



## Mepolizumab in the treatment of eosinophilic esophagitis

Mepolizumab is a humanized monoclonal antibody that binds specifically to and inactivates a protein cell messenger termed IL-5, which plays a major role in the proliferation, maturation, activation and survival of eosinophils. As a result, mepolizumab has been studied in a number of eosinophil-associated diseases, such as asthma, hypereosinophilic syndrome and eosinophilic esophagitis (EE). EE is a clinical entity characterized by eosinophilic infiltration of the esophagus ( $\geq 15$  eosinophils/high power field in one or more fields) in the absence of gastroesophageal reflux. EE is on the rise, and this can not be fully accounted for by increased recognition. Currently, available therapies, although successful in many cases, can be disappointing in some patients, whether from lack of response, negative impact on quality of life, or significant toxicity. In order to better define EE therapy, investigators are evaluating novel drugs, including anti-IL-5 agents such as mepolizumab. Mepolizumab has been demonstrated to significantly reduce mean blood and tissue eosinophil count. It is well-tolerated and no drug-related serious adverse events have been described in the published literature to date. Mepolizumab is currently under clinical investigation and is not yet available for general use.

**KEYWORDS:** anti-IL-5 ■ eosinophilic esophagitis ■ mepolizumab

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Eosinophilic esophagitis (EE) is a clinical entity characterized by eosinophilic infiltration limited to the esophageal epithelium without significant eosinophilic inflammation of the remainder of the upper gastrointestinal tract mucosa. It can occur in isolation or as part of an atopic spectrum together with asthma, allergic rhinitis and/or atopic dermatitis. EE was first described in the literature in the 1970s [1,2]. The healthy esophageal epithelium is devoid of eosinophils. In 1982, Winter *et al.* reported that mild eosinophilic inflammation of the esophagus is indicative of gastroesophageal reflux disease (GERD) [3]. A retrospective study by Attwood and colleagues [4], published in 1993, showed that the presence of high concentrations of eosinophils in esophageal biopsies from patients with dysphagia, normal endoscopy and normal 24-h esophageal pH monitoring represented a distinctive clinicopathologic syndrome. This observation was further elucidated by Kelly *et al.* in 1995, with resultant increasing awareness of EE [5].

Presently, EE is defined as a primary disorder of the esophagus, characterized by esophageal and/or upper gastrointestinal tract symptoms in association with esophageal mucosal biopsy specimens containing 15 or more intraepithelial eosinophils per high power field in one or more fields and in the absence of pathologic GERD as evidenced by a normal pH monitoring study

of the distal esophagus or lack of response to acid-suppressive therapy [6]. Recent data appears to challenge this definition with the possibility of GERD coexisting with EE in a subset of patients [7,8].

While the epidemiology of EE remains to be extensively studied, it has been reported in several countries. In the USA, a national pathology database was used to identify EE cases from a cohort of 74,162 patients undergoing esophagogastroduodenoscopies (EGDs) in 26 states; 363 cases of EE were identified, with all age groups being represented [9]. In addition to its widespread occurrence, EE appears to have an accelerating incidence that cannot be fully accounted for by increased recognition. A large population-based study using a single institution's pathology database in Hamilton County, OH, USA, found 103 children with EE [10]. Of these, only three patients (2.8%) were identified prior to the year 2000. The overall incidence per 10,000 population was estimated to be 1.28 in 2003, suggesting a 0.37 (29%) increase in the frequency from 2000 [10]. Another population-based study conducted in Olmsted County, MN, USA, over a period of 30 years estimated the prevalence of EE in 2007 to be 10.4 per 10,000 population [11]. A male predominance with a male:female ratio of 2:1 has been reported in both pediatric and adult

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studies, and the clinical significance of this gender bias is undefined [9,12,13]. It is unclear if EE is associated with an ethnic or racial predilection.

Clinical manifestations of EE vary with age. Feeding difficulty is the predominant reason for evaluation in infants and toddlers ultimately diagnosed with EE. School-aged children more commonly present with GERD-like symptoms such as heartburn, abdominal pain and emesis [10,12,14]. Dysphagia and food impaction are reported to be the primary complaints in the preadolescent and adolescent years, as well as in adults with EE [15].

