Turk Thorac J 2020; 21(1): 61-8 DOI: 10.5152/TurkThoracJ.2019.180204

Review

Anti-IL-5 Biologicals Targeting Severe Late Onset Eosinophilic Asthma

Leyla Pur Özyiğit[1], Ayşe Bilge Öztürk[1], Sevim Bavbek[2]

[1]Department of Pulmonary Disease, Division of Immunology and Allergy, Koç University School of Medicine, İstanbul, Turkey
[2]Department of Pulmonary Disease, Division of Immunology and Allergy, Ankara University School of Medicine, Ankara, Turkey

Cite this article as: Pur Özyiğit L, Öztürk AB, Bavbek S. Anti-IL-5 Anti-IL-5 Biologicals Targeting Severe Late Onset Eosinophilic Asthma. Turk Thorac J 2020; 21(1): 61-8.

Abstract

Improved knowledge about the pathogenesis of asthma has facilitated the development of novel drugs and provided hope for patients with severe asthma. After the short- and long-term success of omalizumab in severe allergic phenotype, researchers have targeted patients with severe eosinophilic asthma who comprise up to 45% of adult severe asthma. Interleukin (IL)-5 and IL-5 receptor subunit α play crucial roles in the development, maturation, and operation of eosinophils. Currently, patients treated with anti-IL-5 biologicals depleting eosinophils experience the positive efficacy of these drugs, especially with regard to the reduction of exacerbation rate. The aim of this review was to shed 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, biologicals, eosinophils, exacerbations, interleukin 5

Received: *09.01.2019* ***Accepted:*** *25.04.2019*

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 increase with new agents targeting different pathways [1]. After the 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 the recent understanding of asthma [3]. Currently, mepolizumab, the first anti-IL-5 antibody, is an established treatment option for patients with severe eosinophilic asthma. In addition, 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 are intended for 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 a high dose of inhaled corticosteroids (ICSs) and a second controller or oral corticosteroids (OCSs) 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]. Currently, although plasticity between different immune profiles is questionable, patients with severe asthma can be approximately categorized according to their degree of type 2 inflammation [6]. After labeling a patient with severe asthma as type 2 high severe asthma, it is also necessary to comment on the possible 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 non-allergic asthma and may be associated with nasal polyps (or eosinophilic chronic rhinosinusitis), aspirin sensitivity, marked blood eosinophilia (>300 cells/μL), high exhaled nitric oxide fraction (FeNO) (≥50 ppb), and a lower serum total IgE compared with patients with allergic type 2 asthma (≤100 IU/mL), reflecting a stimulus which is independent of a specific exogenous allergen [7,8].

Address for Correspondence: Sevim Bavbek, Department of Pulmonary Disease, Division of Immunology and Allergy, Ankara University School of Medicine, Ankara, Turkey
E-mail: bavbek@medicine.ankara.edu.tr

Eosinophil maturation, activation, migration, and survival are mainly regulated by the effects of interleukin (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 the IL-5 receptor (IL-5R) [9]. IL-5R consists of an α functional subunit (IL-5Rα) 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 remodeling 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, the hypothesis of not having eosinophils has already been questioned through animal models and case reports with regard to safety [11].

Despite strong theoretic background and high expectations, the first large-scale multicenter double-blind placebo-controlled clinical trial using single dose intravenous (iv) mepolizumab, published in 2007, failed to demonstrate any positive clinical result in moderate persistent asthma [3]. The study reported no difference of treatment compared with placebo with respect to baseline forced expiratory volume in 1 second (FEV_1), late asthmatic response to allergen challenge, and clinical symptoms, but, at active drug arm, there was a trend for 50% decrease in severe exacerbation rates (p=0.065). However, the viewpoint has started to change after selecting patients with eosinophilic asthma and determining exacerbations as primary outcome. This review was not only significant for highlighting the importance of inclusion criteria in research but also 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. Currently, anti-IL-5 biologicals targeting eosinophils have provided new and provoking knowledge about patients with severe eosinophilic asthma who are consisting up to 45% of severe adult asthma [12].

