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Mepolizumab in eosinophilic disorders

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Abstract

Mepolizumab (Bosatria[®], GlaxoSmithKline) is a biologic agent developed to treat asthma. It represents a humanized monoclonal antibody of IgG1 κ type, which targets human IL-5 and thus prevents its interaction with the α -chain of the IL-5 receptor. To date, it has not been approved for use in any eosinophil-related disorder; however, several studies have suggested some therapeutic benefit across a spectrum of eosinophil-related disorders. This article evaluates the currently available preclinical and clinical studies, and the impact of mepolizumab against a variety of eosinophilic disorders.

Keywords

anti-IL-5; eosinophilic gastrointestinal disorders; eosinophils; human; IL-5; mepolizumab

Overview of the market

The spectrum of eosinophil-related disorders is wide, and affects children and adults around the world. These disorders include chronic and highly prevalent respiratory disorders such as asthma, chronic gastrointestinal disorders such as eosinophilic esophagitis (EoE), and less common disorders such as the hypereosinophilic and Churg–Strauss syndromes that are often associated with significant clinical morbidity.

In the USA alone, asthma is associated with pathologic pulmonary tissue eosinophilia and affects over 38 million patients at some point in their lifetime. It is estimated that over 300 million individuals suffer from asthma worldwide [1,2]. A variety of drugs, including inhaled and oral steroids, leukotriene antagonists, and short- and long-acting β -agonists, are available and used to treat both the acute and long-lasting features of the disease. To date, a single biologic agent (anti-IgE; omalizumab) is approved for use in asthma. For those patients who have severe asthma, no single therapeutic measure is available to control all of the features of this disease, such that combination therapy is most often employed.

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Eosinophilic esophagitis represents another eosinophil-related disease that has been reported in patients from Australia, Europe, North America, South America, and Asia, with prevalence rates at approximately one per 10,000 [3–8]. It is most commonly a manifestation of food antigen-driven mucosal eosinophilia, such that the primary treatment modality in young children revolves around dietary antigen elimination. Alternative therapy employing steroids such as fluticasone propionate or budesonide that are intended for use in asthma, but which can be swallowed rather than inhaled, is also effective for some patients [9,10].

Until the primary mechanisms underlying the eosinophil-mediated respiratory and gastrointestinal conditions are unraveled to reveal other targets for therapy, there is a need for effective medication with low toxicity that avoids the anticipated side effects of steroid therapy and the difficulties in managing complex dietary eliminations.

Pharmacology

Introduction to the compound

Mepolizumab (Bosatria[®], SB-250563, GlaxoSmithKline) represents a biologic agent that was initially intended as a therapeutic agent to treat allergic asthma. It is a fully humanized mAb Chinese hamster ovary-derived mAb (2b6) that targeted recombinant human IL-5 [11]. This mAb was transformed into a humanized antibody via connection of the IL-5-specific complementary-determining regions to human heavy and light chains from IgG1 κ with a single covalent disulfide bond between the heavy chains, as well as another single bond between the heavy and light chains [12–14]. This humanized antibody is N-glycosylated and has a molecular weight of 149.2 kDa inclusive of the carbohydrate moieties [13].

Mepolizumab's target, IL-5, represents a 134-amino acid protein that forms an approximately 52-kDa homodimer that is related to both granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3 and represents the main cytokine responsible for the maturation, activation and survival of eosinophils [15–24]. Mepolizumab specifically binds to the α -chain of IL-5 with an IC₅₀ of less than 1 nM and a dissociation constant of 4.2 pM, and disrupts its interaction with the α -subunit of the IL-5 receptor, which is present on the eosinophils and their early precursors [12–14,25].

Design

Animal studies

Preliminary and ongoing studies in mice and primates identified the IL-5/IL-5 receptor axis as a plausible means to target eosinophils that are intimately related to the pathogenesis of asthma. Indeed, in an asthma model using mice deficient in IL-5, the knockout mice did not display eosinophilia, airways hyperreactivity or pulmonary injury that was readily apparent in control animals [26]. Treatment with an anti-IL-5 antibody in mice also demonstrated reductions in eosinophilic airways inflammation that were associated with a reduced response to methacholine [27]. Similarly, later studies demonstrated that in mice with one of two disparate genetic deletions that result in eosinophil deficiency (PHIL and Δ dblGATA), both had reduced airways inflammation and hyperresponsiveness in experimental models of asthma [28,29].

In a similar fashion, mouse models of EoE demonstrated significant esophageal eosinophilia along with epithelial hyperplasia, as measured by 5'-bromodeoxyuridine incorporation assays, which were essentially absent in mice deficient in IL-5, or that had been treated with an anti-IL-5 antibody [30].

