REVIEW

Efficacy and steroid-sparing effect of benralizumab: has it an advantage over its competitors?

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Abstract

Severe refractory asthma is characterized by a higher risk of asthma-related symptoms, morbidities, and exacerbations. This disease also determines much greater healthcare costs and deterioration in health-related quality of life (HR-QoL). Another concern, which is currently much discussed, is the high percentage of patients needing regular use of oral corticosteroids (OCS), which can lead to several systemic side effects. Airway eosinophilia is present in the majority of asthmatic patients, and elevated levels of blood and sputum eosinophils are associated with worse control of asthma. Regarding severe refractory eosinophilic asthma, interleukin-5 (IL-5) plays a fundamental role in the inflammatory response, due to the profound effect on eosinophils biology. The advent of the biological therapies provided an effective strategy, even if the increased number of molecules with different targets raised the challenge of choosing the right therapy and avoid overlapping. When considering severe refractory eosinophilic asthma and anti-IL-5 treatments, it is not easy to define which drug to choose between mepolizumab, reslizumab, and benralizumab.

In this article, we carried out an indirect comparison among literature data, especially between OCS reduction studies (ZONDA-SIRIUS) and pivotal studies (SIROCCO-MENSA), evaluating whether the clinical efficacy and the steroid-sparing effect of benralizumab may represent an advantage over other compounds. This data could help the clinician in the decision process of treatment choice, within the different available therapeutic options for eosinophilic refractory severe asthma.

Keywords: comparison, eosinophils, oral corticosteroids, randomized clinical trials, side effects, steroid-sparing effect.

Introduction

Severe refractory asthma is characterized by a higher risk of asthma-related symptoms, morbidities, and exacerbations.[1,2] This disease also determines much greater healthcare costs and a deterioration in health-related quality of life (HR-QoL) as compared to stable asthma.[3] Another concern, which is currently much discussed, is the high percentage of patients needing regular use of oral corticosteroids (OCS),[4] which can lead to several systemic side effects and growth deficit in pediatric patients.[5] In addition, the development of resistance to glucocorticoids (GCs) in therapeutic regimens poses a major threat: it is believed that approximately 30% of all patients receiving treatment experience a degree of GC insensitivity[6] and specifically, 4 to 10% of asthma patients.[7] Airway eosinophilia is present in over 50% of asthmatic patients, and elevated levels

of blood and sputum eosinophils are associated with worse control of asthma, in addition to a higher airflow limitation and greater severity of disease.[8] Eosinophils biology is mostly regulated by interleukin-5 (IL-5), which plays a fundamental role in controlling eosinophils' chemotaxis and recruitment to the inflamed tissue, eosinophil maturation from precursors in the bone marrow, and eosinophil activation, proliferation, and survival.[9,10] As a result, this cytokine has become a key objective of treatment for severe refractory eosinophilic asthma. The development of new biological therapies, that directly target the airway inflammation mechanism, may allow reduction of OCS usage and improvement of global asthma control. Omalizumab, a monoclonal antibody (mAb) that specifically targets IgE, was the first mAb approved for the treatment of severe asthma, in a specific subpopulation of patients with uncontrolled IgE-mediated allergic asthma. Recently, new

options, such as anti-IL-5 mAbs and anti-IL-4/IL-13, are available or will be in the near future.[11] Asthma is increasingly recognized as a syndrome with similar clinical presentations rather than a single disease. The distinction between asthma phenotypes (observable properties of an organism that are produced by the interactions of the genotype and the environment) and endotypes (a specific biological pathway that explains the observable properties of a phenotype) is crucial.[1] This approach, together with the use of biomarkers, enables us to stratify patients and select personalized asthma therapies, thus increasing the probability of response to treatment.

Due to the overlap of the allergic and eosinophilic asthma endotypes, it is inevitable that the risk of an overlap in eligibility for the different mechanisms of action of currently available biologic therapies may occur, not only between drugs of the same class but also between molecules with partly different targets. Careful clinical characterization of asthma control and biomarkers will hopefully result in further personalization and optimization of asthma management. Regarding severe refractory eosinophilic asthma, it is not easy to define which drug to choose between mepolizumab, reslizumab, and benralizumab. In this regard, it is therefore mandatory to identify which parameters can be useful to guide the choice.

The objective of this review is to define whether there may be an advantage in clinical efficacy and the steroid-sparing effect of benralizumab over other compounds, thus further helping the clinician in the decision process of treatment choice.

