

Mepolizumab: A New Class of Treatment for Adolescents with Severe Persistent Asthma

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Mepolizumab and reslizumab are anti-interleukin-5 monoclonal antibodies. Mepolizumab has been approved by the Food and Drug Administration (FDA) as add-on therapy for patients 12 years and older with severe asthma with an eosinophil phenotype. Reslizumab is currently under FDA review for approval also as add-on therapy in patients 12 years and older with moderate to severe asthma with an eosinophil phenotype. The differences between the products include route of administration (subcutaneous for mepolizumab and intravenous for reslizumab) and adverse effect risks. Adverse effects seen more commonly with mepolizumab than placebo included herpes zoster that may not be relevant to an adolescent patient but could be relevant for other viral infections. Anaphylaxis, elevations in creatine phosphokinase, and musculoskeletal events were seen in patients treated with reslizumab.

IN NOVEMBER 2015, the Food and Drug Administration (FDA) approved mepolizumab (Nucala[®]; GSK), an anti-interleukin-5 (IL-5) monoclonal antibody for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype at a dose of 100 mg subcutaneously (SQ) every 4 weeks. This is the first new category of drug to be approved for asthma since the introduction of the initial biologic, omalizumab, in 2003. In December 2015, the FDA Pulmonary-Allergy Drugs Advisory Committee reviewed information on a second IL-5 monoclonal antibody, reslizumab (Cinqair[®]; Teva Pharmaceuticals). The data presented are from the Pulmonary-Allergy Drugs Advisory Committee meetings in June and December 2015 for mepolizumab and reslizumab, respectively.^{1,2}

The American Thoracic Society and European Respiratory Society Task Force define “severe asthma” as disease that requires treatment with high-dose inhaled corticosteroids plus a second controller (long-acting β_2 -agonists or leukotriene modifier/theophylline) for the previous year or use of systemic corticosteroids for $\geq 50\%$ of the previous year to prevent it from becoming “uncontrolled” or that remains “uncontrolled” despite this therapy.³ Per the Task Force, uncontrolled asthma is defined as at least one of the following:

- Poor symptom control: Asthma Control Questionnaire score consistently >1.5 , Asthma Control Test score <20 (or “not well controlled” by guidelines^{4,5}).

- Frequent severe exacerbations: 2 or more bursts of systemic corticosteroid (CS) (>3 days each) in the previous year.
- Serious exacerbations: at least 1 hospitalization, ICU stay, or mechanical ventilation in the previous year.
- Airflow limitation: after appropriate bronchodilator withhold $FEV_1 < 80\%$ predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal).
- Controlled asthma that worsens on tapering of these high doses of inhaled corticosteroid (ICS) or systemic CS (or additional biologics).

The characteristics of “eosinophilic phenotype” have not been fully defined and it is not included as a specific phenotype in the NAEPP or GINA guidelines.^{4,5} Persistent sputum eosinophilia ($\geq 2\%$) refractory to high-dose inhaled corticosteroid therapy tends to be associated with adult-onset (>12 years old) disease that is less driven by an allergic component compared with early-onset (childhood) disease.^{6,7} Characteristics of the “eosinophilic phenotype” specific to an adolescent with severe asthma have not been published.⁸

Severe asthma is present in 5%–10% of the asthma population but accounts for a significant portion of healthcare costs.⁹ Thus, there is a need to identify the characteristics within severe asthma that may be a relevant target for pharmacotherapy. A recent epidemiological study in over 130,000 patients aged 12–80 years found that having a blood

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eosinophil count $>400/\mu\text{L}$ increased the likelihood of having 2 or more exacerbations per year [requiring oral corticosteroids (OCS), hospitalizations, or emergency department visits] by 1.4-fold.¹⁰ IL-5 is the predominant cytokine responsible for the generation, activity, and longevity of eosinophils. Thus, reduction of blood eosinophil levels by use of anti-IL5 monoclonal antibodies in combination with additional controller therapies would be expected to significantly impact these costly outcomes.

Mepolizumab is a humanized IgG1 κ monoclonal antibody that binds to IL-5. After administration of 100 mg SQ in the target population, the volume of distribution ranged from 63 to 82 mL/kg with a clearance of 4.0–4.7 mL/day/kg.¹ The half-life was 3–4 weeks. Mepolizumab is metabolized by proteolytic enzymes in the blood and liver and because of the small molecular size, there is no glomerular filtration in the kidney. Thus, neither liver nor kidney dysfunction would alter the pharmacokinetic parameters. There were no pharmacokinetic differences by race/ethnicity, age, or gender. After mepolizumab administration 100 mg SQ, blood eosinophil counts were reduced by 86% (to $40/\mu\text{L}$) within 3 days with a further slight decrease through week 8. In the 2 Phase III trials, 6% of subjects had antimepolizumab antibodies after treatment, which persisted in about 50% of patients. One patient developed neutralizing antibodies that resulted in a 22% increase in mepolizumab clearance, but otherwise caused no adverse effects.

