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Title: Anti-IL-5 Biologicals targeting severe late onset eosinophilic asthma

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Abstract

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Improved knowledge about the pathogenesis of asthma has facilitated the development of novel drugs and provided hope for patients with severe asthma. After short and long term success of Omalizumab in severe allergic phenotype, researchers have targeted severe eosinophilic asthma patients who are consisting up to 45% of adult severe asthma. Interleukin (IL)-5 and IL-5 receptor subunit α (IL-5-Rα) play crucial role in the development, maturation, and operation of eosinophils. Nowadays, patients treated with anti-IL-5 biologicals depleting eosinophils experience the positive efficacy of these drugs, especially in regards to the reduction of exacerbation rate.

In this review, we aimed shedding light on severe eosinophilic asthma treatment with these new currently available agents selectively targeting IL-5 or its receptor, discussing their usage including pre-treatment concerns such as selecting the target population and choosing the right agent among them, and subsequent assessment of relevant effect and safety issues.

**Keywords:** Asthma-allergy, eosinophils, interleukin 5, exacerbations, biologicals

**Introduction**

Recently, in contrast to one-size-fits-all approach, molecular therapies offer a tailored perspective in severe asthma management and the list of monoclonal antibodies (mAbs) continues to grow with new agents targeting different pathways [1]. After short and long term success of Omalizumab in allergic phenotype, mAbs are now appearing in asthma guidelines as add-on treatment alternatives for patients with severe uncontrolled asthma [2].
As the scientific knowledge of eosinophils in asthma has expanded and phenotyping gained recognition, targeting IL-5, the key cytokine for eosinophils, became an exciting approach for the treatment of severe eosinophilic asthma. Then, clinically positive and negative studies of anti-IL-5 therapies have contributed significantly to today’s understanding of asthma [3]. Nowadays, mepolizumab, the first anti-IL-5 antibody is an established treatment option for severe eosinophilic asthma patients. Withal we will soon enter a period of personalized medicine for eosinophilic asthma, where choosing among different anti IL-5 mAbs will be possible.

Clinical and Research Consequences

Severe eosinophilic asthma as a treatment target

Severity, level of control and phenotype stratifications intended better management strategies in asthma. Asthma severity is mainly assessed according to the level of treatment required [2]. Severe asthma has been described as asthma requiring high dose of inhaled glucocorticoid (GC) and a second controller, or oral GC treatment to maintain disease control or remaining uncontrolled despite these treatments [4]. The subset of patients with severe asthma which are refractory to standard therapies motivated researchers for developing better models of phenotypes and personalized therapy. Then, increased immunological knowledge has added complexity to the earliest ‘extrinsic-intrinsic’ asthma phenotype classification of Sir Rackeman [5]. Now, although plasticity between different immune profiles is questionable, severe asthma patients can be roughly categorized according to their degree of type 2 inflammation [6]. After labelling a severe asthma patient as type 2 high severe asthma , it is also necessary to comment on the possible

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predominance of allergic or eosinophilic endotype. A set of specific clinical features and biomarkers has been recently proposed to differentiate these two endotypes [7]. Generally, eosinophilic type 2 endotype refers to a late-onset nonallergic asthma, may be associated with nasal polyps (or eosinophilic chronic rhinosinusitis), aspirin sensitivity and marked blood eosinophilia (>300 cells/μL), high exhaled nitric oxide fraction (FeNO) (> 50 ppb) and a lower serum total IgE compared to allergic type 2 asthma patients (< 100 IU/ml), reflecting a stimulus which is independent of a specific exogenous allergen [7, 8].

Eosinophil maturation, activation, migration and survival are mainly regulated by the effects of interleukin-5 (IL-5) [9]. IL-5 is a cytokine produced by helper T lymphocytes, group 2 innate lymphoid cells, mast cells and basophils. It circulates through the blood and exerts its effects on target cells via IL-5 receptor (IL-5R) [9]. IL-5R consists of an α functional subunit (IL-5Ra) specific to IL-5 binding, and another signaling subunit which is called β-chain. IL-5, with its functions on eosinophils and several other cells, is involved not only in type 2 inflammation but also in airway remodelling processes [10]. In this regard, IL-5 and its receptor provide an appealing pharmacological target for the treatment of patients with severe eosinophilic asthma. Additionally, concerning the safety, the hypothesis of not having eosinophils has already been questioned through animal models and case reports [11].

