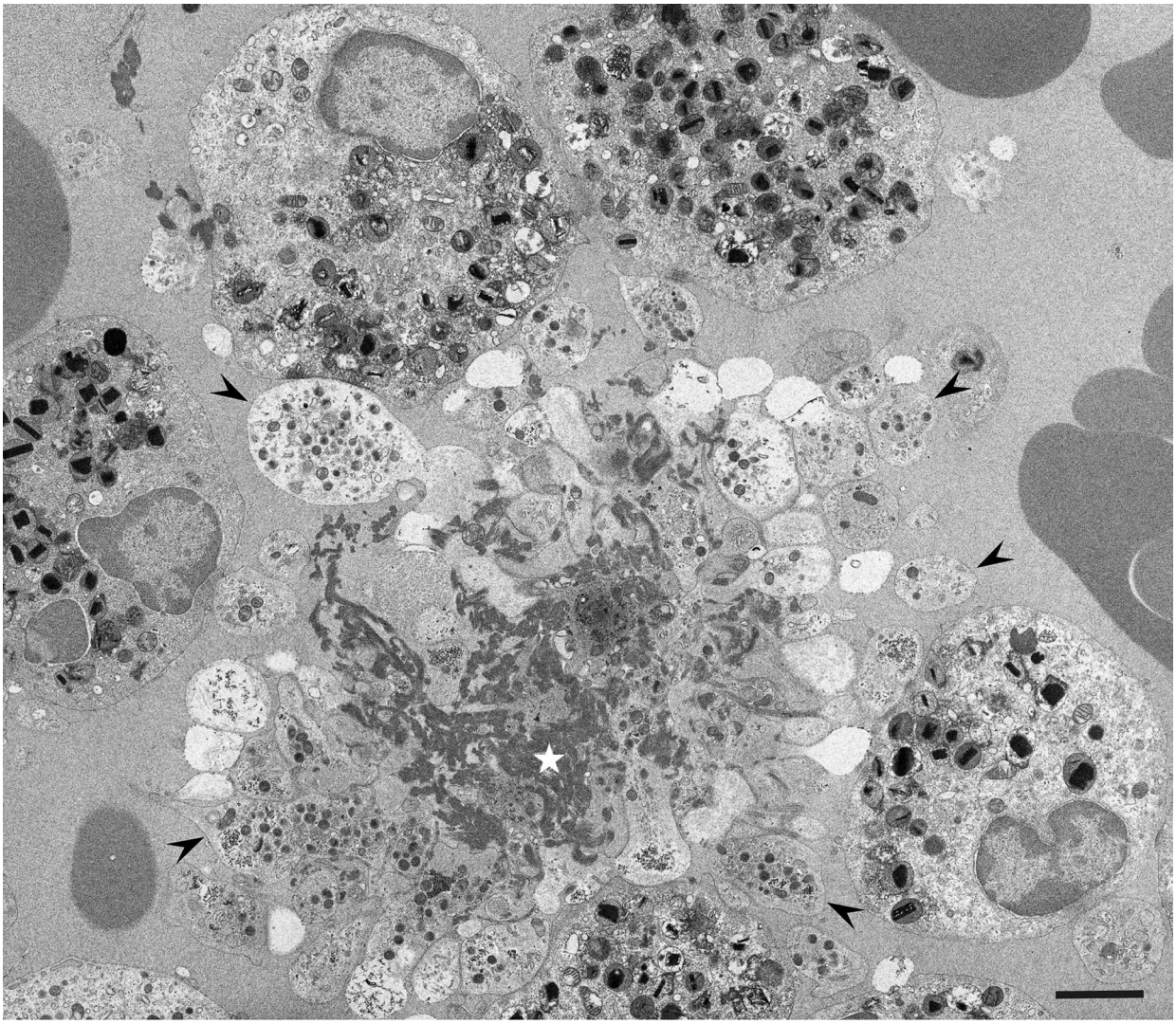

Fig. 3 Coagulation in the vascular lumen. A cross section of sural nerve biopsy specimens obtained from a patient with eosinophilic granulomatosis with polyangiitis. A clot composed of fibrin and platelets is surrounded by eosinophils. A white asterisk indicates an aggregation of fibrin. Arrowheads indicate representative platelets. A sample prepared for transmission electron microscopy. Scale bar = 2 μm

