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Biologic Therapy in Rare Eosinophil-Associated Disorders

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ABSTRACT

Our understanding of the contribution of eosinophils in the pathogenesis of various diseases has grown, particularly in disorders affecting the airways, gastrointestinal tract, and skin. This has led to the development of therapies that specifically target eosinophils or cytokines responsible for their production, activation, and survival – establishing a more focused and effective treatment approach. Recent biologic agents are designed to selectively inhibit eosinophils, cells that interact with or activate them, or components of the type 2 inflammatory cascade, using monoclonal antibodies.

Currently, clinical guidelines generally reserve biologic therapies for patients who are refractory to or intolerant of corticosteroids or immunosuppressants. However, increasing evidence supporting the safety and efficacy of these agents has sparked a growing debate on whether earlier use of biologics could be beneficial. In the present article, we examine the benefits and limitations of currently approved biologics for the treatment of eosinophilic diseases involving the airways, gastrointestinal tract, and skin. Additionally, we discuss emerging biologic therapies, future research directions, and the rationale for considering early intervention with biologics to prevent irreversible tissue damage, disease progression, and organ dysfunction in selected cases.

KEY WORDS: children, eosinophil-associated diseases, eosinophilic gastrointestinal disorders, hypereosinophilic syndrome, monoclonal antibody

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INTRODUCTION

The term eosinophil-associated diseases (EAD) refers to a broad spectrum of conditions in which eosinophils are believed to play a key pathogenic role [1]. While blood eosinophilia is clearly defined as an elevated absolute eosinophil count (AEC) exceeding 0.5 x 10^9/L, the significance of eosinophil infiltration in tissues such as the lungs, gastrointestinal tract, uterus, thymus, spleen, and lymph nodes is less well established. In tissues where eosinophils are not normally present under homeostatic conditions, their presence – or that of their granule proteins – may indicate underlying disease.

Peripheral blood eosinophilia is classified as mild (0.5-1.49 x 10^9/L), moderate (1.5-5.0 x 10^9/L), and severe (> 5.0 x 10^9/L). Eosinophilia may arise due to primary (clonal) causes, involving genetic abnormalities in hematopoietic cells, or secondary (reactive) causes, resulting from underlying conditions, such as infections, drugs, atopic diseases and other conditions [2]. Hypereosinophilic syndrome (HES) and eosinophilic gastrointestinal disorders (EGIDs) are considered classic EADs [2]. Several more prevalent conditions, such as eosinophilic asthma, also exhibit subtypes classified as EADs. Eosinophilic asthma is characterized by a sputum eosinophil percentage $\geq$ 2% and elevated blood eosinophils [3].

Although corticosteroids – both topical and systemic – remain the first-line therapy for EADs and are often effective in reducing eosinophilia and managing symptoms, long-term use is

associated with reduced responsiveness and significant adverse effects. As a result, alternative treatment strategies are often necessary. Biologic therapies offer a targeted approach by interfering with specific cells or molecular pathways, potentially enhancing efficacy and minimizing the off-target effects common to conventional therapies. Eosinophils represent an attractive therapeutic target [4,5], given their unique surface markers and the minimal adverse consequences observed in eosinophil-deficient murine models and human studies [6,7]. Targeting eosinophils or the cytokines that regulate their development and function – such as IL-5, IL-4, and IL-13 – has emerged as a promising strategy.

However, the pathophysiology of reactive eosinophilic diseases is complex and involves interactions between eosinophils and other immune and structural cells, a dynamic cytokine milieu, epithelial barrier dysfunction, and potential microbial triggers. Thus, targeting eosinophils alone may be insufficient to achieve durable clinical remission. The growing arsenal of biologics demands careful evaluation of each agent's benefits and limitations to enable tailored therapy for individual patients [8,9].

This article reviews the advantages and limitations of biologic therapies in EADs, with a focus on diseases characterized by reactive eosinophilia affecting the airways, gastrointestinal tract, and skin—conditions primarily driven by T cell-derived cytokines, though occasionally by tumor cells. We specifically discuss eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP), EGIDs, and rare systemic eosinophilic disorders such as eosinophilic granulomatosis with polyangiitis (EGPA) and HES.