Environmental exposure, allergen sensitization, genetic predisposition, eosinophils and a variety of inflammatory molecules all interplay in EE pathogenesis. Based upon experimental murine models that link EE with allergen-driven pulmonary inflammation, and analysis of human esophageal tissue by microarray profile analysis, there is growing evidence that EE is associated with a Th2-type immune response with Th2 cytokine overproduction both locally and systemically [16–18]. Yamazaki and colleagues [19] studied common food- and environmental allergen-induced cytokine production by peripheral blood mononuclear cells in adults with EE. IL-5 and IL-13 production was noted to be higher in EE patients compared with healthy adults after food- or aero-allergen stimulation.

IL-5, a Th2 cytokine, is essential to the regulation of various major eosinophil functions, including proliferation, maturation, activation and survival. The crucial role of IL-5 in EE pathogenesis has been elucidated in a number of studies. Mishra *et al.* induced EE in transgenic mice by IL-5 overexpression and blocked allergen-induced EE through IL-5 neutralization [16,17]. Moreover, genetically engineered IL-5 deficient mice did not develop experimental EE when induced with an epicutaneous allergen [20]. Straumann *et al.* demonstrated that IL-5 mRNA expression is variably upregulated in esophageal mucosal biopsies of EE patients compared with controls [21,22]. Gupta *et al.* [23] solidified the finding of IL-5 mRNA upregulation in children. However, in a recent study, two EE patients treated with topical steroids reached histologic response following treatment in the absence of any documented IL-5 gene-expression changes [24]. Thus, despite the available evidence supporting the role of IL-5 in EE, this cytokine may not fully explain its pathophysiology.

Although it remains unclear whether remission should be defined histologically or symptomatically, a number of therapeutic options

exist. These include dilation, dietary modification and pharmacological therapy. However, the published data on these is limited, thereby negatively impacting decisions regarding choice of therapy, dosing and duration.

#### ■ Dilation therapy

Some studies report improved patient symptoms following esophageal dilation of EE-related strictures [13,25], although the strictures may recur in a subset of patients, thereby requiring repeated dilations. The stricture recurrence rates range from 7 to 50%, and it generally occurs between 2 and 24 months after dilation [13,26]. Esophageal tearing, chest pain, bleeding and perforation have been encountered with dilation [13,27]. Thus, esophageal dilation, if considered in a patient with EE, should be undertaken with caution.

#### ■ Dietary modification

Removal of dietary allergens may improve both the symptoms and the underlying histopathology in pediatric patients with EE [5,14,28]. Various dietary regimens have been proposed, including specific food elimination (based on allergy testing or clinical history), use of an elemental diet (i.e., a free amino-based formula) and a six-food elimination diet [14,28]. Patient preference, family's lifestyle and the resources required need to be considered, as a significant personal burden may accompany these modifications.

#### ■ Pharmacological therapy

A number of medications have been tried in the treatment of EE, although none have been uniformly studied or successful. Cromolyn sodium failed to show any obvious therapeutic effect in EE patients [14]. Leukotriene receptor antagonists caused symptomatic relief at high doses, but had no effect on esophageal eosinophilia [29]. Gupta *et al.* demonstrated that esophageal mucosal cysteinyl leukotriene levels in EE patients were similar to those in controls [30]. On the other hand, systemic and topical corticosteroids effectively resolve both mucosal eosinophilia as well as clinical symptoms [31–35]. Due to the potential for significant toxicity with systemic steroids, these are considered a bridging therapy to be used only short-term and/or in patients with severe disease. Multiple studies have reported the effectiveness of swallowed topical steroids in reversing the clinicopathological features of EE [32–34], and swallowed fluticasone has become essentially the first-line pharmacological therapy for EE patients. The drug is swallowed, without

the use of a spacer, at a full dose for 4–5 weeks before a weaning schedule is initiated [35]. Aceves *et al.* reported viscous budesonide to be an effective and safe therapeutic option in 16 of 20 (80%) EE patients [36]. In addition to a risk of toxicity with steroid exposure, there is a significant likelihood of disease relapse as the medications are weaned, and some possibility of lack of response [35].

These clinical experiences underline the need to identify and study EE therapies that are safe, patient-friendly and have the potential of serving as maintenance agents. One such therapy on the horizon is anti-IL5 agents. In order to address these unmet needs, anti-IL-5 agents are being explored in patients with idiopathic hypereosinophilic syndrome (HES) and EE.