Methods

A search strategy based on validated keywords filters was conducted to select articles regarding severe eosinophilic asthma and related treatment. In detail, a selective search on Medical Databases (in particular PubMed and Medline) was carried out up to January 2019, and research papers, international guidelines, systematic reviews, and Cochrane meta-analyses relevant to the topic have been considered. The search strategy was based on the following keywords: inflammation, asthma phenotypes, IgE, eosinophils, cytokines, IL-5, costs, benralizumab, mepolizumab, reslizumab, OCS, glucocorticosteroids, and steroid-sparing effect. A total of 114 potential papers were identified in the first search through databases, and 71 of these were considered eligible. Only original studies with human subjects were considered, and only full texts were included among those potentially relevant. Case reports and purely descriptive studies were excluded. Randomized clinical trials (RCTs) are described by their acronyms in this paper. Readers are encouraged to consult the cited references for their full titles.

Eosinophils function and role of IL-5

Eosinophils are fully delineated granulocytes normally present in small numbers in healthy individuals, able to circulate in the blood for 6 to 12 hours and to migrate in connective tissues, where they end their life cycle after 8 to 12 days. Higher levels of eosinophils in the peripheral blood or certain tissues typically signal a pathologic process and they play a central role in inflammation and allergic diseases.[12] They promote inflammation through the release of their granules, which contain different mediators, such as histaminase and arylsulfatase. Other cytokines released by eosinophils are leukotrienes, which are involved in the pathophysiology of asthma, through the increase of eosinophils infiltration as well as mucus secretion and bronchoconstriction.[13,14] Airway eosinophilia can be detected in >50% of asthmatic patients, and elevated eosinophil counts are associated with frequent asthma exacerbations, as well as with a high degree of airflow limitation and disease.[8] IL-5 plays a major role in controlling eosinophils biology and the steps which lead to their maturation and chemotaxis to inflamed tissue. The cells capable of producing and secreting IL-5 are mostly of the lymphoid lineage, specifically Th2 cells, group 2 innate lymphoid cells (ILC2), mast cells, γδ-T cells, and eosinophils themselves.[15,16] A small amount of IL-5 can be produced by other types of cells, such as epithelial cells, natural killer (NK) cells, and NK T cells.[17,18] IL-5 interacts with the α subunit of the IL-5 receptor (IL-5Rα), expressed on eosinophils and to a lesser extent on basophils. The receptor is a heterodimer composed of a unique α chain and a βc chain.[18,19] The binding results in the stimulation of the receptor complex of both IL-5Rα and βc subunits,[20] which subsequently activates multiple signaling pathways.[21] IL-5 seems to act at two different levels: it stimulates the differentiation and maturation of eosinophil precursors[22] and it also appears to act on tissue-specific cells by enhancing eosinophils maturation in the airways, as shown by the enhanced amounts of IL-5, eosinophil progenitors, and mature eosinophils detectable locally in the induced sputum of allergic patients.[23]

Given the key role of IL-5 on the biology of eosinophils, this molecule and its receptor have been broadly considered promising targets in the treatment of eosinophilic disorders. Hence, different mAbs targeting IL-5 (mepolizumab and reslizumab) or its receptor (benralizumab) have been developed and are being investigated in clinical practice, with promising results.

Benralizumab: mechanism of action and development

Benralizumab, formerly known as BIW-8405/MEDI-563, is a humanized mAb (IgG1 k) that binds with high affinity to an epitope within domain 1 of the α-chain of human IL-5R, blocking its activation and signal transduction.[24–26] The high affinity for the binding site, which is in proximity of a conformationally distinct epitope in the domain 1 of the α-chain, is the main reason for the neutralizing activity of the mAb. The molecular modifications on benralizumab structure led to the generation of an afucosylated

oligosaccharide core residue in the CH2 domain of the antibody. This modification of human IgG1 has previously been shown to result in a 5- to 50-fold higher affinity to human FcgRIIIa, the main activating Fcg receptor (FcgR) expressed on NK cells, macrophages, and neutrophils.[27] Hence, afucosylation enhances antibody-dependent cell-mediated cytotoxicity (ADCC) function, specifically in the case of benralizumab, by 1000-fold over the parenteral antibody.[28] In addition, the fucosylated counterparts usually present lower ADCC activity, due to the inhibitory effects explicated by serum IgG; the afucosylated IgGk antibody overcomes this limitation by binding with high affinity to the Fcγ RIIIa region.[29]