Despite strong theoretic background and high expectations, first large-scale multicenter double-blind placebo-controlled clinical trial using single dose intravenous mepolizumab, published in 2007, failed to demonstrate any positive clinical result in moderate persistent asthma [3]. Study reported no difference of treatment compared with placebo in terms of baseline forced expiratory volume in 1 sec (FEV1), late asthmatic response to allergen challenge, and clinical symptoms, but, at active drug arm, there was a trend for 50% drop in in severe exacerbation rates (p= 0.065). However, after selecting eosinophilic asthma patients and determining exacerbations as primary outcome, the viewpoint has started to change. This study was not only significant
for highlighting the importance of inclusion criteria in research, but also it helped to reform our approach to asthma. As the concept of asthma phenotypes gained recognition, new clinical trials were designed targeting subjects with objective evidence of eosinophilic inflammation. Nowadays, anti-IL-5 biologicals targeting eosinophils have provided new and provoking knowledge about severe eosinophilic asthma patients who are consisting up to 45% of severe adult asthma [12].

Biologics targeting IL-5 in severe eosinophilic asthma

1. Mepolizumab

Mepolizumab is a fully humanized monoclonal IgG1 antibody, binding IL-5 and preventing the interaction between IL-5 and its receptor [13]. After reinterpretation of negative mepolizumab paper, subsequent studies have been planned to determine the clinical, pharmacological features of mepolizumab for providing better asthma care. ‘Dose Ranging Efficacy and Safety with Mepolizumab (DREAM)’ and ‘Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma’ were two validation studies that selectively enrolled patients with eosinophilic phenotype and a history of frequent severe exacerbations (≥ 2 per year) [13, 14]. DREAM was planned to determine the dose. Patients with severe, exacerbation-prone eosinophilic asthma with a blood eosinophil count ≥ 300 cells/μL had been randomly assigned to four groups and received 13 intravenous infusions of placebo or one of three doses of mepolizumab (75, 250, or 750 mg) at 4-week intervals. Mepolizumab effectively lowered blood and sputum eosinophil counts, as well as the frequency of...
asthma exacerbations by 39–52%, at all dosages used. However, no significant improvements in either asthma symptoms or lung function were detected [13].

The MENSMA study was a multicenter, randomized, double-blind, double-dummy, phase 3 trial [14]. In comparison with placebo, administration of mepolizumab every 4 weeks for 32 weeks, at dosages of 75 mg intravenously or 100 mg subcutaneously, induced significant decreases in asthma exacerbation rates of either 47% or 53%, respectively. Moreover, both drug doses elicited significant improvements in QoL but modest a modest increase in FEV1. In both studies, the exacerbation rate, which had been determined as primary outcome, roughly halved (39–52%) at the end of the study, but limited evidence for improved health related quality of life (HRQoL) scores and lung function were noted.

Then, ‘Steroid Reduction with Mepolizumab Study’ [15] has shown that mepolizumab (100 mg), when compared with placebo, reduced prednisone need by 50% with a relative reduction of 32% in asthma exacerbation. In randomized, double-blind, placebo-controlled, Phase IIib MUSCA trial, patients treated with 100 mg of subcutaneous mepolizumab reported significant improvement in HRQoL score, and St George's Respiratory Questionnaire (SGRQ) total score [16]. Recently, the Cochrane systematic review based on 8 studies on 1707 participants, reported that mepolizumab can lead to an improvement in HRQoL scores and reduce asthma exacerbations in people with severe eosinophilic asthma [17].