### Introduction to the compound

#### ■ Chemistry

Mepolizumab (SB-240563) is a fully humanized monoclonal antibody (immunoglobulin G1) produced by and purified from the recombinant mammalian cell line, Chinese hamster ovary. It binds specifically to and inactivates a protein cell messenger called IL-5, a key element in the regulation of major eosinophil functions. By binding to free IL-5 with high affinity and specificity, mepolizumab prevents the association between IL-5 and the IL-5 receptors that are present on the surface of eosinophils [37].

#### ■ Nonclinical pharmacodynamics

Pharmacokinetic/pharmacodynamic (PK/PD) analysis of mepolizumab plasma concentrations versus eosinophil counts was studied in monkeys [37]. The resultant drop in circulating eosinophils did not appear to be due to redistribution of eosinophils, as evidenced by the lack of a significant accumulation or absence of eosinophils in any organ on histopathological assessment. Rather, the drop appeared to represent either an absent or decreased signal for eosinophil recruitment from bone marrow. The eosinophil nadir with mepolizumab administration is reached in 3–4 weeks, as demonstrated by Hart *et al.*, indicating a delay relative to the observed time for maximal mepolizumab concentrations [38]. This delay is most likely due to the fact that mepolizumab affects eosinophils indirectly by neutralizing IL-5. A steady-state mepolizumab concentration of approximately 1.5 µg/ml is required to decrease peripheral eosinophil counts by 50% relative to that observed prior to mepolizumab administration, and to then sustain this attenuation [38].

#### ■ Nonclinical pharmacokinetics & metabolism

Zia-Amirhosseini *et al.* examined the PK and PD of mepolizumab in monkeys and noted that intravenous administration exhibited approximately dose-proportional PK over the dose range from 0.05 to 300 mg/kg [37]. Following any administration, concentrations declined in a biexponential manner, with a mean terminal half-life of  $13.0 \pm 2.2$  days. The second phase of the concentration–time profile accounted for the majority of area under the concentration–time curve (AUC;  $\geq 86\%$ ). The plasma clearance and volume of distribution were relatively constant across the examined dose (0.05–300 mg/kg) and ranged from 0.157 to 0.217 ml/h/kg and 65.6–82.1 ml/kg, respectively.

Hart and colleagues [38] reported that a single intravenous dose of mepolizumab at 300 mg/kg had a mean maximal plasma concentration up to 7 mg/ml and AUC of 1450 mg/h/ml. Trough plasma concentrations seemed to plateau after the fourth monthly dose. Additionally, intravenous and subcutaneous dosing were found to be comparable in terms of AUC.

#### ■ Clinical efficacy

Clinical trials in asthmatic patients revealed only a twofold reduction in lung eosinophilia and no major clinical improvement [39]. Recent attention has focused on the potential utility of anti-IL-5 in treating other eosinophil-associated diseases such as HES and EE, and available data will be discussed further.

#### Preliminary studies

An open-label Phase I/II safety and efficacy study of anti-IL-5 in four adult EE patients (aged 18–41 years) with long-standing dysphagia and esophageal strictures was performed by Stein *et al.* [40]. All patients continued their current therapy in addition to three infusions of mepolizumab at a dose of 10 mg/kg, with a maximum of 750 mg, at weeks 8, 12 and 16. Peripheral blood, as well as esophageal eosinophilia, improved significantly after anti-IL-5 treatment (7.9-fold decrease,  $p < 0.05$ , and sixfold decrease,  $p < 0.05$ , respectively). The maximal esophageal eosinophilia, however, did not reach normal levels despite its large sixfold decline, and response to therapy did not seem to correlate with plasma IL-5 or eotaxin-3 levels. Patients self-reported improved clinical symptoms as well as quality of life.

Similar decreases in esophageal eosinophils were seen in a pilot study by Straumann *et al.* [39]. A total of 11 adults with active EE who

had previously discontinued all other EE therapies were randomized to receive either mepolizumab 750 mg as an intravenous infusion at days 0 and 7 or placebo. There were five patients in the mepolizumab group, with a mean age of 32 years, and six patients in the placebo group, with a mean age of 34 years. Patients who at week 4 did not reach remission, defined histologically as less than five eosinophils/high power field, received two further doses of 1500 mg mepolizumab or placebo 4 weeks apart. Follow up was for 21 weeks. While there was a marked drop of both blood and tissue eosinophilia in the treatment group, the primary end point of peak esophageal eosinophils of less than five/high power field was not observed. There was reduced eosinophilic degranulation in esophageal tissue, but no associated drop in the infiltrating T cells and mast cells. Two of the five patients treated with mepolizumab reported some symptom improvement, versus one of the six patients who received placebo. No clinically significant adverse effects occurred.

