



## Mepolizumab in the treatment of severe eosinophilic asthma

IL-5 is crucial in the pathogenesis and evolution of eosinophilic asthma. Mepolizumab is a high-affinity humanized monoclonal antibody of the IgG1/k subtype that inhibits the binding of IL-5 to its receptor expressed on eosinophils, thereby inducing significant reduction in eosinophil circulation, as well as asthma exacerbations and corticosteroid treatment. This review deals with the currently available studies of mepolizumab in the treatment of patients with severe eosinophilic asthma.

**Keywords:** anti-IL-5 therapy • eosinophilic asthma • mepolizumab • severe asthma

### Asthma, a highly prevalent respiratory chronic disease

It is estimated that asthma affects 300 million individuals of all ages and that about 10% of cases remains symptomatic and poorly controlled resulting in rising treatment costs and a burden for patients and society [1,2].

Asthma is recognized as a chronic respiratory disease characterized by airway inflammation, bronchial hyperresponsiveness and airflow obstruction. Although these are common features, asthma represents a heterogeneous disease with different phenotypes resulting from the synergy between genetic and environmental factors.

### Severe eosinophilic asthma, a subclinical phenotype of asthma

Both early onset atopic and late onset non-atopic asthma show hypereosinophilic airway disease. Although fractions of exhaled nitric oxide levels, blood eosinophil counts and serum periostin levels have been evaluated as potential indicators of eosinophilic asthma, the diagnosis of this phenotype is commonly defined by the increased number of eosinophils in the induced sputum (>1–3%) [3,4]. Literature has demonstrated that severe asthmatics have an increased number of eosinophils in bronchoalveolar lavage (BAL) and peripheral blood since 1990 [5]. Eosinophils

tend to increase during exacerbations, correlate with asthma severity and their count in sputum has been used to adjust steroid dose with good results in reducing exacerbations [6,7]. Nevertheless, some patients show persistent airway eosinophilia, despite high dose inhaled corticosteroid treatment raising the need for an alternative therapy targeting eosinophilic inflammation.

The pathogenesis of eosinophilic asthma has been attributed to innate and adaptive immune system responses; both mediated by IL-5.

IL-5 is mainly produced by Th2 lymphocytes following allergic sensitization and has been found increased in the airways of severe asthmatics [8].

Inhaled allergens are presented to Th2 cells by antigen-presenting cells such as dendritic cells or macrophages. This presentation starts the allergic sensitization that leads Th2 cells to produce IL-4, IL-5 and IL-13 resulting in B-cell production of IgE and the recruitment of eosinophils. When the subject is re-exposed to the allergen, the allergen may come into contact with IgE bound to mast cells. This, in turn, activates the mast cells that begin degranulation with the release of mediators such as histamine, prostaglandins, chemokines and leukotrienes. These molecules not only lead to inflammation and

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bronchial obstruction but also perpetuate IgE production and the recruitment and activation of eosinophils and Th2 cells [9].

When eosinophils are activated, their granules secrete inflammatory proteins such as eosinophil cationic protein (ECP), leukotrienes and prostaglandins that damage bronchial epithelium, stimulate smooth muscle contraction, increase mucous secretion and cause vasodilation, ultimately contributing to asthma exacerbation [10]. In addition, the associated release of fibrogenic growth factors mediates the process of airway remodeling. In this instance, Th2 lymphocytes can be the start of the allergic inflammatory cascade and are highly linked to mast cells and eosinophils [11,12].

However, some studies support that persistent eosinophilic inflammation of airways can have different mechanisms apart from allergy. Recent findings have shown that a particular type of lineage negative lymphoid cells, called type 2 innate lymphoid cells (ILC2s), can produce significant amounts of IL-5 and IL-13 in response to the innate cytokines (IL-25, IL-33 and thymic stromal lymphopoietin) released by the bronchial epithelium after its exposure to allergens, viruses or other stimuli [13]. Both Th2 lymphocytes and ILC2s drive eosinophil activation and recruitment through an IL-5 mediated pathway, leading to persistent eosinophilic inflammation in severe asthma.

