New horizons for the treatment of severe, eosinophilic asthma: benralizumab, a novel precision biologic

Abstract: In the last decades, the increasing evidence concerning inflammation mechanisms underlying severe eosinophilic asthma has highlighted new potential therapeutic targets and has paved the way to new selective biologic drugs. Understanding the mechanism of action and the clinical outcomes of a particular drug along with the clinical and biological characteristics of the patient population for which that drug was intended may ensure appropriate selection of patients that will respond to that drug. Under this perspective, the present review will focus on the mechanisms of action and clinical evidence of benralizumab as a treatment option for severe eosinophilic asthma, in order to provide a concise overview and a reference for clinical practice. Benralizumab is a fully humanized afucosylated IgG1 mAb that binds to an epitope on IL-5 Rα, and inhibits IL-5 signaling. Benralizumab also sustains antibody-directed cell-mediated cytotoxicity (ADCC) of eosinophils and basophils and consequently depletes IL-5Rα-expressing cells. As a result, it is responsible for a substantial depletion of blood, tissue, and bone marrow eosinophilia. This unique mechanism of action may account for a more complete and rapid action profile. Randomized clinical trials have demonstrated that benralizumab provides an optimal safety profile, and is able to significantly reduce asthma exacerbations, oral steroid intake, and to improve lung function. Some clinical predictors of enhanced clinical response to benralizumab have also been identified, including: a level of blood eosinophils ≥300 μL⁻¹, oral steroids use, the presence of nasal polyposis, FVC <65% of predicted, and a history of three or more exacerbations per year at baseline. These results can be helpful in identifying the best responder patients to benralizumab. As a step forward, the definition of the responder profile for each of the available biological treatment options will potentially support even more the pathway to precision medicine and the critical matching of the right drug with the right patient.

Keywords: benralizumab efficacy, benralizumab safety, benralizumab mechanism of action, anti IL-5 mAbs, severe asthma, eosinophilic asthma

Introduction

An estimated 5–10% of the 300 million people worldwide who suffer from asthma have a severe form. Patients with eosinophilic airway inflammation represent approximately 40–60% of this population.¹⁻³ Eosinophilic asthma is a relevant subtype of asthma associated with increased risk of severe exacerbations and a difficult control, despite high doses of oral and inhaled corticosteroids. In the last decades, that asthma phenotype has been extensively explored, and the increasing evidence concerning the underlying inflammation mechanisms has highlighted new
potential therapeutic targets and subsequently has paved
the way to new selective drugs.\textsuperscript{4} In the next few years
further biologic and bio-similar molecules selectively
addressing eosinophils and Th2 inflammation will become
available on the market, substantially enlarging the treat-
ment options for the patients with severe eosinophilic
asthma.\textsuperscript{3} On the other hand, the lack of biomarkers speci-
cifically predicting the good clinical response to each bio-
logic, which is currently a potential limitation in the field,
may hamper the selection of the right drug for the right
patient.\textsuperscript{5} Understanding the mechanism of action and the
clinical outcomes of a particular drug along with the
clinical and biological characteristics of the patient popu-
lation for which that drug was intended to treat may ensure
appropriate selection of patients that will respond to that
drug.

Under this perspective the present review will focus on
the mechanisms of action and clinical evidence of benra-
lizumab, in order to provide a concise overview and a
reference for clinical practice useful in increasing the
knowledge of the drug and better defining its position in
the context of the treatment options for severe eosinophilic
asthma.

Methods
A selective search on PubMed and Medline was per-
formed, including the following keywords: benralizumab
efficacy, benralizumab safety, benralizumab mechanism of
action, anti-IL 5 monoclonal antibody, and anti-IL 5 recep-
tor monoclonal antibody. Papers published up to January
2019 were considered. Original articles, randomized clini-
cal trials, and review papers relevant to the topic were
evaluated for inclusion in the review.

Immunologic background: the added value of a receptor-blocking
molecule
It has been known for many years that eosinophilic bronchial
asthma is characterized by increased eosinophil count in the
airways and peripheral blood, which has been shown to posi-
tively correlate with asthma severity.\textsuperscript{6} Under a pathophysi-
ological and clinical perspective, eosinophils in the context of the
other Th2 inflammation molecules and cells, particularly tis-

eue-resident innate lymphoid cells type 2 (ILC2s), drive a
number of mechanisms and humoral mediators (antibodies,
cytokines), which account for disease progression, poor
asthma control, and exacerbations\textsuperscript{7} (Figure 1).

Endothelial cells damaging, altered repair processes,
and induction of fibrosis are the most relevant ones.