Biologicals Targeting IL-5 in Severe Eosinophilic Asthma

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 and 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/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 iv 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 MENSA study was a multicenter, randomized, double-blind, double-dummy, phase 3 trial [14]. The 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, in comparison with placebo. Moreover, both drug doses elicited significant improvements in the quality of life (QoL), but a modest increase in FEV_1. In both studies, the exacerbation rate, which had been determined as primary outcome, approximately halved (39%-52%) at the end of the study, but limited evidence for improved health-related QoL (HRQoL) scores and lung function was noted.

Then, the "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 a randomized, double-blind, placebo-controlled, Phase IIIb MUSCA trial, patients treated with 100 mg of subcutaneous (sc) mepolizumab reported a significant improvement in HRQoL score and St George's Respiratory Questionnaire total score [16]. Recently, the Cochrane systematic review based on eight studies on 1707 participants reported that mepolizumab can lead to an improvement in HRQoL scores and reduce asthma exacerbations in individuals with severe eosinophilic asthma [17].

Based on the data shown, mepolizumab (NUCALA®) as a first anti-cytokine biological asthma drug fulfilled the requirements and was 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 in 2015 [18,19]. Furthermore, mepolizumab was included within the step 5 of the 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 pediatric patients aged 6-17 years in the 31 European countries covered by EMA [20]. The accepted treatment scheme is 100 mg by sc injection into the upper arm, thigh, or abdomen once every 4 weeks, and the commonly approved blood

MAIN POINTS

- IL-5 and its receptor provide an appealing pharmacological target for the treatment of patients with severe eosinophilic asthma.
- Mepolizumab, reslizumab, and benralizumab seem to have similar effects on symptom control and exacerbation rate reduction in patients with severe eosinophilic asthma when they are used in correct doses.
- Guidelines recommend switching between different Th2 targeted therapies when little or no response is observed with a previous one.
- Published data about treatment cessation of anti-IL-5 biologicals are inadequate and further studies are needed.

eosinophil count to determine an eosinophilic phenotype is ≥150 cells/μL at screening or ≥300 cells/μL in the previous year.

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

Reslizumab

Reslizumab is a humanized anti-IL-5 IgG4 mAb binding to IL-5, such as mepolizumab. The pilot study for this drug was a safety study that recruited 32 patients with asthma treated with ICSs and/or OCSs, and reported the 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 its 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 (ACQ) [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 multicenter studies, time to first exacerbation was significantly longer with reslizumab treatment than with 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 anti-drug antibodies [27]. These studies show that reslizumab is well tolerated and effective in patients with severe asthma with a peripheral blood eosinophil count of ≥400 cells/μL [26,27]. Post hoc analysis of the two Phase III studies also showed larger improvements in patients with late onset (≥40 years) asthma and patients with nasal polyps than in those with early onset disease [26,28].

The 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 the safety and efficacy of reslizumab for up to 24 months. Patients with moderate-to-severe eosinophilic asthma who received iv reslizumab 3.0 mg/kg displayed favorable 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 individuals with asthma who had previously received 100 mg sc dose of mepolizumab monthly for at least 1 year, followed by four ıv infusions of 3 mg/kg reslizumab/month. The authors found that the weight-adjusted iv reslizumab was superior to the fixed-dose sc mepolizumab in attenuating eosinophilia which was associated with statistically significant improvements in asthma control and FEV_1. 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 pediatric population, other eosinophilic diseases, such as EGPA, atopic dermatitis, and eosinophilic esophagitis are awaited.