There were 3 pivotal efficacy trials that differed slightly in inclusion criteria and primary outcome. All participants were at least 12 years of age, treated with high-dose ICS plus an additional controller therapy. The key differences between the trials are given in Table 1.

In studies 997 and 588, treatment with mepolizumab resulted in an exacerbation rate ratio of ~ 0.5 ($P < 0.001$). In study 575, the odds ratio for reduction in OCS dose was 2.39 (95% confidence interval: 1.25–4.56) with mepolizumab compared to placebo. The data also indicated that if there was a gap in treatment of 3 months, there was no rebound response for blood eosinophils or exacerbation rate. Twice as many patients were able to wean completely off OCS with mepolizumab compared with placebo. Of the inclusion criteria in study 997 used to predict response, only baseline or historical blood eosinophil count and previous exacerbation rate history were informative and thus used for trials 588 and 575. There was considerable discussion at the FDA

Advisory Committee meeting as to whether a specific blood eosinophil level (historical or baseline) should be used to identify suitable candidates for treatment. Although there was an increase in exacerbation rate in studies 992 and 588 with increasing eosinophil level, there was insufficient evidence to support a strict blood eosinophil level threshold that would define response versus nonresponse. However, the data did suggest that measurement of a baseline eosinophil count of at least $150/\mu\text{L}$ was more predictive of response than a measurement of at least $300/\mu\text{L}$ in the previous year. In addition, those patients who entered into the study with a baseline level of $<150/\mu\text{L}$ (because they had a historical level of at least $300/\mu\text{L}$) had essentially no exacerbation rate benefit. Should further data analysis confirm a specific eosinophil level predictive of response, GSK would submit a label change to the FDA for approval.

There were no anaphylaxis events reported and allergic reactions were similar in mepolizumab- and placebo-treated patients. There was discussion in the advisory committee with regard to the risk of cancer development with long-term use, and a strong pharmacovigilance program was encouraged. The adverse event of greatest interest was activation of herpes zoster during treatment with mepolizumab (6 cases of which 2 were serious, versus 2 in the placebo group). The current prescribing label also describes additional cases of herpes zoster occurring in the ongoing open-label extension studies and includes mention of herpes zoster infections in the warnings and precautions section.¹¹ The labeling also counsels prospective patients to receive varicella vaccination before starting treatment; there is no recommendation for obtaining vaccination against herpes zoster, however. Although the occurrence of herpes zoster in adolescents would be unusual, it would be prudent to remind families to stay current on all vaccinations for this age group, which include tetanus, diphtheria, and pertussis (Tdap), meningococcal, human papillomavirus, and annual influenza vaccinations.

The FDA Advisory committee also recommended in a 10–4 vote that the available efficacy and safety data did not support approval of mepolizumab for adolescents aged 12–17 years of age. The primary reason for the “no” votes was that there were only 16 adolescents exposed to mepolizumab in the 3 trials and there were concerns that lifelong treatment would expose this age group to unknown risks. The committee at large commented that efficacy would be expected to be similar for adolescents and for adults but

TABLE 1. KEY DIFFERENCES IN PIVOTAL CLINICAL TRIALS FOR MEPOLIZUMAB

	Study 997	Study 588	Study 575
OCS inclusion criteria	OCS allowed	OCS allowed	All on OCS
Exacerbation history inclusion criteria	≥ 2 Exacerbations in the past year	≥ 2 Exacerbations in the past year	
Blood eosinophil level inclusion criteria	Blood eosinophil $\geq 300/\mu\text{L}$ or sputum eosinophils $\geq 3\%$ or FENO ≥ 50 ppb or loss of asthma control with $\leq 25\%$ dose reduction in ICS/OCS	Blood eosinophils $\geq 150/\mu\text{L}$ at screening or $\geq 300/\mu\text{L}$ in the past year	Blood eosinophils $\geq 150/\mu\text{L}$ at screening or $\geq 300/\mu\text{L}$ in the past year
Primary outcome	Exacerbation rate (OCS use, ED visit, hospitalization)	Exacerbation rate (OCS use, ED visit, hospitalization)	OCS dose reduction

ED, emergency department; ICS, inhaled corticosteroids; OCS, oral corticosteroids; FENO, fraction of expired nitric oxide.