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (CRSWNP)

CRSwNP is a chronic inflammatory disease of the nasal mucosa and paranasal sinuses lasting ≥ 12 weeks [10]. It frequently coexists with severe eosinophilic asthma and is characterized by type 2 inflammation, involving elevated levels of IL-4, IL-5, and IL-13 [11]. This cytokine profile promotes tissue infiltration by eosinophils, lymphocytes, basophils, and mast cells.

In susceptible individuals, NSAID exposure may exacerbate respiratory symptoms due to dysregulated TSLP-driven immune responses and innate type 2 activation mediated by cysteinyl leukotrienes and IL-33. High IL-5 levels have been detected in nasal polyp tissue from asthmatic patients undergoing polypectomy, and IL-5 neutralization has been shown to reduce local eosinophilia. However, symptom improvement did not always accompany eosinophil depletion. Interestingly, IL-5 levels may predict the presence of comorbid asthma in patients with CRSwNP.

Symptoms include nasal obstruction, anosmia, rhinorrhea, facial pressure, and sneezing – primarily due to mucosal thickening and polyp formation. Dupilumab was the first biologic approved for CRSwNP, followed by omalizumab and mepolizumab. Clinical trials have demonstrated symptom improvement, radiologic resolution, and fewer disease exacerbations in patients treated with these agents [11].

HYPEREOSINOPHILIC SYNDROME

HES encompasses a group of disorders characterized by sustained peripheral eosinophilia (greater than 1500/μL) and eosinophil-mediated end-organ damage. In reactive forms of HES, cytokines such as IL-5, IL-13, and GM-CSF drive eosinophilopoiesis and prolong eosinophil survival, rendering these cytokines and their receptors rational therapeutic targets. EGPA, formerly known as Churg-Strauss syndrome, is an ANCA-associated vasculitis characterized by asthma, blood eosinophilia, and eosinophilic inflammation of small- to medium-sized vessels, resulting in sinusitis, pulmonary infiltrates, neuropathy, and systemic vasculitis.

Mepolizumab and benralizumab have demonstrated clinical efficacy in patients with cutaneous involvement. However, their efficacy varies across HES subtypes, with poor or absent responses observed in myeloproliferative and lymphocytic variant HES. Thus far, biologics have been evaluated as add-on therapies, and their role as first-line agents remains to be clarified.

Mepolizumab, now approved in the US and Europe for HES, has been shown to reduce corticosteroid dependence, eosinophil counts, and disease flares [12]. In a study of PDGFRA-negative HES, benralizumab induced rapid eosinophil depletion and clinical improvement in 17 of 19 patients [13]. A phase 3 trial (NCT04191304) is ongoing. Other biologics under investigation include depemokimab, a long-acting anti-IL-5R monoclonal antibody (NCT05334368), and alemtuzumab, which has shown benefit in retrospective studies [14]. Additionally, dupilumab has demonstrated efficacy in selected HES cases [15].

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS AND CHRONIC EOSINOPHILIC PNEUMONIA

EGPA, formerly Churg-Strauss syndrome, is an ANCA-associated vasculitis characterized by asthma, blood eosinophilia, and eosinophilic inflammation of small- to medium-sized vessels, leading to sinusitis, pulmonary infiltrates, neuropathy, and systemic vasculitis. CEP presents with asthma, sinusitis, eosinophilic airway inflammation, and parenchymal lung infiltrates.

The anti-IL-5 monoclonal antibody mepolizumab received FDA and EMA approval in 2017 for relapsing/refractory EGPA, based on the MIRRA trial [16], which demonstrated reductions in corticosteroid use and disease relapses. Although it is the only biologic currently approved for EGPA, it is typically reserved for patients with persistent symptoms or steroid dependence. Its efficacy appears strongest for asthma and sinusitis, with less evidence supporting benefits in vasculitic manifestations.