Benralizumab

Benralizumab is a humanized IgG1 mAb using an alternative method for IL-5 antagonism. Binding directly to the IL-5Rα, 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 natural killer cells target cells and induce apoptosis, resulting in a rapid depletion of peripheral and tissue blood eosinophils of patients with asthma, 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 iv infusion of benralizumab (as 0.3 mg/kg or 1.0 mg/kg) added to the 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 and eosinophil-derived neurotoxin 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 U.S. and in Europe in 2017, and its efficacy and safety have 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 long-acting β2-agonist (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 sc treatments for 48 weeks according to the following scheme: 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 with placebo, both benralizumab dosages significantly improved pre-bronchodilator FEV_1, 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 the ZONDA trial. The median final doses of OCSs decreased by 75% and 25% in the benralizumab and placebo groups, respectively, with respect to baseline. The recommended dose is 30 mg sc injection in the upper arm, thighs, or belly every 4 weeks for the first three doses and then every 8 weeks [39].

A recent trial has assessed the functionality, reliability, and performance of an accessorized prefilled syringe (APFS) for sc benralizumab home administration in 115 patients with severe, uncontrolled asthma who were receiving medium/high dose ICS/LABA considering patients' preference at home sc administration of biologics. A majority of the subjects or their family members successfully inject 30 mg of benralizumab of an APFS 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 nasal IL-5 levels have also been proposed to classify patients with severe asthma 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

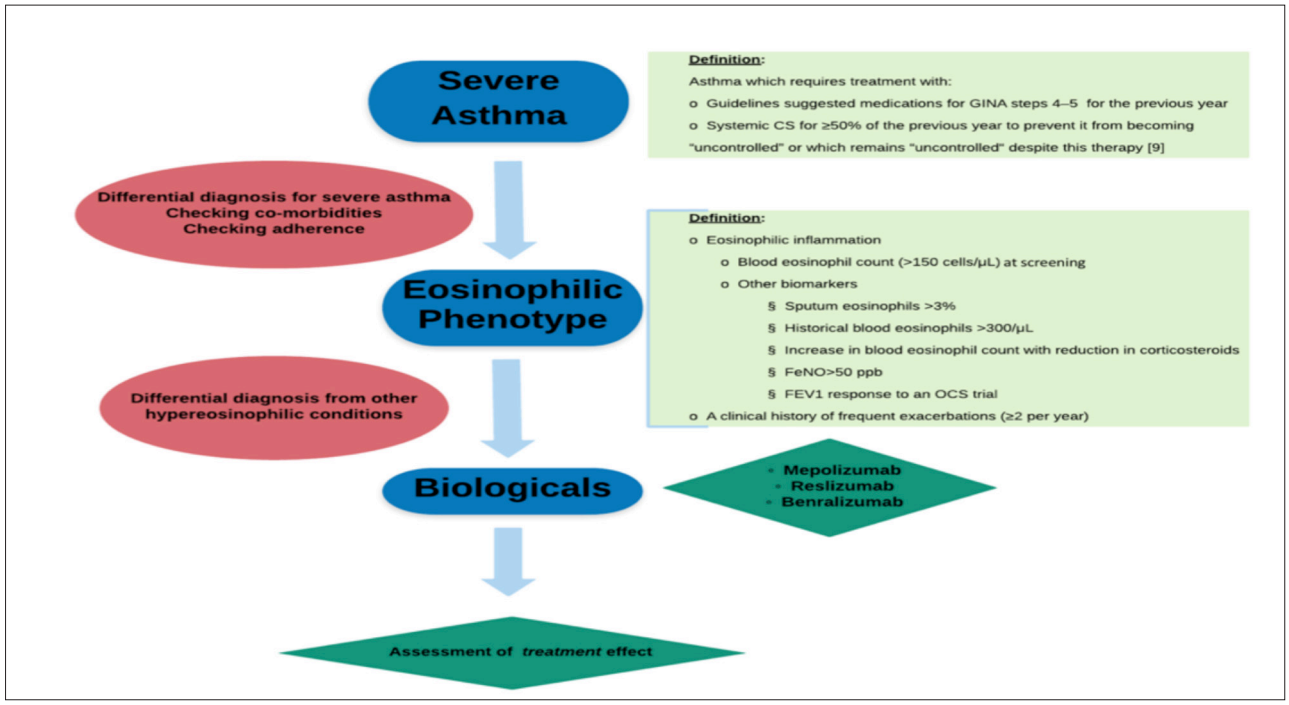

Figure 1. Treatment indication and follow-up [4,43]