## Overview of the market

### Phenotype-specific treatment, anti-interleukin-5 therapy

Current therapies for patients with eosinophilic disorders are mainly based on corticosteroids that do not affect the disease pathogenesis (only alleviating symptoms) and have significant side effects.

Eosinophil generation, differentiation, activation and recruitment are mainly regulated by IL-5 that acts by binding the alpha-chain of the IL-5 receptor expressed on eosinophils and stimulates their development from CD34(+) progenitors [10]. In light of these interactions, IL-5 has been considered an adequate target for eosinophil-related diseases [14]. A monoclonal antibody directed against IL-5 can result in significant reductions in circulating eosinophils and allow steroid treatments to be reduced demonstrated by Rothemberg *et al.* in a randomized, double-blind, placebo-controlled trial in patients with hypereosinophilic syndrome [15].

IL-5 also seems to play a crucial role in the pathogenesis and evolution of eosinophilic asthma. This cytokine is not only essential for eosinophil development but seems also to promote (together with TGF-beta) airway remodeling [16].

Previous studies have demonstrated that IL-5 is significantly increased in BAL and bronchial mucosa

biopsies of severe asthmatics. Additionally, its concentration correlates with asthma symptoms [8,9].

Thus, asthma phenotype categorization becomes especially important for patients with severe asthma. By identifying the unique pathogenesis of each asthma phenotype, clinicians may rely on therapies directed to the specific pathways involved in the inflammation and improve the control of those patients not responding to conventional treatments like inhaled corticosteroids and long-acting beta-agonists.

So far, three monoclonal antibodies have been produced directed at IL-5: reslizumab, benralizumab and mepolizumab.

Reslizumab is an IgG humanized monoclonal antibody, which blocks IL-5 from linking to its receptor. Recent results from Phase 3 randomized controlled trials (RCTs) on subjects with uncontrolled asthma and blood eosinophil count  $\geq 400/\mu\text{l}$  showed that patients receiving intravenous (IV) reslizumab every 4 weeks had a greater reduction in exacerbations compared with those treated with placebo. Common adverse effects were similar between the two groups; although two patients of the reslizumab group experienced anaphylactic reactions [17].

Benralizumab is a monoclonal antibody directed against the alpha-chain of IL-5 receptor. In a 1-year Phase IIb study, benralizumab reduced exacerbation rate only in patients with high values of blood eosinophilia ( $>300/\mu\text{l}$ ) [18].

### Mepolizumab

Mepolizumab is a high-affinity, humanized monoclonal antibody of the IgG1/k subtype, specific for IL-5. Mepolizumab inhibits the binding of IL-5 to its receptor, which is expressed on eosinophils [19].

Mepolizumab is a large-molecular-weight monoclonal antibody (149.2 kiloDaltons). Its mechanism of action against inflammatory pathways is the rationale behind its research as a therapeutic option for patients with eosinophilic disorders.

### Pharmacokinetics, pharmacodynamics & metabolism of mepolizumab

The pharmacokinetics of mepolizumab has been evaluated in both animal and human models including healthy subjects and subjects with hypereosinophilia. Routes of administration (i.e., intravenous, subcutaneous and intramuscular) and a wide range of dosages (from a minimum of 0.05 to a maximum of 10 mg/kg) were explored as recently reviewed by a paper summarizing published and unpublished trials on mepolizumab [20].

Mepolizumab was first evaluated as a single dose of 250 mg in terms of bioavailability, tolerability, safety

and effect on eosinophils in 60 healthy subjects. Compared with the IV route, the lowest bioavailability was recorded for the subcutaneous (SC) injection (64–71% depending on site of injection) with intramuscular (IM) administration showing a bioavailability value of 81%. As expected, subcutaneous administration was associated with a longer time to reach maximum plasma concentration, although a considerable difference was noted depending on site of injection (abdomen 4–14 days; thigh 2–7 days) [20].