active secretion of eosinophil intracellular components occurs through cytolysis and piecemeal degranulation (Fig. 2) [9]. Cytolysis is one mode of degranulation resulting from disrupting the plasma membrane [38]. Eosinophil granules are directly released into the extracellular space as a result of cytolysis. These free granules can secrete their contents in response to stimuli recognized by membrane receptors on the granules [39]. In contrast, piecemeal degranulation can selectively secrete various granular contents by sorting them into distinct vesicular compartments known as eosinophil sombrero vesicles, mobilizing them to the plasma membrane [40, 41]. Eosinophil sombrero vesicles tend to be located near eosinophil-specific granules and are observed as elongated, tubular, curved, or circular structures with a cross-sectional diameter of less than 300 nm [37, 42]. In addition, recent studies

have suggested that the release of chromatin fibers of eosinophils into the extracellular space occurs as result of the disruption of the nuclear envelope and plasma membrane in patients with EGPA [43, 44]. This condition is known as eosinophil ETosis (EETosis) because it is classified as active cytolytic cell death, similar to NETosis [43].

While previous electron microscopy studies have shown that eosinophils in the bloodstream are stable and do not degranulate until they reach target tissues in patients with asthma, allergic rhinitis, and atopic dermatitis [45], a recent study demonstrated that cytolysis and piecemeal degranulation of eosinophils occurred even in the bloodstream of patients with EGPA [9]. The level of eosinophil cationic protein in plasma was an independent risk factor for thrombotic events in humans, suggesting that the release of eosinophil intracellular components is involved in coagulation [46]. In addition, recent research suggests that eosinophils have a proclivity to interact with platelets to form blood clots (Fig. 3) [9, 47]. Indeed, an increased risk of arterial and venous thrombotic events has been recently described in patients with EGPA [48]. These findings suggest that tissue damage induced by eosinophils in EGPA may result from direct injury of neighboring tissues in the extravascular interstitium and intravascular coagulation by intracellular components released into the bloodstream.

CONVENTIONAL THERAPEUTIC STRATEGY

Traditionally, EGPA treatment has been discussed in the context of ANCA-associated vasculitis, alongside MPA and GPA [49]. However, most randomized controlled trials for ANCA-associated vasculitis excluded EGPA because of its unique features [50]. Therefore, EGPA treatment recommendations are based on a lower level of evidence than those for MPA and GPA, including expert opinion [49, 51, 52]. The use of glucocorticoids is recommended to achieve remission induction regardless of the disease severity [49, 51, 52]. For active, severe EGPA with life- or organ-threatening manifestations, including alveolar hemorrhage, cardiac involvement, glomerulonephritis, central nervous system vasculitis, peripheral neuropathy, mesenteric ischemia, and limb/digit ischemia, intravenous pulse or high dose daily oral glucocorticoids with a combination of either cyclophosphamide or rituximab may be prescribed to induce remission [52]. In the case of active, nonsevere EGPA, azathioprine, methotrexate, or mycophenolate mofetil can be used with glucocorticoids to induce remission [51, 52]. The use of glucocorticoids alone can also be considered in selected patients [52].

Treatment for induction remission is usually followed by treatment for maintaining remission, particularly in patients with severe disease [52]. To limit the cumulative dose of cyclophosphamide, a replacement of cyclophosphamide with other agents, such as methotrexate, azathioprine, or mycophenolate mofetil, is recommended once the disease has entered remission [52]. Although the dose of glucocorticoids is decreased once the induction remission is achieved, several patients require long-term glucocorticoids to maintain remission [53]. As many patients with EGPA experience relapses, particularly during the tapering of glucocorticoids and glucocorticoid-related side effects, healthcare resource use and disease burden are high [54].

Furthermore, the clinical benefit of intravenous immunoglobulin (IVIg) as an adjunctive therapy has been suggested in patients with ANCA-associated vasculitis, particularly in those with EGPA [55–57]. In addition to controlling vasculitis activity, a study involving 23 patients with EGPA showed that IVIg efficiently improved residual peripheral neuropathy even when laboratory indices suggest disease remission [55].