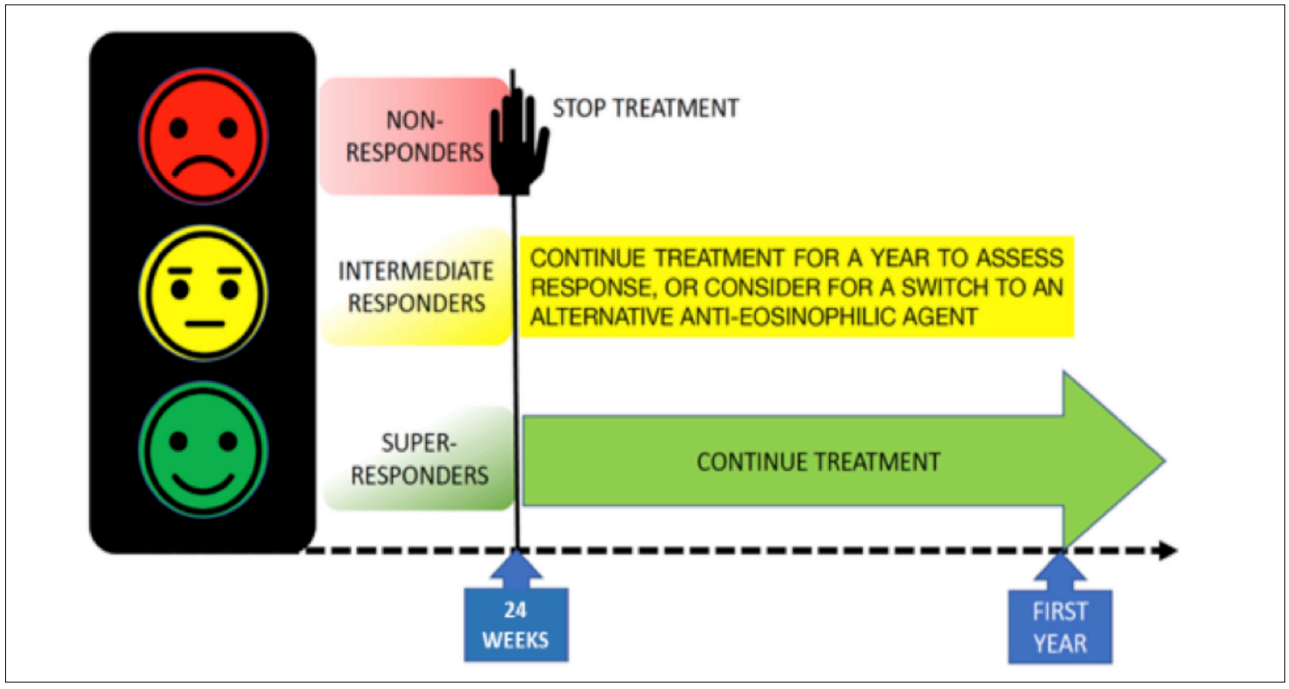

Figure 2. The traffic-light system for response and non-response diagrams adapted with permission from ERS expert task force for severe eosinophilic asthma [2,50]

exacerbation rates may be useful for differentiating therapeutic responders from non-responders, it is challenging since it requires waiting one whole year for comparison. In addition to exacerbation and steroid need, symptom reduction (evaluated by the Asthma Control Test or ACQ), 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 many large clinical trials, adequate safety data have been reported. They have been generally well tolerated in clinical studies so far [45]. Injection site reactions associated with sc administration are perhaps the most common treatment-related adverse effect for mepolizumab and benralizumab. The most commonly reported side effects include headache and back pain for mepolizumab, whereas they include headache and nasopharyngitis for reslizumab. Two reslizumab-treated patients had anaphylaxis that did not require epinephrine, and adverse events significant enough to stop the treatment have been reported for benralizumab [30,32,45]. It is recommended to treat helminth infections prior to therapy with respect to infection. 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 WITH OTHER ANTI-IL-5 AGENTS