In patients with asthma mepolizumab was evaluated as a treatment of single (0.05–10 mg/kg IV) [21] or multiple doses (250 mg SC or 250/750 mg IV) [22]. Overall, mepolizumab pharmacokinetics was linear, dose-dependent and time-independent. Following both IV and SC administration the drug was quantifiable for up to 16 weeks. Terminal half-life was about 20 days in a dose-independent fashion. Inter-subject variability was low [20].

Both in healthy and asthmatic subjects, mepolizumab showed similar pharmacodynamics after IV, SC or IM administration. The reduction in blood eosinophil count and its duration were directly correlated to the dose/kg administered [20]. One study on three multiple IV doses (750 mg) also reported the effects of mepolizumab in bone marrow, skin, nasal lavage and bronchial biopsies [23,24].

Mepolizumab elimination is probably slow, but it is still under study [20]. In all studies, pharmacokinetics and pharmacodynamics were not affected by age and sex.

## Clinical efficacy

### Phase I, II & III studies of mepolizumab in adults & children with severe eosinophilic asthma

Based on the results obtained in primates [25] and murine asthma models [26] anti-IL-5 monoclonal antibodies demonstrated to prevent airway eosinophilia and hyperresponsiveness induced by allergens.

Thereafter, two pilot studies of anti-IL-5 therapy in human patients with mild and severe asthma showed a significant reduction in both circulating and sputum eosinophils [21,27] but no effect on airway hyperresponsiveness [21].

Including the small study by Leckie *et al.*, so far nine randomized double blind and placebo-controlled trials have evaluated the efficacy and safety of mepolizumab in patients with asthma [2–22,28–29] (Table 1). Overall, the nine RCTs studied 1842 patients.

In the study by Leckie *et al.* mepolizumab was administered as a single dose to 24 patients with mild atopic asthma and showed a significant decrease in blood and sputum eosinophils. However, no clinical effects were observed [21].

Flood-Page *et al.* reported that three IV doses of mepolizumab (750 mg) every 4 weeks produced eosinophil depletion in the blood but only a reduction in the airway and bone marrow [22], where a partial maturational arrest was observed [30]. Furthermore, this treatment potentially influenced airway remodeling with a decreased concentration of TGFβ1 in BAL and a reduced expression of extracellular matrix proteins in the reticular basement membrane of bronchial mucosa [31].

However, no significant difference emerged in terms of exacerbation rates, FEV<sub>1</sub> and airway hyper-responsiveness both in patients with mild atopic asthma [22] and in patients with moderately severe asthma under treatment with inhaled corticosteroids [32]. Similar results were found by Buttner *et al.*, who also demonstrated that distribution of T-cell subsets, T-cell activation and cytokine production were not altered during antibody treatment [28].

It is worth noting that further studies [33,34] showed the importance of selecting particular asthma phenotypes, to maximize the benefit from a therapy targeting IL-5, demonstrating the greatest efficacy of mepolizumab in patients with refractory eosinophilic asthma despite corticosteroid treatment. In these trials, treatment and follow-up were significantly longer and the effects previously demonstrated on eosinophils were confirmed and reflected by clinical outcomes.

Nair *et al.* demonstrated on a cohort of patients with persistent airway eosinophilia despite inhaled steroids, a corticosteroid sparing effect of anti-IL-5 treatment (750 mg monthly) over the 26-week study with a reduction of 84% in the prednisone dose in the mepolizumab group (n = 9) as compared with a reduction of 48% in the placebo group (n = 11). Furthermore, a small improvement in FEV<sub>1</sub> was observed [33]. Interestingly, Haldar *et al.* showed that there was a better response to mepolizumab in patients with airway inflammation responsive to oral corticosteroids rather than in patients with marked bronchodilator reversibility [34]. In both studies the lowering of blood eosinophil counts was associated to fewer exacerbations and better quality of life (QoL) pointing out the important link between hypereosinophilia and exacerbations in this population [33,34].