The activation of ADCC is a unique benralizumab mechanism. In fact, the other anti-IL-5 biologics (mepolizumab and reslizumab) directly bind to IL-5 and act by neutralizing the effects of the cytokine and its ability to activate the eosinophils (Figure 1). Therefore, benralizumab is able to reduce the number of circulating eosinophils, as well as those resident in different tissues implicated in the inflammatory response in asthmatic patients, such as the airways, the lung tissue, and the bone marrow.[30] Specifically, blood eosinophils and basophils are barely detectable, and eosinophils precursors are reduced by 80% or more in the bone marrow.[26] These mechanisms and the significant reduction at multiple levels of eosinophils and basophils may be the explanation for the great reductions of asthma exacerbations.[31]
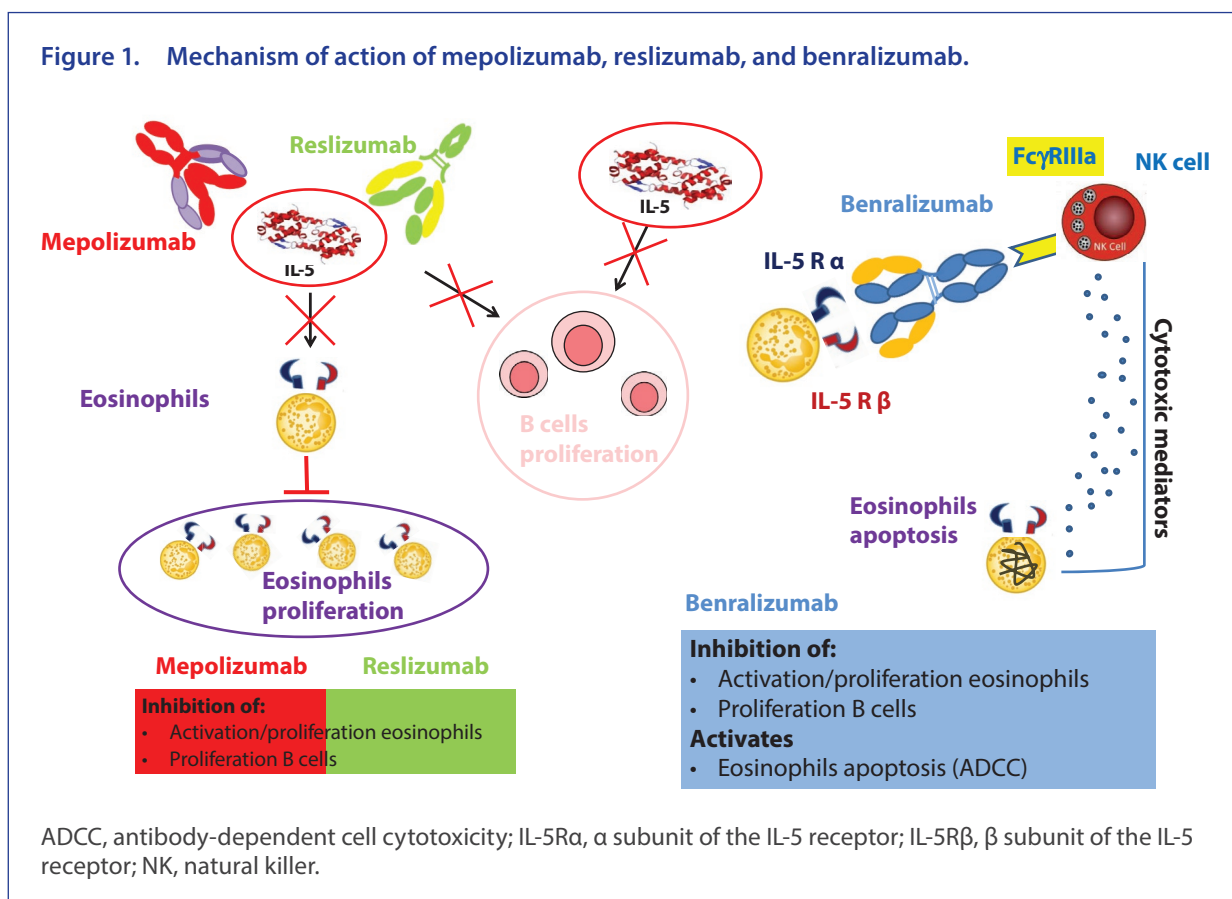
Clinical data on asthma

The clinical development of benralizumab included a phase I randomized, multicenter, open-label, single administration RCT carried out in November 2008 (NCT00512486), with the aim of evaluating the overall incidence of adverse events (AEs) in patients with mild asthma. Overall, the safety profile was acceptable, and the most common AEs reported were reduced white blood cell counts, nasopharyngitis, and increased blood creatine phosphokinase.[32]

A second phase I, double-blind, placebo-controlled trial was carried out between April 2008 and April 2011 (NCT00659659). The main purpose was to evaluate the safety profile of MEDI-563 and estimate outcome on eosinophils reduction.[31] Intravenous (IV) or SC benralizumab produced a median decrease of eosinophils counts from baseline of 61.9 and 95.8% in airway mucosa, 18.7 and 89.9% in sputum, and 100% in blood, respectively. In addition, complete suppression of eosinophils was reached in bone marrow and peripheral blood.