In concert these studies demonstrated a significant role for IL-5 and eosinophils in experimental mouse models of asthma and EoE. Not only was the pathologic eosinophilia ablated in these varied models of disease, but the comorbid features of the respective diseases were also significantly improved in the mice with a defective IL-5 signaling pathway or the frank absence of eosinophils.

Preliminary preclinical animal studies that specifically utilized mepolizumab were performed in cynomolgus monkeys as it represented the only animal model with cross-reactivity between mepolizumab and IL-5 endogenous to the animal [12]. Following sensitization with inhaled *Ascaris suum*, increases in bronchoalveolar lavage eosinophils were suppressed with a single dose of mepolizumab; however, this had no impact on the acute bronchoconstrictor responses typically seen with these inhalations [12].

Pharmacodynamics

The impact of mepolizumab on normal physiology has been evaluated in both preclinical and clinical trials. Mepolizumab did not effectively neutralize IL-5 from mice, rats, guinea pigs or dog, and only neutralized IL-5 from cynomolgus monkeys and humans [12]. In preclinical trials in the cynomolgus monkeys, both subcutaneous and intravenous routes were utilized, and clear suppression of peripheral eosinophilia was noted, as had been seen in mouse studies utilizing a mouse-specific anti-IL5 antibody, TRFK-5 [11,12,31]. No adverse impact on body temperature, cardiovascular, respiratory, renal, or immune function was noted with infusions of mepolizumab and no reduction in bronchoalveolar lavage IgG or total protein was demonstrated [12]. In the first Phase I clinical trial in humans, mepolizumab clearly resulted in a long-lasting reduction in peripheral blood and sputum eosinophilia, as well as the eosinophilia that occurs following allergen challenge in patients with allergic asthma [32]. While mature eosinophil forms appear to be reduced systemically via the use of mepolizumab, the presence of eosinophilia precursors was still apparent in the bone marrow and peripheral tissues [21].

Pharmacokinetics & metabolism

The half-life of mepolizumab has been demonstrated in cynomolgus monkeys to be 13 ± 2 days, and between 16.2 and 21.7 days in man [11,13,14]. These data regarding pharmacokinetics in man are derived from 420 patients who received mepolizumab across several Phase I, II and III studies with a variety of intravenous doses. The maximum concentration following intravenous injection is achieved within minutes and occurs within 4–8 h for the subcutaneous and intramuscular routes, with both AUC and C_{max} increasing proportionally relative to dose [13,14]. To date, antimepolizumab antibodies have been found in only six out of 329 treated subjects [13].

Clinical efficacy/studies

Asthma

The first reported human study utilizing mepolizumab was published in December 2000 in which blood and sputum eosinophil counts and bronchial hyperreactivity (late-phase forced expiratory volume in 1 s [FEV₁]) were monitored in a small, randomized, double-blinded, placebo-controlled study [32]. This study used three separate groups of eight patients who received a single infusion of placebo, 2.5 mg/kg or 10 mg/kg of mepolizumab. Variable reductions in blood and sputum eosinophilia were demonstrated after treatment compared with placebo, but no differences were observed for the measures of bronchial hyperreactivity or fall in FEV₁. Unfortunately, the study was not adequately powered to detect the latter differences.

Another small follow-up placebo-controlled study that utilized only two arms (placebo or 750-mg doses of mepolizumab) was also unable to demonstrate improvement in clinical measures of asthma following a three dose course of treatment [33]. While clinical measures of asthma inclusive of improvement in FEV₁, peak expiratory flow rate and airway hyperreactivity in response to histamine (histamine PC₂₀) did not improve, there was a reduction in bronchial airways eosinophilia and expression of proteins that make up the extracellular matrix (ECM). In addition, the expression of the ECM protein, tenascin, directly correlated with eosinophil counts and was reduced following treatment with mepolizumab. Similar findings for eosinophilia and tenascin were later noted for patients studied for the impact of anti-IL-5 on eczema [34].

The first large placebo-controlled study of mepolizumab in asthma patients enrolled irrespective of their level of eosinophilic airway inflammation also did not demonstrate significant improvement in clinical outcomes except for a modest improvement in peak expiratory flow rate. This occurred in patients receiving a 250-mg dose of mepolizumab (n = 110) compared with placebo (n = 119), and was not noted for patients who received the 750-mg dose of mepolizumab (n = 112) [35]. Other parameters followed including FEV₁, use of β_2 -agonists and a summary symptom score that were no different in each of these three groups.