More recently, the Phase IIb/III DREAM trial confirmed that mepolizumab was able to reduce the frequency of asthma exacerbations (primary outcome) up to 52% (39–52%) in patients with refractory asthma and eosinophilic inflammation [21]. Moreover, adult patients with asthma received 13 infusions of mepolizumab every 4 weeks at different doses (75, 250 or 750 mg group) and all were effective in reducing eosinophils and exacerbations risk irrespective of IgE levels or atopy [35].

Table 1. Summary of randomized controlled trials with mepolizumab.

| Study (year)                    | Study type                      | Population   |             |                     | Intervention                            |                    | Results                                                                                                                                                              |
|---------------------------------|---------------------------------|--------------|-------------|---------------------|-----------------------------------------|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                 |                                 | Subjects (n) | Age (years) | Asthma phenotype    | Mepolizumab                             | Treatment duration |                                                                                                                                                                      |
| Leckie <i>et al.</i> (2000)     | Double-blind Placebo controlled | 24           | 18–45       | Mild atopic         | 2.5 mg/kg or 10 mg/kg (IV) on day 1     | 1 day              | 16 weeks<br>For the 10 mg/kg arm:<br>– Blood eosinophils suppression maintained to week 16<br>– Sputum eosinophils reduction at day 9 and 30                         |
| Buttner <i>et al.</i> (2003)    | Double-blind Placebo controlled | 19           | 20–59       | Mild or moderate    | 250 or 750 mg (IV) every 4 weeks        | 3 month            | 3 month<br>– Blood eosinophils and eosinophil cationic protein reduction                                                                                             |
| Flood-Page <i>et al.</i> (2003) | Double-blind Placebo controlled | 24           | 18–55       | Mild atopic         | 750 mg (IV) every 4 weeks               | 3 month            | 12 weeks<br>– Blood, bone marrow and BAL eosinophils reduction<br>– Reduction in ECM proteins and TGF- $\beta_1$ expression                                          |
| Flood-Page <i>et al.</i> (2007) | Double-blind Placebo controlled | 362          | 18–55       | Moderate persistent | 250 or 750 mg (IV) every 4 weeks        | 3 month            | 8 weeks<br>– Blood and sputum eosinophils reduction sustained for 8 weeks after last infusion                                                                        |
| Haldar <i>et al.</i> (2009)     | Double-blind Placebo controlled | 61           | 21–72       | Severe eosinophilic | 750 mg (IV) every 4 weeks               | 1 year             | – Reduction in exacerbations<br>– Improved QoL<br>– Blood and sputum eosinophils reduction                                                                           |
| Nair <i>et al.</i> (2009)       | Double-blind Placebo controlled | 20           | 18–70       | Severe eosinophilic | 750 mg (IV) every 4 weeks               | 5 month            | 8 weeks<br>– Reduction in exacerbation<br>– Reduction in corticosteroid dose<br>– Blood and sputum eosinophils reduction<br>– Increasing in FEV <sub>1</sub> and QoL |
| Pavord <i>et al.</i> (2012)     | Double-blind Placebo controlled | 621          | 12–74       | Severe eosinophilic | 75, 250 or 750 mg (IV) every 4 weeks    | 13 month           | 4 weeks<br>– Reduction in exacerbations by 39–52%                                                                                                                    |
| Ortega <i>et al.</i> (2014)     | Double-blind Placebo controlled | 576          | 12–82       | Severe eosinophilic | 75 mg (IV) or 100 mg (SC) every 4 weeks | 32 weeks           | 8 weeks<br>– Reduction in exacerbation rate of 47% in IV group and of 53% in SC group<br>– Improvement in asthma control and QoL                                     |
| Bel <i>et al.</i> (2014)        | Double-blind Placebo controlled | 135          | 16–74       | Severe eosinophilic | 100 mg (SC) every 4 weeks               | 20 weeks           | 12 weeks<br>– Median reduction in oral corticosteroid of 50%<br>– Reduction in blood eosinophils<br>– Exacerbation reduction<br>– Improvement in ACQ-5 scores        |

ACQ: Asthma control questionnaire; BAL: Bronchoalveolar lavage; ECM: Extracellular matrix; FEV<sub>1</sub>: Forced expiratory flow in 1 second; QoL: Quality of life.