A phase IIa dose-finding study (NCT00783289) evaluated the safety and tolerability profiles of different doses of SC benralizumab in asthmatic patients.[33] The results showed how, a few days after administration and stably for 160 days, peripheral blood eosinophils were undetectable in all cohorts with an acceptable safety profile.

Another study evaluated the effects of benralizumab on eosinophil counts and activity following administration

Figure 1.   Mechanism of action of mepolizumab, reslizumab, and benralizumab.

ADCC, antibody-dependent cell cytotoxicity; IL-5Rα, α subunit of the IL-5 receptor; IL-5Rβ, β subunit of the IL-5 receptor; NK, natural killer.

to asthma patients enrolled in the previous two trials (NCT00659659 and NCT00783289).[34] After treatment, benralizumab reduced blood eosinophils and EDN and ECP values.[34] These results confirmed the profound anti-inflammatory effect of benralizumab. Furthermore, a phase II, multicenter, randomized, double-blind clinical trial was completed in 2011. The study included patients who presented to the emergency department (ED) with an asthma exacerbation, with partial response to treatment. The results suggested that the single IV dose of benralizumab added to the current standard of care (SOC) for asthma exacerbations significantly affected the rate and severity of exacerbations (49%), blood eosinophil count, and exacerbations resulting in hospitalization (60%) in subjects who presented to the ED with an asthma exacerbation.[35]

Given the promising results, other studies were carried out and a phase IIb dose-ranging study was designed with evaluation of safety and efficacy as main goals (NCT01238861).[28] In eosinophilic individuals, 100 mg benralizumab had led to a reduction of 80% of exacerbation rates compared with placebo. In patients with a baseline blood eosinophils cutoff of at least 300 cells per μL, the results of benralizumab treatments in terms of reduction of exacerbation rates were even more evident. These data strongly suggested that patients with higher levels of eosinophils may represent the ideal target of anti-IL-5 mAbs and benefit from this kind of treatment.

Overall, results of phase II RCTs confirmed that benralizumab is effective in terms of reduction of eosinophils and asthma control compared with placebo while showing a good safety profile with no serious AE evidenced.

Afterwards, AstraZeneca launched the phase III WINDWARD program for benralizumab, made up of six phase III trials, of which the main ones are CALIMA,[36] SIROCCO,[37] ZONDA,[38] and BORA.[39] It is the largest phase III development programme for a biologic medicine in respiratory disease, evaluating a total of 3068 patients in 798 sites across 26 countries.

These studies demonstrated significant clinical efficacy (reduction up to 70% of the annual exacerbation rate compared to placebo), improvement of forced expiratory volume in 1 second (FEV_1) and a significant steroid-sparing effect (reduction of 75% of prednisone dose). No significant side effects were detected at the end of the second year of treatment.

Focus on competitors

Mepolizumab

Mepolizumab was the first biologic available for the treatment of severe eosinophilic asthma. It is a humanized nonglycosylated IgG1 antibody, which targets the α-chain of IL-5 in a manner that two IL-5 dimers are crosslinked by a mepolizumab dimer.[40] Through this mechanism of action, mepolizumab effectively inhibits IL-5 ligation to IL-5Rα (Figure 1). The first studies investigated the application of