In an open-label trial aimed at characterizing the immunologic and hematologic effects of anti-IL-5 in 25 human subjects with diverse eosinophilic disorders, of whom six had isolated EE, 92% of the patients experienced a 20-fold drop in blood eosinophilia, and this effect was sustained for 3 months in 76% [42]. Response to study drug was independent of the initial plasma IL-5 level and, in fact, plasma IL-5 levels increased with therapy. This was hypothesized to be related to a circulating IL-5/anti-IL-5 complex that induced a significant increase in eosinophil IL-5 receptor- $\alpha$  expression, and increased the percentage of CD4<sup>+</sup> and CD8<sup>+</sup> cells that produce IL-5.

A multicenter Phase II study to evaluate the safety and tolerability at week 12, as well as the PK and PD of intravenous mepolizumab in pediatric patients with EE, is underway. This randomized, double-blind, parallel group clinical trial is estimated to be completed by November 2008 [101].

### Phase III trials

There are no ongoing Phase III trials evaluating the efficacy and safety of mepolizumab in patients with EE. Response to mepolizumab was evaluated in an international, randomized, double-blind, placebo-controlled trial that evaluated 85 HES patients at 26 different centers [43]. HES is defined as a blood eosinophil count of more than 1500 per microliter for 6 months or longer, and eosinophilia-related organ involvement

or dysfunction, with no identifiable secondary cause of eosinophilia. Study patients were enrolled when they had achieved a stable clinical status with a blood eosinophil count of less than 1000 per microliter and no new or worsening clinical signs while on prednisone monotherapy or an equivalent dose of another steroid. Patients were randomized to either intravenous mepolizumab (750 mg) or placebo (saline). The doses were administered every 4 weeks for a 36-week period with gradual tapering of steroids. The primary end point was reduction of prednisone dose to 10 mg/day or less for 8 or more consecutive weeks. Secondary end points included, among others, a blood eosinophil count of less than 600 per microliter for 8 or more consecutive weeks, the time to treatment failure and the mean daily prednisone dose at week 36. A total of 84% of patients in the mepolizumab group, versus 43% of patients in the placebo group, reached the primary end point (hazard ratio [HR]: 2.9; 95% CI: 1.5–5.26;  $p < 0.001$ ); all eight of the study patients with gastrointestinal dysfunction achieved this end point. A blood count of less than 600 eosinophils per microliter was reached in 95% of patients on mepolizumab, compared with 45% of the placebo group (HR: 3.53; 95% CI: 1.94–6.45;  $p < 0.001$ ). All other secondary end points also significantly favored the use of mepolizumab. The incidence of adverse events was similar among the two groups; an adverse event considered to be related to the study drug occurred in 37% in the mepolizumab group, versus 29% in the placebo group. No serious adverse events were deemed to be related to the study drug [43].

### ■ Postmarketing surveillance

Mepolizumab is not available for general use. It remains under investigation and in clinical trials.

### ■ Safety & tolerability

Antigenicity of monoclonal antibodies has been reduced dramatically with the switch from murine to humanized antibodies. These reassuring observations need to be tempered with reports of antibody responses noted in preclinical trials of humanized antibodies in monkeys, whose immunoglobulins are more than 90% homologous to that of humans. These responses can vary from increased clearance to anaphylactoid reactions. In the study by Hart and colleagues [38], neither intravenous nor subcutaneous administration of mepolizumab, whether as a single dose or repeated dosing, induced an antibody response to the

drug. Single doses of up to 100 mg/kg had no effect on body temperature, cardiovascular, respiratory and renal function in monkeys; even doses of 300 mg/kg were well-tolerated. In a 6-month toxicity study, intravenous doses of up to 100 mg/kg showed no evidence of any clinical, immunological or histopathological effects.

In the Phase I/II trials of mepolizumab, adverse events were generally mild. In an open-label trial, Garret *et al.* administered anti-IL5 at a dose of 10 mg/kg to four patients with HES [44]. There were no drug-related adverse events except fatigue following the first two infusions in one of the patients, and headaches with every infusion in a patient with a known history of headaches. Headaches and upper respiratory tract infection symptoms were the most common adverse events reported in a study on four EE adult patients [40]. One patient also had symptomatic hypotension during the third infusion requiring volume replacement but without other sequelae. Other reported adverse events included nausea, fatigue, cough and chest pain, which resolved following infusions.