A THERAPEUTIC STRATEGY TARGETING IL-5

As the tissue damage induced by eosinophils also participates in mechanisms of EGPA, a therapeutic strategy to suppress eosinophils has been considered. IL-5 is a good therapeutic target because it plays a central and profound role

Table 1 Characteristics of anti-IL-5 agents for EGPA

	Mepolizumab	Reslizumab	Benralizumab
Trade name	Nucala	Cinqair	Fasenra
Specifics	Humanized IgG1 kappa mAb	Humanized IgG4 kappa mAb	Humanized IgG1 kappa mAb
Target	IL-5	IL-5	IL-5 receptor alpha
Root of administration	Subcutaneous	Intravenous	Subcutaneous
Dosage	300 mg every 4 weeks (100 mg every 4 weeks under evaluation)	3 mg/kg every 4 weeks	30 mg every 4 weeks for the first three doses, and then 30 mg every 8 weeks
Evidence in EGPA	RCT involving 136 patients	Pilot studies	Open-label pilot study
	An open-label extension study to evaluate long-term efficacy is ongoing (NCT03298061)		Case reports
			A phase 3 trial comparing benralizumab to mepolizumab is ongoing (NCT04157348)

EGPA eosinophilic granulomatosis with polyangiitis, *IL-5* interleukin-5, *mAb* monoclonal antibody, *RCT* randomized controlled trial

in various aspects of eosinophils, including their growth, activation, and survival [58–61]. In adaptive immunity, IL-5 is primarily produced by T helper 2 cells [60]. In addition, type 2 innate lymphoid cells in peripheral tissues can produce IL-5, promoting innate and adaptive immune responses [62, 63]. Eosinophils express IL-5 receptor alpha on their surface and can bind IL-5 [64].

Animal studies suggest that IL-5 is needed for developing eosinophilia. For example, mice deficient in IL-5 demonstrated a slight reduction in circulating eosinophils under baseline conditions and did not develop blood and tissue eosinophilia when they were infected with parasites [65]. In contrast, IL-5 transgenic mice had significantly higher levels of eosinophils at baseline [66]. Furthermore, patients with familial eosinophilia, a rare autosomal dominant inherited disorder characterized by increased circulating eosinophil counts, had elevated serum IL-5 and IL-5 receptor alpha levels [67]. Studies on patients with EGPA confirmed a strong link between IL-5 and eosinophilia [33, 68]. The concentration of IL-5 and the number of eosinophils were increased in sera and bronchoalveolar lavage fluids obtained from patients with active EGPA [68]. According to a study using nerve biopsy specimens obtained from patients with EGPA, the number of eosinophils in the vascular lumen and extravascular interstitium of the epineurium was increased in patients with high IL-5 serum levels [33]. These findings support the use of an IL-5-focused treatment strategy for EGPA. Monoclonal antibodies directed against IL-5 or its receptors, in this view, are promising therapeutic agents for suppressing the effect of IL-5 on eosinophils.

Currently, three monoclonal antibodies targeting IL-5 or the receptor for IL-5 have been studied for use in EGPA (Table 1). Among these, mepolizumab was approved in 2017 by the US

Food and Drug Administration (FDA) for treating EGPA following the success of a phase 3 randomized controlled trial [10].

ANTI-IL-5 AGENTS

Mepolizumab

Mepolizumab is a humanized IgG1 kappa monoclonal antibody against IL-5 that inhibits its binding to IL-5 receptor alpha on the surface of eosinophils [69]. In preliminary studies involving patients with eosinophilic dermatitis and esophagitis who also had peripheral blood eosinophilia, mepolizumab administration resulted in a significant reduction in peripheral blood and tissue eosinophils [70, 71]. Although early clinical trials of mepolizumab involving patients with mild-to-moderate asthma failed to demonstrate clinical benefit [72, 73], trials involving severe eosinophilic asthma could reduce asthma exacerbations [74, 75]. Under the trade name Nucala, the drug was first approved by the FDA in 2015 as a first-in-class, add-on maintenance treatment for severe asthma with eosinophilic phenotype in patients aged 12 years and older, and other countries quickly followed it [64]. Subsequently, phase 3 trials demonstrated the efficacy of mepolizumab in patients with other eosinophil-associated diseases, including EGPA [10], hypereosinophilic syndrome [76], and chronic rhinosinusitis with nasal polyps [77].