Two later papers published simultaneously assessed the impact of mepolizumab in asthma patients who had significant sputum eosinophilia, with the hypothesis that this particular asthma phenotype might derive a unique benefit. In the first of these two reports [36], patients received a monthly dose of either mepolizumab or placebo over the course of 1 year. These patients had a history of refractory eosinophilic asthma and frequent exacerbations. The study monitored the number of severe asthma exacerbations, asthma symptoms, improvement in the Asthma Quality of Life Questionnaire (AQLQ), measures of FEV₁, airway hyperresponsiveness and eosinophil counts in the blood and sputum [36]. The number of asthma exacerbations during the year were reduced to two in the mepolizumab group, compared with 3.4 in the placebo group (p = 0.02). In addition, the AQLQ score was increased over baseline by 0.55 in the treated group versus 0.19 in the placebo groups. No change in asthma symptoms, FEV₁ or airways hyperresponsiveness was noted, although reductions in blood and sputum eosinophilia were readily and clearly documented. Along with these primary measures, the authors also noted a reduction in airways wall thickness in patients who received mepolizumab as compared with their placebo-treated controls, supporting the interesting notion that there might be a positive impact on airways remodeling, as had been suggested by the earlier report describing alterations in ECM protein expression [33,36].

The second report evaluated similar patients who had prednisone-dependent asthma with sputum eosinophilia that was evident during asthma exacerbations [37]. A total of 20 patients were recruited for the study from a group of 800 patients with severe asthma. Two patients were inappropriately included (no sputum eosinophilia) and data from these patients were not fully analyzed as part of the research study. In addition, it appears that all patients were inadvertently crossed over from the placebo to treated groups as well as from treated to placebo groups on one occasion [37]. Despite these limitations, there was a significant reduction in exacerbations in the mepolizumab-treated relative to placebo-treated patients. Only one exacerbation occurred in the mepolizumab-treated group (n = 9 patients), whereas 12 exacerbations were seen in the placebo-treated group (n = 11 patients). In addition, and in contrast to other studies to date, this report described a modest improvement in FEV₁ following therapy with mepolizumab, as well the now well-recognized control of eosinophilia in the blood and sputum.

To summarize, good control of peripheral eosinophilia has been readily demonstrated, but there has been only marginal improvement in FEV₁ reported in only a single study. Two studies have now demonstrated fewer asthma exacerbations in a small subgroup of patients who have severe asthma associated with sputum eosinophilia and who are dependent on oral corticosteroids [36,37]. From the studies reported to date, patients who have steroid-dependent asthma without sputum eosinophilia have not benefited consistently from the use of mepolizumab, although this has not been directly addressed in any of these studies.

Eosinophilic esophagitis/eosinophilic gastrointestinal disorders

Eosinophilic esophagitis represents a chronic condition in which either dietary-antigen elimination or the off-label use of swallowed fluticasone propionate or budesonide are employed as therapy. Histologically, EoE is characterized by increases in eosinophils, lymphocytes and mast cells, along with hyperplasia of the basal cell layer [38–40]. The criteria for making a clinical diagnosis of EoE requires that there be at least 15 eosinophils per high-powered field in a hematoxylin- and eosin-stained endoscopic biopsy specimen from a patient who does not have gastroesophageal reflux disease or other causes of tissue eosinophilia, as defined by the First International Gastrointestinal Eosinophil Research Symposium [8]. While seemingly a relatively uncommon disorder, with annual incidence rates in different populations varying between 0.1 and 1.2 per 10,000 population, this places it on par with the rates seen for inflammatory bowel disease, 0.3–0.7 per 10,000 population [41–46]. Furthermore, EoE represents the second most common cause of chronic esophagitis following gastroesophageal reflux disease.

In a small initial study evaluating anti-IL-5 in four patients with EoE, the mucosal eosinophil count was reduced whether measured using the mean, median, and maximum number of eosinophils per high-power field. Additionally, basal cell hyperplasia was improved in three of the four patients. For mast cells, the picture is somewhat less clear as mast cell number fluctuated in these four patients. These results suggested that mepolizumab could provide some benefit for patients with EoE [47]. A later larger study with 11 patients divided into placebo (n = 6) and mepolizumab-treated group (n = 5) also demonstrated clear reduction in the mean and peak eosinophil counts in the mepolizumab-treated groups that was not noted in the placebo-treated group with only minimal improvement in symptomatology [48].