No significant effect was noted on lung function and QoL suggesting that in patients with severe asthma there might be dissociation between daily symptoms and risk of exacerbations. These findings confirmed previous analysis demonstrating that eosinophilic airway inflammation correlates well with the risk of exacerbation [36,37,7], while perceived symptoms may not be a significant predictor of it [38].

Pavord *et al.* [35] identified blood eosinophil count and exacerbation rate in the previous year, as the variables most associated to mepolizumab response, suggesting that patients with airway hypereosinophilia and repeated exacerbations despite conventional treatments are the population of choice for anti-IL-5 therapy.

The pivotal role of eosinophils was confirmed by a 12-month follow-up analysis of the patients who had completed a 1-year study with mepolizumab. Cessation of mepolizumab was associated with an increase in blood and sputum eosinophil count soon after stopping the therapy then followed by a rise in exacerbations at 3–6 months [39]. The risk of worsening of eosinophilic airway inflammation after mepolizumab therapy, hypothesized by Stein *et al.* [40], was rejected by the fact that at the end of follow-up patients treated with both mepolizumab and placebo had the same frequency of exacerbation [39].

A meta-analysis of the published RCTs until the year 2013 demonstrated that the effects of administering either monthly or every 4 weeks mepolizumab for a period ranging from 1 day to 52 weeks consisted of lowering blood and sputum eosinophils, reducing frequency of exacerbations and increasing QoL. However, no significant effect was revealed on lung function and asthma control [41].

Importantly, the analysis showed that mepolizumab had greater efficacy in reducing eosinophils and risk of exacerbations in patients with eosinophilic asthma compared with other asthma phenotypes [41].

In 2014, two further studies [29,42] evaluated mepolizumab in patients with severe eosinophilic asthma with more than two exacerbations in the previous year despite a high dose of inhaled steroids plus an additional controller and a blood eosinophil count greater than 150/ $\mu$ l at screening or greater than 300/ $\mu$ l within the last 12 months.

The second Phase III SIRIUS study analyzed the efficacy of a low dose of mepolizumab (100 mg) administered subcutaneously every 4 weeks with primary outcome as the reduction in oral corticosteroids in patients on continuous treatment with oral prednisone for at least 6 months. Every 4 weeks steroid dose was reduced by 1.25–10 mg for a period of 16

weeks. Mepolizumab was then stopped and the dose of prednisone maintained for further 4 weeks with a follow-up visit at week 32. Results showed that, compared with the placebo group, those who received SC mepolizumab had significantly greater reductions in the maintenance oral glucocorticoid dose (up to 50%), fewer exacerbations, better QoL and asthma control [42].

The 32-week MENSA study compared the efficacy of different doses of mepolizumab (75 mg IV and 100 mg SC) to placebo in a cohort of patients with severe asthma showing FEV<sub>1</sub> reversibility >12% or variability of >20% between two clinic visits or positive methacholine or mannitol challenge in the last year. Both dosages showed significant reductions in frequency of asthma exacerbations (75 mg IV: 47%; 100 mg SC: 53%) and improvement in QoL [28]. Both studies showed a modest improvement in FEV<sub>1</sub> [29,42].

In 2004, mepolizumab received orphan drug status for first-line treatment in patients with hypereosinophilic syndrome in the USA and the EU and in November 2014 the company filed regulatory submissions in the USA and Europe for approval of mepolizumab (100 mg via subcutaneous injection every 4 weeks) as a maintenance treatment for patients with severe eosinophilic asthma on high dose of inhaled steroids and additional controller therapy, identified by a blood eosinophil count of at least 150 cells/ $\mu$ l at the start of treatment or 300 cells/ $\mu$ l in the past 12 months.