In terms of using mepolizumab in EGPA, the first successful patient treatment with mepolizumab despite resistance to conventional therapies was reported in 2010 [78]. Soon after this case report, results of an open-label pilot study involving seven patients with glucocorticoid-dependent EGPA were published [79]. In that study, mepolizumab reduced eosinophil counts and allowed for safe glucocorticoid reduction without significant adverse events in all patients. However, the manifestations of EGPA and eosinophilia recurred on the cessation of mepolizumab. On the basis of these early findings suggesting the usefulness of this drug as an add-on agent for EGPA, a phase 3 trial for EGPA was conducted [10]. This double-blind, placebo-controlled trial randomized 136 patients with relapsed or refractory EGPA who received either 300 mg mepolizumab subcutaneously every 4 weeks or placebo with standard therapy using glucocorticoids with or without immunosuppressive agents. During the 52-week study period, mepolizumab treatment led to significantly more accrued weeks of remission defined as the Birmingham Vasculitis Scale of 0 and the receipt of prednisolone or prednisone at a dose of 4.0 mg or less per day than placebo (odds ratio, 5.91; 95% confidence interval, 2.68 to 13.03; $p < 0.001$). In particular, 28% of the participants in the mepolizumab group, as compared with 3% of those in the placebo group, had remission for at least 24 weeks. In addition, the proportion of participants in remission at both week 36 and week 48 was also significantly higher in the mepolizumab group than the placebo group (32% vs. 3%; odds ratio, 16.74; 95% confidence interval, 3.61 to 77.56; $p < 0.001$). However, it is worth noting that nearly half (47%) of the 68 patients who received mepolizumab did not meet the remission criteria set as the primary endpoint, indicating mepolizumab non-responders in this trial.

Although initial studies of mepolizumab for EGPA used a high dose of 750 mg intravenous administration every 4 weeks [79, 80], the design of a phase 3 trial now suggests subcutaneous administration of 300 mg mepolizumab every 4 weeks [10]. However, recent studies suggested that a lower dose of 100 mg subcutaneous administration every 4 weeks, which is equivalent to the approved dose for severe eosinophilic asthma and chronic rhinosinusitis with nasal polyps, was also effective for suppressing the disease activity [81, 82].

Long-term efficacy is currently being evaluated in the open-label extension study of the first trial that enrolled 104 patients who previously required prednisolone or its equivalent of 5 mg a day or more for adequate EGPA control (NCT03298061) [83]. The patients were treated with 300 mg mepolizumab subcutaneously every 4 weeks.

Reslizumab

Reslizumab is a humanized IgG4 kappa monoclonal antibody against IL-5 [69]. An early study enrolling patients with severe persistent asthma demonstrated that a single intravenous injection of reslizumab dose-dependently reduced circulating eosinophil count and resulted in a trend toward improving airway function [84]. The efficacy of reslizumab for eosinophil-associated diseases was supported by randomized, placebo-controlled trials involving chronic rhinosinusitis with nasal polyps and eosinophilic asthma [85, 86]. Following phase 3 trials of reslizumab administered intravenously at a dose of 3 mg/kg every 4 weeks or placebo [87], the FDA approved the drug in 2016 under the trade name of Cinqair as an add-on maintenance treatment for severe eosinophilic asthma in patients at least 18 years old.

Regarding the efficacy of reslizumab for EGPA, a study involving nine patients with oral glucocorticoid-dependent EGPA and severe eosinophilic asthma showed a significant reduction in mean maintenance oral glucocorticoid dose following 48 weeks of monthly intravenous reslizumab treatment [88]. Another study involving ten patients with EGPA showed a significant reduction in the daily oral glucocorticoid dose after seven monthly reslizumab treatments [89]. The results of these pilot studies may warrant further clinical trials to validate the efficacy and safety of reslizumab for EGPA.