A larger multicenter parallel group trial also demonstrated reductions in both peak and mean esophageal eosinophil counts of greater than 50% after receiving three doses of mepolizumab in up to 77% of patients. In addition, peripheral blood eosinophil counts were also decreased. However, most mucosal biopsies did not return completely to normal (defined as fewer than four eosinophils per high-power field for this study) [49].

Hypereosinophilic syndromes

Primary eosinophilic disorders such as hypereosinophilic syndrome (HES) have also been targeted in clinical trials utilizing mepolizumab. The first case report involved a 51-year-old man with a 4-year history of persistent eosinophilia that was resistant to treatment with prednisone and hydroxyurea [50]. He had a concomitant diagnosis of lymphomatoid papulosis that did not respond to therapy with methotrexate and ultraviolet A light therapy. He was treated with three separate doses of mepolizumab and following each there was transient clearance of his dermatologic lesions and peripheral eosinophilia, along with an apparent improvement in his respiratory symptoms. A later case report described three patients who had hypereosinophilic syndrome with eosinophilic dermatitis who also demonstrated dramatic and generally longer-lasting improvements in blood eosinophilia, symptoms and skin lesions [51]. These patients lacked the Fip1-like 1 gene (FIP1L1) and

PDGF receptor α (PDGFRA) fusion gene-product that is linked with myeloproliferative forms of HES, and whose primary treatment revolves around the use of imatinib as first line and chronic therapy [51–55].

In addition to this study of patients who had eosinophilic dermatitis, a simultaneous small open-label Phase I/II trial designed primarily to monitor drug safety, recruited four patients with HES or EoE. Three patients, who met criteria for HES, demonstrated marked reduction of eosinophil counts despite simultaneous and chronic oral steroid therapy that had previously failed to control their eosinophilia. In addition, these patients all reported improvement in quality-of-life measures as measured by a validated general health score [56].

In aggregate, these studies led to a more recent large placebo-controlled study of mepolizumab that recruited 85 FIP1L1–PDGFRA fusion gene-negative patients with HES on prednisone monotherapy. Treatment with mepolizumab allowed 84% of the patients to achieve the primary end point of low-dose prednisone therapy (≤ 10 mg/day) as compared with 43% of patients on placebo ($p < 0.001$), while also normalizing eosinophil counts in 95% of treated patients compared with 45% of patients on placebo ($p < 0.001$) [57]. During this study, a single death was noted in the mepolizumab-treated group in a young man with pre-existing cardiovascular disorder and the apparent failure of an internal pacemaker defibrillator. The number of adverse events was otherwise no different in the mepolizumab versus the placebo-controlled group, and no adverse event was ultimately deemed by the investigators to be due to drug. As such, these results are encouraging and suggest the need for additional study of mepolizumab in patients who have severe systemic eosinophilia.

Churg–Strauss syndrome

A case report in January 2010 revealed a significant improvement in the pathology and symptoms in a female patient who was diagnosed with antineutrophil cytoplasmic antibody (ANCA)-negative Churg–Strauss syndrome [58]. This form of ANCA-negative Churg–Strauss syndrome has been associated with both lung and cardiac involvement [59]. In this particular case, improvements in peak flow, improved CT scan findings of parenchymal disease, along with control of peripheral eosinophilia and eosinophil cationic protein, with reduction in the patient's regular dose of prednisone were all reported as she was treated over the course of 2 years. As has been seen in patients with idiopathic hypereosinophilic syndrome, an elevated serum IL-5 level was readily apparent in this patient prior to therapy, and increased with the treatment with mepolizumab. This increase essentially represents the increased half-life of a biologically inactive mepolizumab/IL-5 complex that has been described previously [60].

A later open-label study that studied seven patients with Churg–Strauss syndrome treated with only four doses of mepolizumab, demonstrated that mepolizumab was safe and well-tolerated while also reducing the corticosteroid requirement in all seven patients during the course of the study [61]. While no improvements in clinical scores related to Churg–Strauss syndrome and asthma were noted during this study period, the patient's symptoms remained stable and well-controlled during the treatment phase with mepolizumab while undergoing reduction in corticosteroid dosing. However, once treatment with mepolizumab was completed, all seven patients required bursts of corticosteroid treatments.