## Safety & tolerability

### Side effects of mepolizumab treatment

Overall, IV mepolizumab was well tolerated at all doses with acceptable side effects and minimal adverse events. Adverse events were comparable between placebo and mepolizumab. No predisposing risk factors were identified.

In the experience reported by Ortega *et al.* mepolizumab showed the same safety profile of placebo. The most common adverse events were headache and nasopharyngitis with an incidence of those related to the drug ranging between 16 and 20% in the different groups [29]. The SC administration showed a 9% incidence of injection-site reaction versus a 3% of the IV administration [29]. These percentages were very similar to those reported also by Pavord *et al.* in the DREAM trial (5–12% depending on dosage) with an increased risk of nonallergic reactions in the treated group compared with placebo group. Serious adverse events were described in 7% of patients of the IV group versus 8% in SC group and 14% in the placebo group, none related to treatment [35].

Headache and nasopharyngitis were the most common adverse events also in the study by Bel *et al.* [42]. Adverse events attributed to mepolizumab administration were reported in 30% of patients (n = 21) compared with 18% in patients (n = 16) receiving placebo; a systemic or local reaction after mepolizumab was registered in 8 (4 and 4, respectively) patients compared with 5 patients (3 and 2, respectively). Mepolizumab safety profile was similar to placebo [42].

A recent open-label extension study evaluated the safety of mepolizumab in 78 patients with hypereosinophilic syndrome with a mean exposure to therapy of 251 weeks and showed good tolerance and no neutralizing antibodies [43].

### Anti-mepolizumab antibodies in the treated population

The trials by Bel [42] and Ortega [29] evaluated the production of neutralizing antibodies in the blood of patients with eosinophilic asthma under mepolizumab treatment.

Bel *et al.* reported that of the 135 patients involved, 6 (4%) had positive results for anti-mepolizumab antibodies with only one having neutralizing antibodies. No serious adverse events related to immunogenicity were reported [42].

In the study by Ortega *et al.* positive anti-mepolizumab antibodies were found in about 4.5% of patients (n 19: 4% in the IV group, 5% in the SC group and 2% in the placebo group) and neutralizing antibodies in none [29].

## Conclusion

### Positive impact of mepolizumab in adults & children with severe eosinophilic asthma

Mepolizumab did not show significant benefits in studies in which patients were identified only on clinical criteria [18]. Further trials demonstrated that patients, who are likely to respond to anti-IL-5 treatment and thus mepolizumab, are those that show the eosinophilic asthma phenotype [34]. This selection leads to a significant decrease in exacerbations [33–35] and maintenance dose of corticosteroids [33,42].

Hence, a persistent blood eosinophil count of more than 150 cells per microliter or elevated eosinophil count in sputum despite high doses of corticosteroids can identify patients who are likely to benefit from anti-IL-5 therapy.

Compared to the significant side-effects of long-term corticosteroid treatment such as increased risk of infections, adrenal suppression, hyperglycemia, weight gain, osteoporosis, cataract and glaucoma, the good tolerance of anti-IL-5 therapy makes mepolizumab a valid therapeutic option for patients with severe eosinophilic asthma.

### Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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## Executive summary

### Mechanism of action

- Mepolizumab is a high-affinity humanized monoclonal antibody of the IgG1/k subtype that blocks the binding of IL-5 to the IL-5 receptor expressed on eosinophils.

### Pharmacokinetic properties

- Mepolizumab is measurable in plasma for up to 16 weeks at IV doses >0.05 mg/kg. Mean initial half-life is 2 days and terminal half-life is 20 days independently of dose.

### Clinical efficacy

- Mepolizumab reduces exacerbation risk and eosinophils (blood, sputum, BAL) in patients with eosinophilic asthma.

### Safety & tolerability

- Minimal side effects and well tolerated. Anti-mepolizumab antibodies were found in a minimal percentage of patients but no adverse events related to immunogenicity were reported.

### Drug interaction

- None.

### Dosage & administration

- Mepolizumab 100 mg via subcutaneous injection every 4 weeks.

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