Based on the data shown, mepolizumab (NUCALA®) as a first anti-cytokine biologic asthma drug fulfilled the requirements and granted approval by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) as maintenance treatment for severe eosinophilic asthma in patients aged 12 years and older in 2015 [18, 19]. Further, mepolizumab was included within the step 5 of GINA (Global Initiative for Asthma) guidelines as an add-
on therapy for severe eosinophilic asthma, uncontrolled by standard treatments [2]. Just recently, its license was extended for paediatric patients aged six up to 17 years in the 31 European countries covered by EMA [20]. The accepted treatment scheme is 100 mg by subcutaneous injection into the upper arm, thigh, or abdomen once every 4 weeks and commonly approved blood eosinophil count to determine an eosinophilic phenotype is ≥150 cells/μL at screening or ≥300 cells/μL in the past year.

Published data about treatment cessation is inadequate. However Haldar et al,’s post hoc analysis reports the reversal of biological and clinical benefits including the reduction in exacerbations of mepolizumab starting from 3 months after treatment cessation [21]. Mepolizumab has also been shown to be beneficial in some common asthma comorbidities like chronic rhinosinusitis, severe atopic dermatitis and other eosinophilic disorders such as hypereosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA) and eosinophilic esophagitis [22]. Long term data of mepolizumab continues to demonstrate good safety and efficacy [23].

2. Reslizumab

Reslizumab is a humanized anti-IL-5 IgG4 mAb binding to IL-5 like mepolizumab. The pilot study for this drug was a safety study that recruited 32 asthma patients treated with ICS and/or oral corticosteroids and reported drug’s effectiveness in reducing blood and sputum eosinophil counts at a dose of 1 mg/kg administered intravenously (IV) [24]. Then, Phase II and Phase III randomized studies were conducted to assess its efficacy, optimal dose and safety. The first large Phase IIb study of reslizumab was encouraging since it clearly demonstrated significant benefit in those patients who had refractory
eosinophilic asthma. The clinical efficacy of the drug administered IV (3 mg/kg, 4 weekly) was assessed by comparing Asthma Control Questionnaire [25] scores, eosinophil counts, and lung function in the treatment group versus the placebo group. Enrolled patients had confirmed airway reactivity, induced eosinophil sputum counts of ≥3%, and were on a high-dose ICS and a second controller. Reslizumab significantly reduced eosinophil numbers in sputum and improved lung function (p=0.002). ACQ scores showed a trend toward better asthma control in the treatment group, and this was significant in the subgroup analysis of patients with nasal polyps [26]. In the two key Phase III multicentre studies, time to first exacerbation was significantly longer with reslizumab treatment compared to placebo. Reslizumab significantly reduced the annual rate of clinical asthma exacerbations by 50–59% compared with placebo. In the studies, the drug was well tolerated with few local infusion reactions with no difference existed between the drug and placebo, but two reslizumab-treated patients had anaphylaxis. Although these patients have not required epinephrine and responded to standard treatment, they were withdrawn from the study, and were negative for antidrug antibodies [27]. These studies show that reslizumab is well-tolerated and effective in severe asthmatic patients with peripheral blood eosinophil count of ≥400 cells/μL [26, 27]. Post hoc analysis of the two Phase III studies also showed larger improvements in late onset (≥40 years) asthma patients and patients with nasal polyps compared to the ones with early onset disease [28, 26].

Aforementioned clinical trials have granted the approval of reslizumab IV (CINQAIR®) as an add-on maintenance treatment for patients aged ≥18 years with severe asthma with an eosinophilic phenotype by the FDA and the EMA in 2016 [29]. An open-label extension study evaluated safety and efficacy of reslizumab for up to 24 months. Patients with moderate-to-severe eosinophilic asthma received intravenous reslizumab 3.0 mg/kg displayed favourable long-term safety and sustained long-term efficacy. Initial improvements in lung function and asthma control were maintained for up to 2 years [30].
Interestingly, a single-blind, placebo-controlled sequential trial investigated 10 prednisone-dependent asthmatics who had previously received 100 mg subcutaneous dose of mepolizumab monthly for at least 1 year and followed by 4 infusions of 3 mg/kg reslizumab monthly. The authors found that the weight-adjusted IV reslizumab was superior to the fixed-dose subcutaneous mepolizumab in attenuating eosinophilia which was associated with statistically significant improvements in asthma control and FEV1. The authors proposed that reslizumab could, therefore, be also used as an alternative for those patients who show no improvement with mepolizumab [31]. Results of ongoing trials investigating reslizumab’s efficacy and safety for paediatric population, other eosinophilic diseases like EGPA, atopic dermatitis, eosinophilic esophagitis are awaiting.

