

# MONOCLONAL ANTIBODY-BASED THERAPY FOR EOSINOPHILIC OESOPHAGITIS

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## ABSTRACT

Eosinophilic oesophagitis is an inflammatory condition associated with marked eosinophil accumulation in the mucosal tissues of the oesophagus. Eosinophils are major pro-inflammatory cells thought to make a significant contribution to allergic diseases that affect the upper and lower airways, skin, and gastrointestinal tract. Type 2 cytokines such as interleukin (IL)-5 and IL-13 are central to eosinophil maturation and release from the bone marrow, and their subsequent accumulation, activation, and persistence in the tissues. Humanised monoclonal antibodies with potent IL-5 or IL-13 neutralising effects represent potential treatments for eosinophilic-driven diseases. This review will consider the current status of these biologics in the treatment of eosinophilic esophagitis.

**Keywords:** Mepolizumab, reslizumab, eosinophilic oesophagitis (EoE), interleukin-5 (IL-5), interleukin-13 (IL-13), eosinophils.

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## INTRODUCTION

Eosinophilic oesophagitis (EoE) is a severe inflammatory condition of the oesophagus clinically manifesting itself as dysphagia in both adults and children, that can be confused at presentation with gastro-oesophageal reflux disease (GORD) or proton pump responsive oesophageal eosinophilia.<sup>1</sup> However, unlike GORD, EoE is unresponsive to acid reduction therapy, including antacids, proton pump inhibitors, or histamine H2 receptor antagonists. In common with other allergic diseases, EoE has an increasing prevalence of up to 50 per 100,000 in the USA and Europe. It also has a strong (70%) gender predisposition for males<sup>2</sup> and an association with allergic disease often manifested by reactivity to both food and aeroallergens.<sup>3-6</sup> Eosinophils are absent from the normal oesophagus; EoE is characterised by a marked mucosal eosinophil accumulation, with a count of >15 cells per microscopic high-power field considered diagnostic for this condition. It was initially seen as an idiopathic condition reflecting the rather poor understanding of the underlying pathogenic mechanisms.<sup>3</sup> It is now apparent that EoE is in fact

a complex disease with major contributions made by genetic predisposition, environmental exposure, allergen sensitisation, and involvement of other cells and mediators in addition to eosinophils that, in turn, greatly influence therapeutic approaches.<sup>4</sup> Eosinophilic gastroenteritis (EG) is a similar disease, characterised by eosinophilic infiltration of the gastrointestinal (GI) tract resulting in variable clinical GI pathology. Type 2 cytokines and the potent eosinophil chemo-attractant, eotaxin, are believed to have an important role in the pathogenesis of this disease.<sup>5</sup> Histopathological examination of biopsies from subjects with EoE demonstrate thickening of the epithelium, particularly in the basal zone, together with dilated intercellular spaces (spongiosis), fibrosis of the lamina propria, microabscesses, and a marked infiltration by eosinophils.<sup>6</sup> Other pro-inflammatory cell numbers also increase, including T cells and tissue mast cells, with increased expression of Type 2 cytokines.<sup>7</sup> Mouse studies have demonstrated that respiratory antigen exposure, but not oral or gastric exposure, promotes increased oesophageal eosinophil numbers.<sup>8</sup>

The treatment of EoE is complex, requiring the use of corticosteroids, diet-based approaches, and dilation. However, there are concerns over these regimes, including the long-term safety issues associated with corticosteroids and the compliance by EoE patients with what can be 'difficult to implement' dietary changes. Thus, EoE represents a condition with a clear unmet clinical need; issues that are comprehensively detailed in a number of recent reviews.<sup>8-10</sup> This narrative review is based on English-language original articles in PubMed or MEDLINE that reported on the effectiveness of the targeting of cytokines with biologics in patients with EoE.

## EOSINOPHILS

The importance of eosinophil involvement in inflammatory conditions affecting the skin, GI, and upper and lower airways has been widely accepted for several decades.<sup>9</sup> Infiltrating tissue eosinophils release their potent pro-inflammatory arsenal, including granule-derived basic proteins, lipid mediators, cytokines, and chemokines.<sup>10</sup> In addition to their role as degranulating effector cells, eosinophils have the capacity to act as antigen-presenting cells; this results in T cell proliferation and activation, thereby propagating inflammatory responses.<sup>11,12</sup> Activated tissue eosinophils are potent sources of a diverse array of cytokines and perspectives on their role in diverse diseases continue to evolve<sup>11</sup> in both innate and adaptive responses to parasitic, viral, fungal, and bacterial infections.<sup>12</sup>