In the Phase III trial of HES patients, while the duration of exposure to mepolizumab was longer than placebo, adverse events were reported at similar rates among the two study groups (93% in mepolizumab group versus 98% in placebo group). One patient receiving mepolizumab withdrew from the study due to an adverse event thought to be not related to the study drug. A total of 16 of 43 patients had drug-related adverse events including fatigue, arthralgia, headache, pruritis, myalgia, erythema and rash, but these were comparable to the placebo group. Seven of 43 patients in the mepolizumab group had serious adverse events, but none was thought to be associated with the study drug. These included asthma, clinical flares of HES, pneumonia, renal failure, bronchitis, hepatitis, pancreatitis, cardiac arrest, dehydration, rhinitis, pyrexia and spinal compression fracture [44]. An ongoing open-label trial involving 78 patients from this trial will hopefully provide long-term information regarding safety issues.

#### ■ Regulatory affairs

Mepolizumab is in clinical trials, but has been granted orphan status by regulatory authorities in the USA and the EU [45]. In the USA, the Orphan Drug designation applies to a disease that affects fewer than 200,000 persons based on the Orphan Drug Act.

#### Conclusion

Mepolizumab is a novel monoclonal antibody that has the ability to reduce blood eosinophilia and the potential to prevent eosinophil-mediated organ tissue damage. As such, it brings hope to many patients with EE or other hypereosinophilic disorders whose disease has been refractory to current therapies or who suffer from their side effects. Additionally, advancements in mepolizumab development have expanded our understanding of various hypereosinophilic conditions.

#### Expert commentary & future perspective

EE has a complex pathogenesis in which multiple etiologic factors interact. Dietary and environmental factors, in addition to the genetic predisposition, contribute to disease expression. Although the natural history of EE is yet to be studied systematically, clinical experience coupled with current literature support its chronicity with the added risk of long-term complications such as small-caliber esophagus, fibrosis and structuring [25,27]. These issues underscore the need to define therapeutic options that impact induction as well as maintenance of remission. Should treatment be aimed at symptom resolution, histological remission or both? Will all, most, or just a few patients progress to have irreversible fibrotic changes? How will therapy impact the disease course and complications? This multitude of queries can be answered through natural history studies, disease course on and off therapy and elucidation of EE pathogenesis.

Current therapies, whether nutritional or steroid-based, can induce clinical as well as histological remission in most patients; however, some patients remain severely dependent, resistant or merely intolerant of therapy. Recognition of disease subtypes, whether through clinical phenotypes, biomarker profiles or both, becomes crucial in identifying those subgroups of patients at risk of a more aggressive disease course. This information will help tailor therapy based on phenotypic subsets and allow for targeted therapeutic interventions early in the disease course.

Novel therapeutic approaches such as anti-IL5 agents bring new hope to those with recalcitrant disease. Studies thus far have shown trends in symptom improvement and reductions in tissue as well as peripheral eosinophilia. In addition, these agents appear to be generally well-tolerated. However, although anti-IL5 has shown promising results, it has consistently failed in inducing histological remission. Hence, whether

anti-IL-5 will alter the natural progression of EE depends on how critical it is to achieve histological eosinophilic resolution. It is important to note, however, that most of the patients who responded to anti-IL-5 had longstanding disease and severe tissue pathology, indicating that a major component of EE remains reversible even in the adult population and with severe manifestations.

These promising preliminary results of anti-IL-5 for EE invariably leave a number of questions unanswered. Will rebound eosinophilia recur when treatment is discontinued? Who are the ideal candidates for this therapy? What is the preferred dose to attain a sustained response?

More studies are required to solidify the existing evidence and shed light on these questions. Nonetheless, these are exciting times as clinicians expand the armamentarium of therapies directed towards EE and other eosinophilic disorders.

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**Executive summary**

- Eosinophilic esophagitis appears to have an accelerating incidence, and current therapy can still be disappointing in some patients, whether due to lack of response or significant toxicity.
- Mepolizumab is a fully humanized monoclonal antibody that binds specifically to and inactivates a protein cell messenger called interleukin-5, a key element in the regulation of major eosinophil functions.
- Mepolizumab has been shown to significantly reduce blood as well as tissue eosinophilia, irrespective of the circulating IL-5 levels.
- Mepolizumab has been well tolerated by subjects and has shown a favorable side-effect profile.

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