mepolizumab in diseases other than asthma, such as idiopathic hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis (EGPA),[41] and demonstrated a significant reduction in the use of OCS and a better control of the disease. On the other hand, early studies on asthma patients did not fully achieve the primary outcomes, as administration of mepolizumab was not linked to relevant changes in asthma clinical manifestations, lung function, bronchial hyperresponsiveness, and activation status of T lymphocytes, even if there was a significantly reduction in laboratory parameters (eosinophil numbers in both blood and induced sputum).[42,43] However, several studies underlined the presence of a bias in patients' recruitment, as they had not been properly stratified and selected according to their blood eosinophils and asthma severity. Subsequently, new studies were designed in which the specific severe chronic asthma phenotypes were identified and characterized by recurrent exacerbations and bronchial eosinophilia refractory to standard therapy. These studies highlighted a significant efficacy of mepolizumab in reducing asthma exacerbations and eosinophil levels in both blood and induced sputum.[44,45] Moreover, bigger RCTs such as DREAM, MENSA, and SIRIUS showed the ability of this drug to significantly improve the control of asthma with a significant steroid-sparing effect in patients with severe asthma with blood eosinophils >300 cells per μL.[46–48] In addition, the MUSCA trial has confirmed that mepolizumab significantly improved the health-related QoL with an early improvement of prebronchodilator FEV_1 values sustained up to week 24.[49]

A *post hoc* analysis of DREAM and MENSA RCTs showed that baseline blood eosinophil count represents a biomarker predictive of mepolizumab clinical efficacy.[50] The authors highlighted clinically relevant reductions in exacerbation rate in patients with a count of 150 cells per μL or more at baseline. Notably, measurement of eosinophils count could represent an easy-to-achieve inclusion parameter, due to its routine application, which would allow for better selection of patients when compared to the rather complex-to-perform cellular analysis of induced sputum that requires specific laboratory infrastructures as well as trained personnel.[51] In parallel, the drug demonstrated an excellent safety profile and a long-lasting and stable effect, as highlighted by the COSMOS study.[52]

Reslizumab

The third anti-IL-5 mAb is reslizumab, a humanized anti-IL-5 monoclonal (IgG4/k) antibody, that binds to circulating IL-5 and downregulates the IL-5 signaling pathway (Figure 1).[53] This mAb addresses patients with uncontrolled eosinophilic asthma and blood eosinophil level >400 cells per μL. In the RCTs, the primary outcome was slightly different, evaluating the change from baseline in prebronchodilator FEV_1 over 16 weeks; whereas secondary endpoints included Asthma Control Questionnaire (ACQ) scores, forced vital capacity (FVC), and forced expiratory flow at 25 to 75% of FVC. The results showed a significant decrease in sputum eosinophil count,

improvement in QoL, FEV$_1$, and reduction of exacerbation rate.[54,55]

A *post hoc* analysis of two identical pivotal trials (studies 3082 and 3083) showed that patients with asthma, chronic sinusitis with nasal polyposis (CSwNP), and higher blood eosinophilia level (400 cells per μL) received significant therapeutic benefit with reslizumab, with an 83% reduction of the annual rate of exacerbations compared to an overall reduction of 54%.[56] Given the high eosinophilia of the patients included in these trials, the data further suggested that a major clinical benefit may be reached in patients with higher eosinophilia levels when considering anti-IL-5 treatments. In an open-label extension trial, 1051 patients received IV 3.0 mg/kg reslizumab up to 2 years, with a good safety profile and sustained long-term efficacy in terms of lung function improvements and asthma control.[57] These results reinforce the evidence of long-term safety and efficacy in anti-IL-5 mAbs.

A practical limitation of reslizumab is its IV administration, which is the only formulation approved by United States Food and Drug Administration (FDA) and European Medicines Agency (EMA), as it depends on the availability of a venous access followed by infusion over 20 to 50 minutes. On the other hand, a recent study showed that the IV formulation may have other benefits, such as a better pharmacokinetic profile in reaching the airway. In fact, a weight-adjusted dosage of reslizumab represented a potential added value, especially in overweight or obese patients. The study evaluated the response to weight-adjusted IV reslizumab in ten prednisone-dependent patients with asthma who were previously treated with 100 mg SC mepolizumab.[58] Reslizumab was shown to further reduce airway eosinophilia compared to mepolizumab SC, with concomitant improvement in asthma control. Two ongoing phase III RCTs are evaluating the efficacy of reslizumab SC (ClinicalTrials.gov identifier: NCT02452190 and NCT02501629) and a phase II to III study is investigating the monthly infusion of 3 mg/kg IV reslizumab for 4 months in patients with prednisone-dependent eosinophilic asthma previously treated with SC mepolizumab (ClinicalTrials.gov identifier: NCT02559791).

In view of the current commercial limitations of reslizumab, the absence of comparable studies with benralizumab (such as those on the steroid-sparing effect), and the route of administration, in this review we will focus on the comparison mainly between benralizumab and mepolizumab.