A marked T helper Type 2 (Th2)-dependent component, driving accumulation of eosinophils in the oesophageal mucosa, appears important in EoE and it is believed that enhanced production of Type 2-associated cytokines may be in response to both food and environmental allergens. An allergen challenge of mice genetically manipulated to lack eosinophils resulted in reduced basal hyperplasia and strictures, although oesophageal motility dysfunction persisted,<sup>13</sup> further supporting the notion of a role for other cells in EoE pathogenesis. Furthermore, in a mouse model of EoE, antigen challenge-induced oesophageal eosinophilia, angiogenesis, basal zone hyperplasia, and fibronectin deposition were all significantly attenuated by the selective depletion of eosinophils using an anti-siglec F antibody.<sup>14</sup> Increased expression of the potent eosinophil chemokine CC motif ligand 26 (CCL26) (eotaxin-3)

has been reported in EoE, while the gene for CCL26 is markedly upregulated in oesophageal biopsies from EoE patients with expression correlating with disease severity.<sup>15</sup>

## INTERLEUKIN-13

Both interleukin (IL)-4 and IL-13 are important in eosinophil accumulation and are key factors in immunoglobulin E synthesis by B cells. Each exerts its actions through the IL-4R- $\alpha$ /IL-13R- $\alpha$ 1 receptor complex, which then activates the transcription factor STAT-6, which has an important role in activating genes associated with the differentiation of naïve T cells into Th2 effector cells, airway inflammation, and airway hyper-responsiveness.<sup>16</sup> The epithelium of the oesophagus is a major source of CCL26 production that is strongly enhanced by stimulation with IL-13,<sup>8</sup> while peripheral blood mononuclear cells from EoE patients exhibit enhanced production of IL-13.<sup>7</sup> Animal models of EoE have demonstrated that eosinophil accumulation is induced by intratracheal administration of IL-13 and this effect is ablated by a specific monoclonal antibody (mAb) to IL-13.<sup>17</sup> The intercellular adhesion molecule desmoglein-1 is important in regulating epithelial barrier function; its expression is downregulated by IL-13, with expression also markedly decreased in oesophageal biopsies from subjects with EoE.<sup>18</sup> In a recent Phase II, double-blind, randomised controlled trial, Rothenberg et al.<sup>19</sup> examined the safety and efficacy of a 12-week course (6 mg/kg every 4 weeks) of intravenous anti-IL-13 mAbs (QAX576, Novartis, Switzerland) in adult subjects with EoE, in whom conventional intervention using dietary approaches or topical steroid treatment had largely failed. The primary endpoint was a 75% reduction in the number of eosinophils in the oesophagus compared with baseline. This was achieved in 40% of patients receiving anti-IL-13 treatment compared with 13% of placebo patients. The study had a relatively small number of subjects, but does provide proof of principle that QAX576 significantly decreased intraepithelial oesophageal eosinophil numbers and modulated dysregulated oesophageal disease-related transcripts in adults with EoE. Although not significant, the observed trends for improved clinical responses, taken together with the histological findings, support the case for a larger study using subjects selected on the basis of biomarkers, as seen in guiding the use of an increasing number of biologics in eosinophil refractory asthma.<sup>20,21</sup>

## INTERLEUKIN-5

The tissue localisation of IL-5 in disease, together with studies in IL-5-knockout and transgenic mice,<sup>22,23</sup> suggests IL-5 is crucial to the development and release of eosinophils from the bone marrow, their enhanced adhesion to endothelial cells lining the post-capillary venules, and their activation and secretion in the tissues.<sup>24,25</sup> IL-5 plays a critical role in the promotion of eosinophil accumulation in the oesophagus.<sup>26</sup> Clinical trials have demonstrated increased levels of IL-5 mRNA in biopsies from patients with EoE, compared with healthy volunteers; intracellular IL-5 levels were also elevated in CD4<sup>+</sup> T cells in the peripheral blood of patients with EoE.<sup>15</sup> Anti-IL-5 therapy may therefore have systemic effects on eosinophil trafficking and survival with a positive local effect in the oesophagus. It should also be considered that other mediators are potent attractants for eosinophils. For example, CCL26 is a potent chemotactic chemokine for eosinophils, and a gene polymorphism for CCL26 has been shown to be associated with EoE.<sup>27</sup> Moreover, IL-5 responses of tissue eosinophils may be inhibited. For example, the membrane-anchored IL-5R- $\alpha$  isoform is downregulated, while the antagonistic soluble IL-5R- $\alpha$  variant is upregulated in bronchoalveolar lavage derived eosinophils from asthmatic patients<sup>28,29</sup> and eosinophils present in nasal polyp tissue.<sup>30</sup>