Tissue eosinophils have an important role in innate immune
response to exogenous agents, but they can also damage tissues
by degranulation. Consequently, accumulation of eosinophils
releasing their granule-associated basic proteins, lipid medi-
tors, cytokines, and chemokines leads to potentiated airway
inflammation and tissue remodeling, with increased mucus
secretion and bronchial wall thickening.\textsuperscript{7}

Interleukin 5 (IL-5) is a 13-amino acid protein that forms a
52-kDa homodimer binding to the IL-5 receptor on cells sur-
face, a heterodimer composed of two subunits. The α subunit is
specific for IL-5, and the β subunit is shared with the granulo-
cyte-macrophage colony-stimulating factor (GM-CSF) and
interleukin 3 (IL-3) receptors and is responsible for cell
signaling.\textsuperscript{8,9} IL-5 receptor alpha (IL-5Rα) is expressed on
human eosinophil and basophil progenitors in bone marrow
as well as on mature circulating and tissue eosinophils and
basophils. It plays an important role in promoting growth,
differentiation, and maturation of eosinophils in the bone mar-
row, along with their survival and activation in peripheral
tissues.\textsuperscript{9}

All these findings led to the consideration of IL-5 as a
potential target for severe, difficult to treat, eosinophilic
asthma. Two main approaches were evaluated against the
action of IL-5 on eosinophil-mediated inflammation. The
first one was to block the circulating cytokine, and the second
was to interfere with the IL-5Rα on eosinophils. Both anti-
IL5 monoclonal antibodies (mAbs) (mepolizumab and resli-
zumab) and anti-IL5Rα (benralizumab) had been shown to
reduce circulating eosinophils and improve asthma control in
patients with severe eosinophilic asthma, in particular in
patients with elevated eosinophilic blood count at baseline.\textsuperscript{10}

Despite its clinical effectiveness, some studies highlighted
that mepolizumab administration resulted in increased IL-5Rα
expression and IL-5 local production, suggesting a kind of
endogenous auto-regulatory pathway. Eosinophil persistence
that has sometimes been detected during IL-5 mAbs treatment
in clinical studies may be explained by the action of other
cytokines, including IL-3 and GM-CSF, converging on IL-5
receptor and involved in eosinophil migration and activation
despite soluble IL-5 blocking.\textsuperscript{11,12} Moreover, the formation of
immune complexes between IL-5 and mepolizumab could act
as an IL-5 reservoir leading to an incomplete or less sustained
response to therapy.\textsuperscript{13}

Benralizumab is a fully humanized afucosylated IgG1κ
mAb that binds to an epitope on IL-5Rα, and inhibits IL-5
signaling, independently of the ligand presence.\textsuperscript{14} (Figure 1).
Thanks to its restricted expression on human eosinophils and basophils and their progenitors in the bone marrow, IL-5Rα represents an ideal target for specific cell depletion.\textsuperscript{15} Benralizumab also induces antibody-directed cell-mediated cytotoxicity (ADCC) of eosinophils and basophils and, consequently, depletes IL-5Rα-expressing cells. In fact, afucosylation of the oligosaccharide core of human IgG1 has previously been shown to result in a 5–50-fold higher affinity to human Fcγ receptor IIIa (FcγRIIIa), expressed on natural killer (NK) cells, macrophages, and neutrophils.\textsuperscript{16} Therefore, afucosylation enhances the interaction between benralizumab and FcγRIIIa and improves ADCC functions (Figure 1). As a result, a total depletion of eosinophils in the bone marrow and blood, and an almost complete depletion in sputum and tissues (90\% and 96\%, respectively) can be observed.\textsuperscript{17} According to the current evidence, this aspect is very unique of benralizumab mechanism of action. Furthermore the sustained depletion of eosinophils makes benralizumab action independent of IL-5 levels, which can increase during asthma exacerbation, decreasing IL-5 mAbs effectiveness.\textsuperscript{18}

In phase 1 and 2 randomized controlled studies on patients with sputum eosinophils ≥2\%, benralizumab 30 mg SC showed a significant reduction not only of blood eosinophils, but also of inflammatory biomarkers such as derived neurotoxin (EDN) and eosinophil cationic protein (ECP).\textsuperscript{19}

Basophils are also associated with inflammation, asthma severity, and exacerbations. In vitro studies have demonstrated that basophils constitutively express IL-5Rα but do not require IL-5 for their survival.\textsuperscript{16} Benralizumab potently induces basophil apoptosis in vitro, even though no significant data are available for in-vivo studies due to median low count of basophils at baseline in patients recruited in clinical studies.\textsuperscript{11,14}

A proteomic analysis approach showed that benralizumab is able to significantly reduce (FDR<0.05) in the expression of: genes associated with eosinophils and basophils homeostasis, such as CLC, IL-5Rα, and PRSS33; immune-signaling complex genes (FCER1A); G-protein-coupled receptor genes (HRH4, ADORA3, P2RY14); and immune-related genes (ALOX15 and OLIG2).\textsuperscript{20}