Considerations from literature data and comparison with competitors

Mechanism of action

Benralizumab has a very particular mechanism of action when compared to other anti-IL-5 mAbs, because of its ability to reduce eosinophils count by enhancing ADCC. When considering the overall effects of the drug, different advantages may be highlighted as compared to competitors, especially mepolizumab. First of all, this compound is insensitive to the effect of other cytokines such as IL-3 and GM-CSF, due to the profound depletion of eosinophils.[26] In addition, a recent study described the effects of benralizumab on inflammatory markers in blood and immune-related signaling pathways by proteomic and gene-expression analyses in patients with asthma and COPD. The results suggested that benralizumab is highly selective, because protein and gene-related immune signaling pathways and immune cell markers, other than eosinophils and basophils, were unchanged post-treatment; thus, the drug only affected the expression of proteins and genes specifically associated with eosinophils or basophils, and that this effect was most prominent in patients with high baseline blood eosinophil counts.[59]

Clinical efficacy and OCS reduction

Overall, the reduction of exacerbations with benralizumab has led to very promising results with regard to reduction of average dose of OCS, with a response already evident after a single dose. Specifically, data from the ZONDA trial substudy showed that tissue depletion of eosinophils induced by benralizumab was greater than other anti-IL-5 MAbs.[38] Furthermore, one concern linked to other anti-IL-5 treatments, specifically to mepolizumab, is the possible creation of IL-5 reservoirs through the composition of an immune complex between mepolizumab and IL-5, which may ultimately result in a partial response to treatment (underdosing).[60] The effect of benralizumab on the improvement of FEV$_1$ is evident, even in patients with fixed airflow obstruction (FAO) and obesity, as highlighted by the *post hoc* analysis of the SIROCCO and CALIMA studies.[61,62] It may be of great interest to evaluate the steroid-sparing effect of these drugs and, with the available data so far, some conclusion may be drawn from the ZONDA and SIRIUS trials on benralizumab and mepolizumab, respectively.[38,48] The indirect comparison suggests a greater effect of benralizumab. In fact, the ZONDA trial had promising results with both benralizumab dosing regimens (30 mg administered subcutaneously either every 4 weeks or every 8 weeks – with the first three doses administered every 4 weeks), which meaningfully reduced the median final OCS doses from baseline by 75% in the OCS doses ($p<0.001$ for both groups). Contrarily, the SIRIUS trial showed that the median percentage reduction from baseline in the OCS dose was 50% in the mepolizumab group (100 mg administered SC every 4 weeks for 20 weeks), as compared with no reduction in the placebo group ($p=0.007$). In future, direct comparative studies will be needed to fully address this aspect and exploit the potential of benralizumab.

Moreover, it should be taken into consideration that the prefilled syringe and the administration every 8 weeks reinforce the drug profile in terms of compliance and usability.

In accordance with these findings and the clinical evidence, the baseline factors that positively impact on response to benralizumab are a higher dose of OCS, frequent asthma exacerbations, nasal polyposis, and FVC <65% predicted.[63]

Safety concerns may be related to the negative effects of the sustained tissue depletion of eosinophils induced by benralizumab, with regard to the theoretical risk of tumors, infections, and autoimmune diseases. However, different from neutrophils deficiency,[64] several data have confirmed that the absence of eosinophils from mammals is not associated with any pathology.[65] In addition, *in vivo* models of eosinophil-deficient mice do not show any characteristic syndrome nor global health issues and strongly support that under usual laboratory conditions eosinophils do not play a critical role in maintaining mammalian well-being. The available data suggest that current anti-eosinophils therapies are safe, although long-term studies are needed to confirm their safety.

The clinical efficacy and the steroid-sparing effect of benralizumab may be driving factors in treatment choice?

GCs are universally accepted agents for the treatment of anti-inflammatory and immunosuppressive disorders and in the setting of severe asthma. There is a high percentage of patients needing regular use of OCS,[4] which can lead to several systemic side effects including growth deficit in pediatric patients,[5] as well as the possible insurgence of chronic inflammation associated with GC resistance, characterized by insensitivity of the immune system to GC.[66] Therefore, an important aspect of the therapeutic options with new mAbs is the possibility of reducing OCS usage in asthmatic patients. Normally, RCTs for the different mAbs included the possibility of using OCS for randomized patients, thus including a variable that should be remembered when evaluating the net benefit of the investigation arm *versus* the SOC. When focusing on the steroid-sparing effect, there were two RCTs, SIROCCO and MENSA on benralizumab and mepolizumab, respectively, that showed a significant benefit in the investigation arm compared with SOC, regardless of steroid dosage (Figure 2).[37,46] The disease severity level (prebronchial FEV_1, and eosinophilic counts of >300 cells per μL) of patients in the two studies were comparable, with a slight advantage toward patients from SIROCCO in terms of: comorbidities (nasal polyposis) and allergic trait (rhinitis); similar doses of ICS/LABA; different doses of OCS; and different percentage of patients treated with OCS (15.2 mg/day in 18% of patients enrolled in SIROCCO *versus* 12.6 mg/day in 27% of patients enrolled in the MENSA trial). Considering patient characteristics, there was a higher baseline exacerbation rate for patients in the MENSA study compared with those in the SIROCCO study (3.8 *versus* 2.8). Thus, when carefully evaluating these aspects, patients may have used OCS treatment often at a higher dosage than the real clinical needs.[37] Interestingly, after OCS discontinuation, exacerbation