Starting One Among the Anti-IL-5s

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 biological 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 biological 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]. The recent Cochrane meta-analysis including 13 studies (4 with mepolizumab, 4 with reslizumab, and 5 with benralizumab) on 6000 participants concluded that these treatments approximately 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 biological 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]. Anti-IL-5 drug prescriptions for severe eosinophilic asthma can risk to be influenced by marketing strategies of pharmaceutical companies until evidence from comparative studies will be collected.

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 [48,49]. An expert task force and GINA guideline reported that at least 24 weeks is needed before an initial response assessment and suggested a traffic-light system to determine response [2,50] (Figure 2). Reassessment at the first year or a switch to an alternative anti-eosinophilic therapy is recommended for intermediate responders after 6 months of therapy according to this system [2,50].

Table 1. Administration method and advantages of approved anti-IL-5 biologicals in severe eosinophilic asthma

	Administration	Advantage (randomized, placebo-controlled studies)
Mepolizumab	• Subjects age ≥12 years • Eosinophil cut-off: 150–300 cells/μL • Every 4 weeks • Reconstitution needed • Fixed dose • Subcutaneous injection	• Steroid-sparing effect (+) • Reduces asthma exacerbation rates • Improves pre-bronchodilator FEV_1 • Decreases eosinophil blood count
Reslizumab	• Subjects aged ≥18 years • Eosinophil cut-off: 400 cells/μL • Every 4 weeks • Reconstitution needed • Weight-based dosing • Intravenous infusion	• Reduces asthma exacerbation rates • Improves pre-bronchodilator FEV_1 • Decreases eosinophil blood count
Benralizumab	• Subjects aged 12–75 years • Eosinophil cut-off: 300 cells/μL • Every 8 weeks (every 4 weeks for the first three doses) • Prefilled syringe-no reconstitution needed • Fixed dose • Subcutaneous injection	• Steroid-sparing effect (+) • Reduces asthma exacerbation rates • Improves pre-bronchodilator FEV_1 • Single dose effect in emergency proposed • Eosinophil depletion in blood

Non-Responder Problem

Despite a careful patient and treatment selection and adherence to therapy, a quarter of patients with severe eosinophilic asthma may not show the expected response to anti-IL-5 treatments [51]. For these cases, diagnosis may be reconsidered, and problems in addition to 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 iv weight-adapted reslizumab can be recommended [51]. However, additional research is needed to elucidate indications for a switch between these agents.