TABLE 2. KEY DIFFERENCES IN PIVOTAL CLINICAL TRIALS FOR RESLIZUMAB

	3081	3082	3083	3084 (adults only)
OCS inclusion criteria	OCS not allowed	OCS allowed (≤ 10 mg/day)	OCS allowed (≤ 10 mg/day)	OCS not allowed
Exacerbation history inclusion criteria	Not required	≥ 1 Exacerbations in the past year	≥ 1 Exacerbations in the past year	Not required
Blood eosinophil level inclusion criteria	$\geq 400/\mu\text{L}$	$\geq 400/\mu\text{L}$	$\geq 400/\mu\text{L}$	Any level
Asthma Control Questionnaire—7 Score	≥ 1.5	≥ 1.5	≥ 1.5	≥ 1.5
Primary outcome	Change in FEV ₁	Exacerbation rate (OCS use/increase ICS dose, unscheduled office visit, ED visit, hospitalization) plus symptoms or lung function decline consistent with asthma worsening	Exacerbation rate (OCS use/increase ICS dose, unscheduled office visit, ED visit, hospitalization) plus symptoms or lung function decline consistent with asthma worsening	

that there simply were not enough data to support approval. In the FDA summary review, there was no further elaboration as to why the FDA decided to include adolescents for approval.¹²

Reslizumab is another humanized IgG4 κ monoclonal antibody that binds to IL-5 that was reviewed at the December FDA Pulmonary-Allergy Drugs Advisory Committee meeting. The members voted in favor of approval for adults (11 to 3) but were unanimous in not recommending approval for adolescents aged 12–17 years.²

There were 4 pivotal studies conducted with reslizumab in patients treated with at least medium dose ICS with or without an additional controller medication; 1 study was on adults only and is not discussed further. The key differences between the trials are given in Table 2.

In studies 3082 and 3083, treatment with reslizumab resulted in an exacerbation rate ratio of 0.4–0.5 ($P < 0.0001$).

However, there was no reduction in exacerbation rate for adolescents in either study. Reslizumab also increased lung function by 115–160 mL but there was no effect in adolescents. As in the mepolizumab clinical program, there were very few adolescents in the reslizumab studies (16 adolescents exposed to reslizumab). In addition, there was no increased effect on exacerbation rate or FEV₁ in patients with higher baseline eosinophil levels, but this could be explained by the inclusion criteria requirement for a screening level of at least 400/ μL .

There are several key differences between mepolizumab and reslizumab (Table 3).

The risk of anaphylaxis is an issue of concern for reslizumab. Based on data from another monoclonal antibody (cetuximab), it is hypothesized that there may be reaction to the α -gal component (a blood group oligosaccharide produced during the manufacturing process using a murine cell

TABLE 3. KEY DIFFERENCES BETWEEN MEPOLIZUMAB AND RESLIZUMAB

	<i>Mepolizumab</i>	<i>Reslizumab</i>
Dosing	100 mg subcutaneously every 4 weeks	3 mg/kg i.v. every 4 weeks
Intended population	Patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.	Patients with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids (could include patients with moderate or severe persistent asthma).
Adverse effects risk	No anaphylaxis events during clinical program. No neutralizing antibodies measured. Risk of herpes zoster.	Three confirmed anaphylaxis events in reslizumab-treated patients (none in placebo groups). Neutralizing antibodies not measured (no available assay). Elevations in creatine phosphokinase levels measured before treatment. Musculoskeletal events 24 h after dosing.
Dose selection	Dose ranging studies confirmed proposed dose	Dose ranging studies included 0.3 and 3 mg/kg only.

line) in reslizumab and that previous sensitization resulting from a specific tick bite induces production of IgE antibodies to α -gal. Several of the elevations in creatine phosphokinase (CPK) ($>10\times$ upper limit of normal) and associated musculoskeletal adverse events (rhabdomyolysis) were serious or potentially life threatening. There is no clear mechanism for the anaphylaxis or musculoskeletal events during the clinical program, which raises the question as to whether a dose lower than 3 mg/kg would be effective but with less risk. There were only 3 reports of herpes zoster in the clinical program (2 in placebo and 1 in reslizumab-treated patients, respectively).

In conclusion, both mepolizumab and reslizumab are similarly effective in reducing the risk for exacerbations in patients with moderate to severe persistent asthma with an eosinophilic phenotype. Mepolizumab is indicated only as add-on maintenance treatment for patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. The primary differences between mepolizumab and reslizumab are in the route of administration, which may influence costs that are in addition to drug acquisition and treatment-related adverse effects. The efficacy for both drugs in adolescents is largely unknown because too few in this age group were included in the clinical program for either drug. Similarly, whether adverse events would be different for adolescents is not clear. However, severe persistent asthma can be debilitating for adolescents and consideration for treatment with an anti-IL5 monoclonal antibody may be warranted. Careful discussion of the risks to be watchful for should be included in the dialog between the family and prescriber before use.

Author Disclosure Statement

No competing financial interests exist.

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