rates increased in the SOC arm of ZONDA and SIRIUS studies, but not in benralizumab-treated patients, determining an absolute benefit in the investigation arm. These results highlighted how the OCS use in RCTs may hide positive effects of mAb, as it minimizes the improvement in exacerbation rate in treated patients when compared to the SOC group. Therefore, for a correct clinical evaluation of the effectiveness of different mAbs, it is mandatory to optimize OCS use up to the minimum effective dose that will achieve symptom control. As a consequence, OCS tapering may be possible with mAbs, even up to a complete withdrawal.

Two more RCTs specifically addressed the possibility of OCS reduction, up to possible complete suspension, with mAbs treatment (Figure 2). The ZONDA study on benralizumab demonstrated its ability to reduce daily OCS intake while ensuring the maintenance of clinical disease control.[38] In this study, patients (eosinophils >150 cells per μL) were on OCS maintenance treatment for at least 6 months. Afterwards, they started a period of OCS optimization divided into three different phases with a total duration of up to 6 weeks: an induction phase, during which patients received their OCS dose as before; a dose-reduction phase, during which the OCS dose was reduced at regular intervals; and a dose-maintenance phase, during which the reduced OCS dose was maintained or, in patients in whom OCS therapy was discontinued, no further OCS were received. The primary endpoint was the overall reduction of OCS dose from randomization to maintenance period (week 24–28), and among secondary endpoints there was the 100% reduction of OCS in patients with optimized prednisone dose of 12.5 mg. The other study, the SIRIUS RCT on mepolizumab, included eligible patients, who had at least a 6-month history of OCS treatment and eosinophils counts of >150 cells per μL before entering the study (or 300 cells per μL in the previous 12 months).[48] Subsequently, a period of OCS optimization therapy of 3 to 8 weeks was designed to establish the lowest dose of maintenance OCS associated with acceptable asthma control. After the beginning of mepolizumab therapy (every 4 weeks induction phase), during which the patient continued the OCS dose achieved during optimization, the reduction phase began: OCS dose was reduced according to a prespecified schedule by 1.25 to 10 mg per day every 4 weeks on the basis of asthma control and symptoms of adrenal insufficiency. No further adjustment in the OCS treatment was made up to the 24-week study period. The primary endpoint was the overall reduction of OCS from randomization to maintenance period (week 20–24). A first analysis of the two studies showed a benefit in terms of OCS reduction, which may be underestimated to be of the same level (about 50% net). However, the percentage of those who were not able to reduce OCS treatment or lost asthma control during maintenance of OCS treatment was higher for mepolizumab than benralizumab (36 and 21%, respectively), while the proportion of those able to discontinue OCS therapy was greater for benralizumab than mepolizumab (52 and 14%, respectively; and number needed to treat [NNT] 3 for

benralizumab as compared to NNT 17 for mepolizumab). Moreover, the evaluation of the secondary endpoints of the ZONDA and SIRIUS studies on the reduction of exacerbation rate, FEV_1, and symptoms control after OCS weaning showed a net benefit in benralizumab-treated patients, as compared to those treated with mepolizumab for all parameters of severe asthma control. In detail, benralizumab obtained an NNT of 0.8 with regard to exacerbations compared to an NNT of 1.5 for mepolizumab; the improvement of FEV_1 obtained in patients treated with benralizumab was statistically significant (week 1–20) as compared to SOC, whereas improvement of FEV_1 after treatment with mepolizumab was not significant (Figure 2); ACQ significantly improved as compared to the SOC group in both studies, but with a different benefit pattern of improved symptom control after the first 4 weeks for benralizumab.