Atopic dermatitis/mepolizumab in experimental dermal eosinophilia

A clinical trial evaluating the use of mepolizumab in atopic dermatitis has also been reported and this study utilized a clinical tool (Scoring Atopic Dermatitis [SCORAD]) to assess for any clinically relevant differences between the placebo and treatment arms [62]. No

clinically significant differences for SCORAD were noted between the groups, following a single administration of either drug or placebo. As has been observed in other studies described in this article, peripheral eosinophilia was clearly reduced in patients receiving mepolizumab relative to the placebo-treated group [62]. Mepolizumab has also been studied in a human model of late-phase inflammation of the skin in which patients who had asthma and atopy received intradermal injections of an allergen to which they had had a positive response on aeroallergen skin-prick testing. Skin biopsies at these intradermal injection sites were obtained shortly before and after single treatments with mepolizumab or placebo and demonstrated significant reduction in skin eosinophilia and tenascin in the mepolizumab-treated group as compared with the placebo-treated group [34].

Comparison to other agents

For the treatment of asthma, mepolizumab has not been effective for all patients in the broader spectrum of patients with asthma, but may be useful for that subpopulation with evidence of significant sputum eosinophilia.

The primary agents available for treatment of patients with eosinophilic disorders include the use of imatinib for FIP1L1–PDGFRA-positive HES. Systemic steroid agents, and sometimes cytotoxic agents, are employed for these systemic eosinophilic disorders such as HES or Churg–Strauss syndrome. The steroid agents have well-known systemic effects and side effects, and other agents such as IFN- α , hydroxyurea, vincristine, and cyclophosphamide have short and long-term toxicities that can make the use of any of these medications problematic [63–66]. Both mepolizumab and reslizumab, another anti-IL-5 drug under study, have reported to have an impact on nasal polyposis in patients with elevated IL-5 in nasal secretions, a disease state that would otherwise be treated with oral/topical steroids or surgical polypectomy in select cases [67,68].

Safety & tolerability

In studies reported to date, mepolizumab has been well tolerated, with antimepolizumab antibodies of unknown significance found in fewer than 2% of the treated population. In the largest study to date, adverse events were essentially the same after either placebo or active drug administered.

Conclusion

Mepolizumab is an interesting biologic agent with the potential to provide significant relief for patients with severe chronic eosinophilic disorders such as HES and Churg–Strauss syndrome, but that has been less effective in trials against mild/moderate asthma and EoE. In these larger mepolizumab trials for asthma and EoE there have been predictable and consistent reductions in peripheral blood and tissue eosinophils, but the overall clinical benefit for the study patients with asthma or EoE from the use of mepolizumab as single-agent therapy has been lacking to date. However, in patients with severe eosinophilic asthma, studies have demonstrated fewer asthma exacerbations.

It is currently unknown if a more thorough clearance of the tissue eosinophilia and eosinophil granule constituents via modification of mepolizumab dosing or duration would result in a further beneficial response in asthmatic patients in general.

Expert commentary

In the studies to date utilizing mepolizumab over a broad range of eosinophilic disorders, no clear toxicity has been noted across these varied disorders, along with limited evidence

demonstrating antibody formation against mepolizumab. This suggests that mepolizumab is a well-tolerated drug, with the potential for use in the appropriately targeted population.

Five-year view

For the more common eosinophilic disorders such as asthma and EoE, it will be necessary to determine whether there is a select population that is best-suited for therapy with mepolizumab. Otherwise, it might be possible to use mepolizumab as part of combination therapy with medications and/or dietary antigen elimination to manage the broader population that has disease recalcitrant to currently available therapeutic modalities. The most likely effective use for the drug during the next 5 years will be for patients with severe and difficult to control eosinophilic disorders.

Key issues

- Mepolizumab (Bosatria®) is a fully humanized monoclonal antibody against IL-5.
- Mepolizumab may indeed have a positive effect in systemic eosinophilic diseases such as the Churg–Strauss and hypereosinophilic syndromes.
- Limited impact of mepolizumab is noted for both mild/moderate asthma and eosinophilic esophagitis to date, and any future use of mepolizumab will need to be targeted against a subset of patients who achieve significant benefits from its use or from the use of modified dosing regimens.

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J Pablo Abonia is an Assistant Professor of Pediatrics at Cincinnati Children's Hospital Medical Center and is Co-Director of the Registry for Eosinophilic Gastrointestinal Disorders (REGID). J Pablo Abonia is currently a site principal investigator for a clinical trial for the anti-IL-5 drug, reslizumab, sponsored by Cephalon, Inc. J Pablo Abonia is funded as a co-investigator on NIH grant NIH/NIDDK R01 DK076894-03S1. Philip E Putnam is a Professor of Pediatrics and Medical Director of the Cincinnati Center for Eosinophilic Disorders (CCED) at the Cincinnati Children's Hospital Medical Center. J Pablo Abonia and Philip E Putnam have also participated as investigators in clinical trials of mepolizumab.

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