Benralizumab

Benralizumab is a humanized IgG1 kappa monoclonal antibody against IL-5 receptor alpha [69, 90]. The drug induces antibody-dependent cell-mediated cytotoxicity due to its high affinity for Fc gamma receptor IIIa on natural killer cells [90, 91]. The enhanced activity of antibody-dependent, cell-mediated cytotoxicity reduces blood eosinophils and basophils. In an early open-label phase 1 study, benralizumab induced a decrease in peripheral blood eosinophils in patients with mild asthma for 12 weeks after a single intravenous dose [92]. In a multicenter, double-blind, placebo-controlled phase 1 study, a single intravenous dose (1 mg/kg) and three monthly subcutaneous doses (100 mg or 200 mg) of benralizumab improved tissue and blood eosinophilia in patients with eosinophilic asthma [93]. Following phase 3 trials of benralizumab administered subcutaneously at a dose of 30 mg either every 4 or 8 weeks or placebo [94–96], the drug was first approved in 2017 by the FDA, under the trade name Fasenra, for the add-on maintenance treatment of severe eosinophilic asthma in patients at least 12 years old.

Case reports suggested that benralizumab is also effective for various manifestations of EGPA [97–99]. An open-label study involving ten patients with EGPA showed that subcutaneously administering 30 mg benralizumab reduced oral glucocorticoid dose [100]. Five patients achieved a glucocorticoid dose of 0 mg after 40 weeks of treatment [100]. In addition, the efficacy of benralizumab was reported even in patients with EGPA refractory to mepolizumab [101, 102]. Currently, a phase 3 trial comparing benralizumab with mepolizumab in relapsing or refractory EGPAs is ongoing (NCT04157348) [103].

CONCLUSIONS AND FUTURE DIRECTIONS

Although the treatment for EGPA is described in the context of ANCA-associated vasculitis along with MPA and GPA, a therapeutic approach to suppress eosinophils is also considered. Monoclonal antibodies directed against IL-5 or its receptors are good candidate therapeutic agents because IL-5 plays an important role in eosinophil growth, activation, and survival. Three monoclonal antibodies targeting IL-5 (mepolizumab and reslizumab) or its receptors (benralizumab) are currently being studied for use in EGPA. Among these monoclonal antibodies, mepolizumab is already approved for treating EGPA on the basis of the results of a phase 3 randomized controlled trial involving relapsing or refractory patients [10]. Because patients with organ-threatening or life-threatening manifestations were not included in this trial [10], mepolizumab may be recommended

for remission induction in patients with active, nonsevere disease and treatment of relapse [52]. Although the efficacy of benralizumab was reported even in patients with EGPA refractory to mepolizumab [101, 102], clear differences in the clinical efficacy of these anti-IL-5 agents have not yet been established in large trials.

It is worth noting that the disease process of EGPA consists of at least two distinct mechanisms: necrotizing vasculitis associated with ANCA and tissue damage associated with eosinophils [8, 9]. In fact, nearly half (47%) of the 68 patients with EGPA who received mepolizumab did not meet the remission criteria set as the primary endpoint in the phase 3 trial [10]. Given the differential mechanisms of tissue damage related to ANCA and eosinophils in EGPA, it may be possible to predict the efficacy of anti-IL-5 agents in a simplified manner by considering ANCA and IL-5 statuses [33]. Recently, a patient with EGPA who developed myocarditis despite a normal eosinophil count during mepolizumab therapy was reported [104]. Functional analysis of T lymphocytes in this patient revealed that the frequencies of Th1- and Th17-related cytokines increased in parallel with worsening of cardiac symptoms.

Clinical trials for severe eosinophilic asthma suggested that anti-IL-5 agents are usually well tolerated [74, 75, 87, 94–96]. The safety profile of mepolizumab for EGPA was similar to that observed in these studies [10]. However, the safety of long-term treatment with anti-IL-5 agents for EGPA has not been fully elucidated. Although patients with eosinophil deficiency and eosinophil-deficient mice do not display any distinctive syndrome associated with eosinophil reduction [105], a close monitoring of the long-term safety of anti-IL-5 therapy would be desirable. Additionally, it is currently unknown whether long-term treatment should be recommended for sustained disease control by suppressing eosinophils. Therefore, further studies are needed to clarify long-term safety and efficacy of anti-IL-5 agents and establish indications of individual therapeutic agents tailored to individual conditions of patients with EGPA.

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