The differences may be explained by the particular pharmacodynamic characteristics of benralizumab when compared to other anti-IL-5 strategies.[67,68] As previously described, and as further evidenced in other studies, benralizumab is able to guarantee a faster effect in the reduction of plasma eosinophils,[69] as well as produce a greater reduction in the absolute number of eosinophils, both at plasma level (reaching almost eosinophils elimination) and tissue, compared with mepolizumab. Furthermore, another important aspect is the reduction of blood eosinophils precursors, inversely to what happens with mepolizumab.[55,65] These effects are due to the binding of the epitope on the α-subunit of the IL-5 receptor, present both on eosinophils and mature basophils and on their precursors, and the subsequent induction of ADCC.[59] Mepolizumab's mechanism of action is quite different, as it targets the cytokine IL-5 and is therefore characterized by the blockage of the binding of IL-5 to eosinophils through direct antibody-cytokine binding.[67] Even if preliminary data showed a high affinity binding of mepolizumab to IL-5, data

from other studies demonstrated a limited avidity of the cytokine/mAb complex, due to a reduced stereochemical capacity of Fab chains to interact with the antigen, thus determining numerically reduced bonds (stoichiometric ratio 1:1).[70] In addition, it is of relevant importance that the immune complexes are small and with a short circulating half-life, thus IL-5 is quickly able to revert to an active form, which circulates and explicates its normal activities. Mepolizumab may function as a 'reservoir' of IL-5. Moreover, eosinophils may still be able to mature and migrate to other tissues, as suggested by other studies in which the tissue self-regulation was mediated by other cytokines different from IL-5.[71]

All of this evidence contributes to the hypothesis that OCS treatment may represent a reliable marker for the evaluation of the benralizumab response, and, more generally, that the OCS dose can correlate with the effectiveness of the mAb. Notably, in the recent study by Bleecker and colleagues,[63] the OCS dose was the predictor marker of benralizumab efficacy in terms of reduction of exacerbations and FEV_1 improvement. It was found to be more significant for the eosinophil threshold of >300 cells per µL; therefore, it may represent a useful marker that quantifies the net benefit of mAb therapy in patients with steroid-dependent asthma.
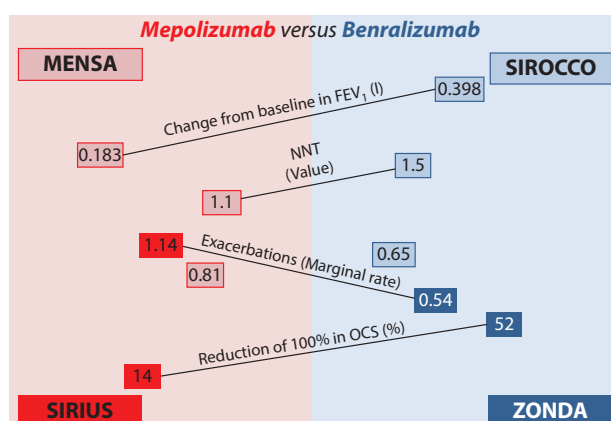
Conclusions

In this article, we carried out an indirect comparison among literature data, advancing the hypothesis of a superior effect of benralizumab on mepolizumab both as a clinical advantage and as a superior steroid-sparing effect in patients with eosinophilic severe refractory asthma.

Based on the assumption that patients had a comparable level of disease severity in the evaluated RCTs (ZONDA-SIRIUS and SIROCCO-MENSA), we carried out an indirect comparison on OCS reduction. The increase in the incidence of exacerbations in the control arm is appreciated both in ZONDA (1.83) and in SIRIUS (2.12), as compared to SIROCCO (1.33) and MENSA (1.75), where the OCS dose had not been changed. Interesting data that emerged from this analysis were that the performance of benralizumab in the ZONDA study was clinically identical to that of the investigation arm in the SIROCCO study (0.54 versus 0.65); whereas, the analogous data of mepolizumab in SIRIUS did not match the data in the MENSA study (1.14 versus 0.81). This suggests a superior benefit of benralizumab versus mepolizumab after OCS withdrawal.

In conclusion, we summarized how benralizumab may be of advantage in the treatment of eosinophilic refractory severe asthma and how it may have a competitive superiority, due to the particular mechanism of action, clinical efficacy, and greater steroid-sparing effect. Furthermore, to date no safety profile issues have emerged with benralizumab treatment. These data could help the clinician in the decision process of treatment choice, within the different available therapeutic options for eosinophilic refractory severe asthma.

Figure 2.   Outcomes comparison between mepolizumab and benralizumab.

FEV_1, forced expiratory volume in 1 second; NNT, number needed to treat; OCS, oral corticosteroids.

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