3. Benralizumab

Benralizumab is a humanized IgG1 mAb, using an alternative method for IL-5 antagonism. Binding directly to the IL-5 receptor alfa subunit, it offers two theoretical advantages over anti IL-5 mAbs [32]. First, as IL-5 receptors are also expressed on eosinophil progenitors, and basophils, it equally affects these populations [33]. Second, it has an enhanced antibody-dependent cell-mediated cytotoxicity function, where NK cells target cells and induce apoptosis, resulting in a rapid depletion of peripheral and tissue blood eosinophils of asthmatic patients, mainly dependent on inhibition of eosinophil maturation and survival in both bone marrow and inflamed tissues [34]. This acute effect on circulating eosinophil might provide another beneficial effect in patients presenting acutely with an exacerbation associated with an eosinophilia [35]. In a Phase II placebo controlled study investigators have evaluated the effects of a single intravenous infusion of benralizumab (as 0.3 mg/kg or 1.0 mg/kg) added to current standard treatments prescribed at discharge from
emergency department on recurrence of asthma exacerbations and/or on hospitalization for acute asthma. Compared with placebo, the effects induced by benralizumab 12 weeks after drug administration resulted in significant 49% and 60% reductions of asthma exacerbation rates and exacerbations leading to hospitalization, respectively. At the same time-point, blood eosinophil numbers and serum levels of eosinophilic cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) were markedly decreased. All these effects were observed with both doses of benralizumab [34].

Through three phase 3 trials, SIROCCO, CALIMA and steroid tapering effect trial ZONDA, benralizumab is approved in the US and in Europe in 2017 and the efficacy and safety has been shown as add-on therapy in patients with severe asthma and blood eosinophil counts ≥300 cells/μL who are inadequately controlled with high-dose ICS plus LABA [36-39]. A total of 1205 patients treated with high doses of ICS/LABA were enrolled in the SIROCCO trial. Subjects were randomized to receive one of three add-on subcutaneous treatments for 48 weeks, according to the following scheme; the placebo arm; benralizumab 30 mg every 4 weeks (Q4W); and benralizumab 30 mg every 8 weeks (Q8W). Compared with placebo, at week 48, the annual rates of asthma exacerbations were found to be reduced by 45% and 51% in Q4W and Q8W subgroups with ≥300 blood eosinophils/μL, respectively. Interestingly, the annual exacerbation rate decreased by 17–30% in patients with <300 blood eosinophils/μL. Moreover, when compared to placebo, both benralizumab dosages significantly improved pre-bronchodilator FEV1, where the mean increases with respect to baseline were 106 and 159 mL in Q4W and Q8W regimens, respectively. Asthma symptoms improved only in the Q8W group [35]. Benralizumab rapidly depletes eosinophils, reduces exacerbations of patients with severe eosinophilic asthma and has a clear steroid sparing effect as shown in ZONDA trial. With respect to baseline, the median final oral
doses of corticosteroids decreased by 75% and 25% in benralizumab and placebo groups, respectively. The recommended dose is 30 mg subcutaneous injection in the upper arm, thighs or belly every 4 weeks for the first 3 doses, and then every 8 weeks [39].