Efficacy issues: expected outcomes in practice
Similarly to other biological drugs, benralizumab has first been evaluated as an add on therapy for severe uncontrolled asthma, with the aim to reduce exacerbations and daily oral corticosteroids (OCS) dose in steroid dependent patients.\textsuperscript{21,22} The first clinical trial\textsuperscript{21} demonstrated that benralizumab treatment significantly impacted on exacerbation rate in the active group. In detail, it was a randomized, controlled, double-blind,
dose-ranging phase 2b study which investigated the subcutaneous administration of 2 mg, 20 mg, or 100 mg of benralizumab vs placebo in patients with eosinophilic asthma. By selecting patients with at least 300 cells/μL in the blood, the administration of benralizumab at the dose of 20 and 100 mg resulted in reducing exacerbations compared with placebo (0.30 vs 0.68, reduction 57%, 80% CI=33–72, p=0.015 for 20 mg dose; 0.38 vs 0.68, difference 43%, 80% CI=18–60, p=0.049 for 100 mg dose). CALIMA and SIROCCO confirmed the efficacy of benralizumab by showing consistent exacerbation rate reductions in patients with high eosinophil counts.23,24 As mentioned above, the OCS sparing effect of benralizumab represented the other main endpoint that was evaluated in clinical trials. The ZONDA study specifically addressed the reduction of OCS intake in patients treated with benralizumab. A 75% median reduction of OCS dose was shown in patients who received benralizumab compared to the placebo group, which showed a reduction of 25% (p<0.001).25 Besides a reduction of exacerbations and systemic steroid dose, in the main studies a significant effect on lung function was also observed. In fact, the BISE study demonstrated that benralizumab treatment was able to obtain an improvement of pre-bronchodilator FEV1 greater than 80 mL (95% CI=0–150; p=0.04) after 3 months of therapy; on the other hand, no significant change was detected in the placebo treated patients.26

When comparing benralizumab to the other currently marketed anti IL-5 biologics, namely mepolizumab and reslizumab, poor evidence is available. An indirect treatment comparison, relying on literature data summarized in a Cochrane review, was recently published.27 As a main result it highlighted the superiority of mepolizumab in reducing clinically significant exacerbations and asthma control in comparison with reslizumab and benralizumab in patients with comparable levels of blood eosinophilia. Bourdin et al10 recently published a similar analysis, actually showing quite different results. They performed a matching-adjusted indirect comparison between benralizumab, mepolizumab, and reslizumab. Similar outcomes were described for benralizumab and mepolizumab in terms of reduction of the overall exacerbation rate (52% and 49%, respectively) in comparison with placebo (rate ratio [RR] =0.94, 95% CI=0.78–1.13, n=1,524). Both benralizumab and mepolizumab decreased by 52% (RR=1.00, 95% CI=0.57–1.75; n=1,524) the percentage of clinically significant and severe exacerbations. Also the impact on pre-bronchodilator FEV1 was similar. A comparison between benralizumab and reslizumab was excluded from the analysis due to the different clinical characteristics of the population evaluated in both studies. In fact, a systematic matching-adjusted comparative analysis was not applicable. However, through an indirect comparison of the final treatment outcomes, a similar overall efficacy of benralizumab and reslizumab was described.

Table 1 provides a summary of clinical characteristics of current market available anti-IL-5 mAbs.

Of note, not negligible methodological limitations have to be considered when interpreting the results of an indirect comparison analysis, as suggested by the quite different results reported by the above-mentioned comparative studies. In fact, head-to-head studies would be required in order to obtain more reliable data. Furthermore, the evidence coming from the clinical trials certainly provides the basis for the use of these drugs in the real world. However, it is well known that substantial differences may occur between randomized clinical trials (RCTs) and real world studies, especially in terms of patients’ characteristics and follow-up and monitoring modality, which may impact on the drug effectiveness.

In addition to the need for identifying patient’s responder profile, the steroid sparing effect, reduction in exacerbation rate, and improvement in lung function shown in patients treated with benralizumab need to be verified in the real-world scenario outside of randomized, controlled trials.28–30