Benralizumab and reslizumab have shown preliminary promise in

small open-label studies [17,18], and ongoing trials (NCT03010436, NCT04157348) aim to clarify their role. Reslizumab, however, did not significantly improve vasculitis activity scores, suggesting limited benefit for extrapulmonary involvement.

Case reports on omalizumab in relapsing/refractory EGPA have yielded mixed results, with limited steroid-sparing effects and no consistent impact on eosinophil counts [19]. Promising outcomes have been reported with rituximab (anti-CD20), and randomized controlled trials are ongoing (e.g., NCT02807103).

EOSINOPHILIC GASTROINTESTINAL DISEASES

EGIDs are chronic conditions characterized by gastrointestinal symptoms and an abnormal accumulation of eosinophils in the GI tract, without a known secondary cause for increased eosinophils. The most extensively studied form of EGID is eosinophilic esophagitis (EoE), an allergic or immune-mediated condition associated with Type 2 responses. Growing evidence suggests that eosinophilic gastritis (EoG) also exhibits type 2 features; however, less is known about eosinophilic enteritis and eosinophilic colitis. As understanding of EGID pathogenesis has expanded, new therapeutic targets have been identified, leading to the development of biologic therapies [20,21]. Most data to date have come from studies on EoE, with published trials of anti-IgE (omalizumab), anti-IL-5 (mepolizumab and reslizumab), anti-IL-13 (QAX576, RPC4046, now cendakimab), and anti-IL-4R (dupilumab), while trials of anti-IL-5R (benralizumab) and anti-siglec-8 (lirentelimab) are still ongoing. For EoG and eosinophilic duodenitis (EoD), phase 2 studies have demonstrated efficacy with lirentelimab, whereas benralizumab and dupilumab are under investigation. Notably, dupilumab, cendakimab, benralizumab, and lirentelimab have advanced to phase 3 trials for EoE, and lirentelimab and benralizumab are in phase 3 trials for EoG/EoD, following encouraging phase 2 outcomes [22]. Research on treatments is progressing rapidly; however, some recent trials – including a proof-of-concept study of benralizumab in EoG (NCT03473977) and phase 3 trials of lirentelimab for EoE and EoG/EoD (NCT04322708 and NCT04322604, respectively) – did not fully achieve their primary endpoints. Although histologic improvements were observed, symptom relief was insufficient compared with placebo groups.

FUTURE DIRECTIONS AND CONCLUSIONS

Eosinophil-associated disorders are currently a major focus of research aimed at elucidating their pathophysiology and refining therapeutic strategies. A diverse array of biologic agents is under investigation in clinical trials for the treatment of these conditions. Despite initial concerns regarding the potential risks of rapidly depleting eosinophils – such as impaired tumor surveillance or dysregulated immune responses – no significant safety signals have emerged to date. Although eosinophils contribute to immune regulation and may participate in anti-tumor responses [23,24], clinical and preclinical evidence indicates that their sustained depletion is generally well tolerated [25]. Long-term trials of anti-IL-5 therapies, including mepolizumab, demonstrate durable eosinophil suppression without increased infections, malignancies, or immune complications (26), a finding supported by real-world analyses of anti-IL-5 and anti-IL-4Rα biologics [27]. Extended follow-up with benralizumab further confirms the safety and durability of prolonged eosinophil depletion in routine practice [28]. Collectively, these data indicate that targeted eosinophil reduction exhibits a reassuring long-term safety profile despite initial theoretical concerns.

The efficacy of biologic therapies varies depending on the specific agent and the eosinophilic condition being addressed. As the therapeutic landscape continues to expand, individualized treatment decisions will require a nuanced understanding of each drug's mechanism of action, therapeutic potential, and limitations in the context of the underlying disease biology. The continued development and integration of biologics into clinical practice holds promise for improved outcomes in patients with eosinophil-driven diseases.

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Conflicts of interest statement

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Author's contributions

All authors have read and approved the final version of the manuscript and agree with its submission to the journal.

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