Considering patients’ preference at-home subcutaneous administration of biologics, a recent trial has assessed functionality, reliability, and performance of an accessorized pre-filled syringe (APFS) for subcutaneous benralizumab home administration in 115 severe, uncontrolled asthma patients who were receiving medium- or high-dosage ICS/LABA. A majority of the subjects or their family members successfully inject 30 mg of benralizumab of an accessorized prefilled syringe subcutaneously at home [40].

**Predetermining responders and assessment of relevant treatment effect**

The burden of asthma has increased over the past two decades and severe exacerbations were found to be particularly costly to the health system regardless of the prior disease severity [41]. Therefore, anti-eosinophil drugs, targeting mainly reducing exacerbations, are expected to be highly demanded among physicians dealing with severe asthma. Thus, for the management of severe eosinophilic asthma, one should think about the high cost due to frequent asthma exacerbations versus the cost of biologicals, knowing that adequate cost-effectiveness may only be achieved by predetermining responders to these biological agents before the treatment. Figure 1 summarizes the management diagram that can be used before starting anti-IL-5 biologicals [42]. Another challenge of the management is to be able to distinguish therapeutic responders during the treatment.

Evaluating blood eosinophil counts is the strongest predictor of reduction in exacerbation rates and efficacy of mepolizumab [13]. This was also demonstrated in other anti–IL-5 therapies, reslizumab (400 cells/μL) and benralizumab (300 cells/μL), in which patients with high blood eosinophil counts...
derived greater clinical benefit from the therapy [36, 43]. FENO value of 50 ppb or greater or nasal IL-5 levels have also been proposed to classify severe asthma patients with regard to their possibility of responding to anti-IL-5 therapies. However, it is still an open question and further studies are needed [43].

An adequate response to treatment has already been determined for mepolizumab as at least 50% fewer asthma exacerbations needing systemic CS in those people with four or more exacerbations in the previous 12 months, or a clinically significant reduction in continuous OCS use while maintaining or improving asthma control [44]. Although comparing exacerbation rates may be useful for differentiating therapeutic responders from non-responders, it is challenging since it requires waiting one whole year for comparison. Besides exacerbation and steroid need, symptom reduction (evaluated by the Asthma Control Test (ACT) or Asthma Control Questionnaire), improvement of HRQoL, physical fitness, lung function, reduction of eosinophils in peripheral blood, or their combination may help to distinguish treatment responders [25].

Safety issues

Since anti-IL-5 agents have been studied in numerous large clinical trials, adequate safety data has been reported. They have been generally well tolerated in clinical studies so far [45]. Injection site reactions associated with subcutaneous administration are perhaps the most common treatment-
related adverse effect for mepolizumab and benralizumab. Commonly reported side effects include headache and back pain for mepolizumab, headache and nasopharyngitis for reslizumab. Two reslizumab-treated patients had anaphylaxis that didn’t require epinephrine and adverse events significant enough to stop the treatment have been reported for benralizumab [30, 32, 45]. In terms of infection, it is recommended to treat helminth infections prior to therapy. The longer-term effects and their safety in pregnancy are still rather undetermined. New trials are ongoing, investigating the safety of self-administrated mepolizumab for improving patient/physician convenience and for reducing costs.

Comparison to other anti-IL-5 agents
Starting one among the anti-IL-5’s
Anti-IL-5 treatment decision for patients with severe eosinophilic asthma should consider access to these agents, national guidelines, patient needs and differences among these biologic drugs. No direct comparative evaluation has been made between mepolizumab and either the other IL-5 inhibitor reslizumab, or the IL-5Rα antagonist benralizumab. However, a recent global and indirect meta-analysis of 10 randomized placebo-controlled trials, involving 3421 patients, demonstrated no clear superiority of one of these three biologic drugs when appropriate dosages were compared. Indeed, mepolizumab, reslizumab, and benralizumab provided similar patterns of persistent symptom control and exacerbation rate reduction in patients with severe eosinophilic asthma [46]. Recent Cochrane meta-analysis including 13 studies on 6000 participants (4 with mepolizumab, 4 with reslizumab, and 5 with benralizumab) concluded that these treatments roughly halve the rate of asthma exacerbations in patients with severe eosinophilic asthma but there is limited evidence for improved HRQoL scores and lung function [45].
Direct comparisons of the biologic therapies targeting IL-5 do not exist in the literature (Table 1). Although indirect meta-analyses exist and found slight differences between these three drugs, head-to-head comparison studies are needed for better decisions [47]. Until evidence from comparative studies will be gathered, anti-IL-5 drug prescriptions for severe eosinophilic asthma can risk to be influenced by marketing strategies of pharmaceutical companies.