Patients with severe eosinophilic asthma suffer from recurrent severe asthma exacerbations and have a low QoL. Fortunately, a new era for asthma has started, and severe eosinophilic asthma treatment has improved from high doses of CSs to several personalized biologicals targeting eosinophils. In our armamentarium, we have now three approved anti-eosinophilic biological drugs (i.e., mepolizumab, reslizumab, and benralizumab) for providing a personalized care to this subgroup of patients with asthma. 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 have an easily measured biomarker which is blood eosinophil count with well-determined cut-offs. However, further knowledge about optimal treatment duration, more information on patient selection, monitoring outcomes, and long-term effect plus their role in other eosinophilic conditions is still needed.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.B., L.P.Ö.; Design - A.B.Ö., L.P.Ö., S.B.; Supervision - S.B.; Data Collection and/or Processing - L.P.Ö., S.B., a.B.Ö.; Analysis and/or Interpretation - L.P.Ö., S.B., A.B.Ö.; Literature Search - L.P.Ö., S.B., A.B.Ö.; Writing Manuscript - L.P.Ö., S.B., A.B.Ö.; Critical Review - S.B., A.B.Ö.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Legrand F, Klion AD. Biologic therapies targeting eosinophils: current status and future prospects. J Allergy Clin Immunol Pract 2015;3:167-74. [CrossRef]
2. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Revised asthma guidelines 2019. Available at: https://ginasthma.org/wp-content/uploads/2019/01/2010-GINA.pdf. Last accessed: 13 May 2019.
3. Flood-Page P, Swenson C, Faiferman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med 2007;176:1062-71. [CrossRef]
4. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73. [CrossRef]
5. Rackemann FM. A working classification of asthma. Am J Med 1947;3:601-6. [CrossRef]
6. Woodruff PG, Modrek B, Choy DF, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. Am J Respir Crit Care Med 2009;180:388-95. [CrossRef]
7. Zervas E, Samitas K, Papaioannou AI, et al. An algorithmic approach for the treatment of severe uncontrolled asthma. ERJ Open Res 2018;4:DOI:10.1183/23120541.00125-2017. [CrossRef]
8. Pavord ID, Hilvering B, Shrimanker R. Emerging Biologics in Severe Asthma. Immunol Allergy Clin North Am 2016;36:609-23. [CrossRef]