Safety issues: eosinophils depletion and beyond

The safety profile of benralizumab is certainly one of the most discussed issues related to the use of the drug in clinical practice. In fact, the almost complete depletion of eosinophils in serum and in the bone marrow may raise some concerns and is currently under debate.31 Overall, reviewing the safety data of the published trials, it is possible to conclude that benralizumab administration was not related to serious adverse events, and its safety profile is similar to the other anti-IL-5 drugs.21–26 Fever, rhino-pharyngitis, muscle pain, and asthenia, although rare, were the most frequently reported side-effects during the trials course. More serious adverse events included herpes zoster, thyroid storm, and urticaria, of which onset was rare.31 The safety and tolerability of long-term benralizumab administration have recently been evaluated in the BORA study, published as an extension of CALIMA24 and SIROCCO.23 The main serious adverse
events recorded during the study time frame were: worsening of asthma (3–4%), pneumonia (<1–1%), and bacterial pneumonia (0–1%). As far as neoplasias are concerned, 1% of patients enrolled in BORA had new malignancies, with only one (prostate cancer in Q8W administration) which was considered drug related by physicians. Notwithstanding this observation, a longer period of observation is necessary to completely exclude or warn about cancer risk, as already done for omalizumab. Although the results about safety in clinical trials are encouraging, even those in the long-term assessment, what can happen by reducing the number of eosinophils so drastically deserves to be monitored overtime. In order to hypothesize a safety expectation of benralizumab in the real world, we can rely as well on the data already described. No evidence of abnormalities related to eosinophil reduction have been reported from data regarding patients with immunodeficiency disorders. Furthermore, in a lab experimental setting with eosinophil-deficient mice, no health failure or particular syndromes have been observed, allowing us to hypothesize that eosinophils could not play a critical role in the well-being and homeostasis of mammals. Notwithstanding these observations, the most relevant data concerning the long-term safety of this drug will be obtained after a longer period of use, and collected from the data related to post-marketing pharmaco-vigilance. Monitoring the benralizumab safety profile in the real word setting is mandatory. In fact, common conditions such as smoke, old age, or multi-drug regimens represent exclusion criteria for clinical trials and may impact on the drug safety profile.

**Table 1** Anti-IL-5 at a glance comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration route</th>
<th>Regimen</th>
<th>Target population</th>
<th>Main clinical peculiarities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab</td>
<td>Subcutaneous</td>
<td>30 mg every 4 weeks for the first 3 doses, then every 8 weeks</td>
<td>Eosinophilic asthma ≥300 cells/µL, CRSwNP</td>
<td>High affinity for IL-5 receptor and ADCC activity, eosinophils sustained tissue depletion, improvement of pulmonary function even in patients with FAO, steroid sparing effect</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Subcutaneous</td>
<td>100 mg every 4 weeks</td>
<td>Eosinophilic asthma ≥300 cells/µL</td>
<td>Excellent safety profile, steroid sparing effect</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Intravenous</td>
<td>3 mg Kg⁻¹ every 4 weeks</td>
<td>Eosinophilic asthma ≥400 cells/µL</td>
<td>Personalized dose, improvement of pulmonary function</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADCC, Antibody-Dependent Cell Cytotoxicity; CRSwNP, Chronic sinusitis with nasal polyposis; FAO, Fixed airway obstruction; IL-5Ra, Interleukin-5 receptor alpha subunit.

**Target population: potential predictors of efficacy**

When considering the prescription requirements of the currently available anti IL-5 mAbs (Table 1), a not negligible overlapping area in terms of target population potentially emerges. Overall, in the absence of biomarkers specifically predicting the good clinical response to each biologic drug, the patient selection process still represents a critical issue. In the context of a pooled analysis of data from SIROCCO and CALIMA studies, Bleecker et al. identified some baseline clinical features associated to a better clinical response to benralizumab. A level of blood eosinophils ≥300 µL⁻¹, OCS use, history of nasal polyposis, and FVC <65% of predicted represented predictors of enhanced benralizumab efficacy. Similarly, FitzGerald et al. explored the clinical response to benralizumab with respect to different patients’ characteristics before the treatment start. A pooled analysis of the results from SIROCCO and CALIMA was performed. As a main finding, a greater improvement in annual exacerbation rate was observed in the presence of a combination of increased blood eosinophil thresholds and a history of three or more exacerbations per year at baseline. Furthermore, even in patients with fixed airflow obstruction and obesity, a significant improvement of lung function has been observed during benralizumab treatment course. Benralizumab also demonstrated a greater steroid-sparing effect in comparison with other anti IL-5 drugs.

The results reported above can be helpful in identifying the best responder patients to benralizumab and suggest that, up to now, in the absence of univocal biomarkers...
predictive of good clinical response, considering the patient’s characteristics, including lung function, asthma exacerbations, nasal polyposis, ongoing dose of OCS, is of utmost relevance in the treatment selection process.

As a step forward, the definition of the responder profile for each of the available biological treatment options, maybe through head-to-head comparative studies, will potentially support even more the pathway to precision medicine and the critical matching of the right drug with the right patient. The analysis of non-responder patients in the real world will also be essential in achieving the goal.

Disclosure
The authors declare that they have no conflicts of interest in this work.

References