Another concept that needs to be well-thought-out is that asthma endotypes can change over time, therefore close follow-ups and reassessments may be needed in this regard [48]. An expert task force reported that at least 16 weeks is needed before an initial response assessment and suggested a traffic-light system to determine response [49] (Figure 2). According to this system, reassessment at the first year or switch to an alternative anti-eosinophilic therapy is recommended for intermediate responders after 4\textsuperscript{th} month of therapy [49].

**Non-responder problem**

Despite a careful patient and treatment selection and adherence to therapy, a quarter of the severe eosinophilic asthma patient may not show the expected response to anti-IL-5 treatments [50]. For these cases, diagnosis may be reconsidered and problems besides asthma including other causes of hypereosinophilia such as fungal or parasitic infections may be suspected. Under-dosing may also be considered for obese patients given the fixed mepolizumab dosage. For such cases a switch to intravenous, weight-adapted reslizumab can be recommended [50]. However, additional research is needed to elucidate indications for a switch between these agents.
Conclusion

Patients with severe eosinophilic asthma suffer from recurrent severe asthma exacerbations and have a low quality of life. Fortunately, a new era for asthma has started and severe eosinophilic asthma treatment has improved from high doses of corticosteroids to several personalized biologicals targeting eosinophils. In our armamentarium, we have now three approved anti-eosinophilic biological drugs for providing a personalized care to this subgroup of asthma patients: mepolizumab, reslizumab and benralizumab. These agents, inhibiting key drivers of eosinophilic lung inflammation are efficacious, appear to be safe and well tolerated in short- and medium- term. Furthermore, we also have an easily measured biomarker which is blood eosinophil count with well-determined cut-offs. However, we do need further knowledge about optimal treatment duration, more information on patient selection, monitoring outcomes, and long-term effect plus their role in other eosinophilic conditions.

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<table>
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<th>Administration</th>
<th>Advantage (randomized, placebo controlled studies)</th>
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| **Mepolizumab** | • Subjects ≥ 12 year-old  
• Eosinophil cut-off: 150-300 cells/μL  
• Every 4 weeks  
• Reconstitution needed  
• Fixed dose  
• Subcutaneous injection  
• Steroid sparing effect (+)  
• Reduces asthma exacerbation rates  
• Improves prebronchodilator FEV₁  
• Decreases eosinophil blood count |
| **Reslizumab** | • Subjects ≥ 18 year-old  
• Eosinophil cut-off: 400 cells/μL  
• Every 4 weeks  
• Reconstitution needed  
• Weight-based dosing  
• Intravenous infusion  
• Reduces asthma exacerbation rates  
• Improves prebronchodilator FEV₁  
• Decreases eosinophil blood count |
| **Benralizumab** | • Subjects 12-75 year-old  
• Eosinophil cut-off: 300 cells/μL  
• Every 8 weeks (every 4 weeks for the first three doses)  
• Prefilled syringe—no reconstitution needed  
• Fixed dose  
• Steroid sparing effect (+)  
• Reduces asthma exacerbation rates  
• Improves prebronchodilator FEV₁  
• Single dose effect in emergency proposed  
• Eosinophil depletion in blood |
Table 1. Administration method and advantages of approved anti-IL-5 biologicals in severe eosinophilic asthma

- Subcutaneous injection
Figure 1. Treatment indication and follow-up [4, 43]
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Figure 2. The traffic-light system for response and non-response diagram adapted with permission from ERS expert task force for severe eosinophilic asthma [49]
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