9. Molfino NA, Gossage D, Kolbeck R, et al. Molecular and clinical rationale for therapeutic targeting of interleukin-5 and its receptor. Clin Exp Allergy 2012;42:712-37. [CrossRef]
10. Flood-Page P, Menzies-Gow A, Phipps S, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. J Clin Invest 2003;112:1029-36. [CrossRef]
11. Gleich GJ, Klion AD, Lee JJ, Weller PF. The consequences of not having eosinophils. Allergy 2013;68:829-35. [CrossRef]
12. van Veen IH, Ten Brinke A, Gauw SA, et al. Consistency of sputum eosinophilia in difficult-to-treat asthma: a 5-year follow-up study. J Allergy Clin Immunol 2009;124:615-7. [CrossRef]
13. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012;380:651-9. [CrossRef]
14. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014;371:1198-207. [CrossRef]
15. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371:1189-97. [CrossRef]
16. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med 2017;5:390-400. [CrossRef]
17. Powell C, Milan SJ, Dwan K, et al. Mepolizumab versus placebo for asthma. Cochrane Database Syst Rev 2015:CD010834. [CrossRef]
18. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm, (2015).
19. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/nucala#overview-section, (2015).
20. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003860/smops/Positive/human_smop_001336.jsp&mid=WC0b01ac058001d127, (2018).
21. Haldar P, Brightling CE, Singapuri A, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. J Allergy Clin Immunol 2014;133:921-3. [CrossRef]
22. Roufosse F. Targeting the Interleukin-5 Pathway for Treatment of Eosinophilic Conditions Other than Asthma. Front Med (Lausanne) 2018;5:49. [CrossRef]
23. Khatri S, Moore W, Gibson PG, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. J Allergy Clin Immunol 2019;143:1742-51.e7. [CrossRef]
24. Kips JC, O'Connor BJ, Langley SJ, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. Am J Respir Crit Care Med 2003;167:1655-9. [CrossRef]
25. Bagnasco D, Ferrando M, Varricchi G, et al. Anti-Interleukin 5 (IL-5) and IL-5Ra Biological Drugs: Efficacy, Safety, and Future Perspectives in Severe Eosinophilic Asthma. Front Med (Lausanne) 2017;4:135. [CrossRef]
26. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 2011;184:1125-32. [CrossRef]
27. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3:355-66. [CrossRef]
28. Brusselle G, Germinaro M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. Pulm Pharmacol Ther 2017;43:39-45. [CrossRef]
29. Teva Respiratory LLC. CINQAIR® (reslizumab) injection, for intravenous use. Highlights of prescribing information, (2016).
30. Murphy K, Jacobs J, Bjermer L, et al. Long-term Safety and Efficacy of Reslizumab in Patients with Eosinophilic Asthma. J Allergy Clin Immunol Pract 2017;5:1572-81.e3. [CrossRef]
31. Mukherjee M, Aleman Paramo F, Kjarsgaard M, et al. Weight-adjusted Intravenous Reslizumab in Severe Asthma with Inadequate Response to Fixed-Dose Subcutaneous Mepolizumab. Am J Respir Crit Care Med 2018;197:38-46. [CrossRef]
32. Laviolette M, Gossage DL, Gauvreau G, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol 2013;132:1086-96.e5. [CrossRef]
33. Busse WW, Katial R, Gossage D, et al. Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma. J Allergy Clin Immunol 2010;125:1237-44.e2. [CrossRef]
34. Ghazi A, Trikha A, Calhoun WJ. Benralizumab--a humanized mAb to IL-5Ralpha with enhanced antibody-dependent cell-mediated cytotoxicity--a novel approach for the treatment of asthma. Expert Opin Biol Ther 2012;12:113-8. [CrossRef]
35. Nowak RM, Parker JM, Silverman RA, et al. A randomized trial of benralizumab, an antiinterleukin 5 receptor alpha monoclonal antibody, after acute asthma. Am J Emerg Med 2015;33:14-20. [CrossRef]
36. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016;388:2115-27. [CrossRef]
37. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388:2128-41. [CrossRef]
38. Nair P, Wenzel S, Rabe KF, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med 2017;376:2448-58. [CrossRef]
39. Prescribing information for Fasenra (benralizumab). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf (2017).
40. Ferguson GT, Mansur AH, Jacobs JS, et al. Assessment of an accessorized pre-filled syringe for home-administered benralizumab in severe asthma. J Asthma Allergy 2018;11:63-72. [CrossRef]
41. Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. BMC Pulm Med 2009;9:24. [CrossRef]
42. Haldar P. Patient profiles and clinical utility of mepolizumab in severe eosinophilic asthma. Biologics 2017;11:81-95. [CrossRef]
43. Yancey SW, Keene ON, Albers FC, et al. Biomarkers for severe eosinophilic asthma. J Allergy Clin Immunol 2017;140:1509-18. [CrossRef]
44. (NICE). NIfHaCE. Mepolizumab for treating severe refractory eosinophilic asthma. Available from: https://wwwniceorguk/guidance/ta431 2017.
45. Farne HA, Wilson A, Powell C, et al. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev 2017;9:CD010834. [CrossRef]

46. Cabon Y, Molinari N, Marin G, et al. Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials. Clin Exp Allergy 2017;47:129-38. **[CrossRef]**
47. Busse W, Chupp G, Nagase H, et al. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison. J Allergy Clin Immunol 2019;143:190-200.e20. **[CrossRef]**
48. Matucci A, Vultaggio A, Maggi E, Kasujee I. Is IgE or eosinophils the key player in allergic asthma pathogenesis? Are we asking the right question? Respir Res 2018;19:113. **[CrossRef]**
49. Ozturk AB, Sönmez SC, Göğebakan E, Özyiğit LP, Çağlayan B. Well Known and Unknown Asthma Phenotype: Allergic Asthma. EMJ Allergy Immunol 2019;4:76-87.
50. Buhl R, Humbert M, Bjermer L, et al. Severe eosinophilic asthma: a roadmap to consensus. Eur Respir J 2017;49:pii: 1700634. **[CrossRef]**
51. Drick N, Seeliger B, Welte T, et al. Anti-IL-5 therapy in patients with severe eosinophilic asthma - clinical efficacy and possible criteria for treatment response. BMC Pulm Med 2018;18:119. **[CrossRef]**