Reslizumab is a potent IL-5 antagonist with an extremely long duration of action in mice, monkeys, and guinea pigs.<sup>31</sup> Data from limited pilot studies suggested that reslizumab is a potentially efficacious and well-tolerated treatment for EoE, EG, and both hyper eosinophilic and eosinophilic polyposis.<sup>32</sup> A Phase I/II, open-label clinical trial assessed single doses of reslizumab (1 mg/kg intravenously) in adult patients (n=4) with EG and a food allergy. Treatment with reslizumab resulted in mean reductions in absolute peripheral blood eosinophil counts of 70% and 83% at 24 and 48 hours, respectively. Moreover, a 50–70% decrease in GI eosinophils was observed in three patients. However, one patient demonstrated a 43% increase in GI eosinophils and overall GI symptom scores were not improved in any patient. Rebound of disease was observed in two patients at 7–8 weeks after dosing; this was associated with increased eosinophil numbers and GI symptom scores substantially greater than pretreatment levels, although these returned to baseline within

2–4 weeks.<sup>33</sup> A randomised clinical trial evaluated the safety and efficacy of reslizumab (1, 2, or 3 mg/kg intravenously in four cycles administered every 4 weeks) in 226 children and adolescents with EoE (aged 5–18 years). The co-primary endpoints were oesophageal eosinophil counts and physician EoE global assessment, with secondary endpoints of symptom assessment and health questionnaires. Compared with the placebo arm, all doses of reslizumab gave significant reductions in oesophageal eosinophil counts but improvements in symptoms were observed in both the treatment and placebo groups.<sup>34</sup> One explanation for the lack of a relationship between symptoms and reduced eosinophil counts is the involvement of other effector cells such as mast cells, that have been shown to be present in greater numbers, together with evidence of degranulation in subjects with EoE.<sup>35</sup>

The anti-IL-5 mAb mepolizumab was also shown to significantly modulate oesophageal eosinophil counts in children with EoE,<sup>36</sup> while a study in adult patients with active EoE also reported reductions in eosinophil numbers in oesophageal tissues, together with modulation of the expression of molecules associated with oesophageal remodelling. However, symptom improvement was not significantly different from that seen in the placebo arm of this study.<sup>37</sup>

## CONCLUSION

Taken together, clinical outcomes with both mepolizumab and reslizumab cast doubt on the approach of targeting IL-5 in isolation in EoE. In this regard, there is evidence from animal models that IL-5 and eotaxin may work in a synergistic manner to promote eosinophil accumulation in the tissues.<sup>38</sup> Thus, a combination of reslizumab and a chemokine CC motif receptor-3 (CCR3; eotaxin is a ligand for CCR3) antagonist may prove an effective approach to limit or prevent eosinophil toxicity in EoE. Such an approach is supported by the observation that mice lacking CCR3 were protected from developing experimental EoE.<sup>4</sup> IL-13 is an important mediator of eosinophil accumulation and the findings from the clinical trial with anti-IL-13 mAb QAX576 are encouraging, with results from larger trials awaited. It would be interesting to study if any synergism exists between IL-13 and IL-5, but it may be that targeting the IL-13/eotaxin-3/CCR3 axis is a more promising approach. Dupilumab (SAR231893/REGN668) is

a fully humanised mAb against the IL-4R- $\alpha$  chain, a shared receptor component for IL-4 and IL-13. Dupilumab has been studied in large numbers of patients with asthma<sup>39,40</sup> and other Type 2 inflammatory conditions such as atopic dermatitis, chronic sinusitis, and nasal polyposis with very encouraging and significant clinical outcomes reported.<sup>41-44</sup> It therefore represents a potentially effective biologic-based therapy for EoE. Data from the reslizumab trial in patients with nasal polyposis<sup>45</sup> suggested that only a subgroup of patients exhibited a significant reduction in polyp size following treatment. This indicated that anti-IL-5 treatment may only benefit a subgroup of patients with an eosinophil-mediated disease. Targeting anti-IL-5 to carefully defined patient populations is an important consideration as demonstrated recently in several clinical trials, in which mepolizumab attenuated aspects of eosinophil-induced airway inflammation refractive to glucocorticoid therapy in highly selected

asthma patient populations.<sup>46,47</sup> An important goal, therefore, is the identification of biomarkers that would aid in the identification of patients with EoE most likely to respond to biologic-based therapy. An additional consideration is that the placebo group in trials of biologics in EoE often exhibit a marked improvement in symptoms, which may reduce the likelihood of significant findings being observed for the test compound. This is most likely due to the close monitoring of trial subjects, ensuring greater compliance in adherence to their normal anti-inflammatory/allergen avoidance therapy. Although the few early stage clinical trials of biologics targeting IL-13 (QAX576) or IL-5 (mepolizumab and reslizumab) used relatively small numbers of subjects with EoE and did not meet primary endpoints, they did demonstrate tissue responses. Further studies of these and related biological agents in larger trials with longer duration in EoE patients are clearly required to fully assess the utility of such approaches.

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