Original Article

Long-term Safety and Efficacy of Reslizumab in Patients with Eosinophilic Asthma

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What is already known about this topic? Placebo-controlled trials in patients with eosinophilic asthma show that intravenous reslizumab, an anti-IL-5 monoclonal antibody, has a safety profile similar to placebo. Reslizumab reduces asthma exacerbations and improves lung function and asthma control.

What does this study add to our knowledge? This open-label extension study with overall reslizumab exposure up to 3 years, when including exposure during the double-blind treatment periods of the 3 pivotal studies, demonstrates acceptable safety and maintenance of improved lung function and asthma control in patients with moderate-to-severe eosinophilic asthma treated with intravenous reslizumab.

How does this study impact current management guidelines? The safety and efficacy results of this study support reslizumab treatment for long-term control of moderate-to-severe eosinophilic asthma. There is no evidence of an increased incidence of adverse events with long-term reslizumab exposure compared with the reslizumab-naïve group or compared with the placebo-treated patients in the double-blind trials.

BACKGROUND: In placebo-controlled trials, reslizumab, an anti-IL-5 monoclonal antibody, significantly reduced asthma exacerbations and improved lung function and asthma control in patients with eosinophilic asthma.

OBJECTIVE: This open-label extension study evaluated safety and efficacy of reslizumab for up to 24 months.

METHODS: After participation in 1 of 3 placebo-controlled, phase III trials in moderate-to-severe eosinophilic asthma, patients received reslizumab 3.0 mg/kg intravenously every 4 weeks for up to 24 months. Adverse events (AEs), lung function, and patient-reported asthma control were evaluated.

RESULTS: In the open-label extension, 1,051 patients received ≥1 reslizumab dose (480 reslizumab-naïve, 571 reslizumab-experienced); median (range) exposure was 319 (36-840) and 343 (36-863) days in reslizumab-naïve and reslizumab-experienced patients, respectively. Continuous exposure, including during the placebo-controlled studies, was ≥12 months for 740 patients and ≥24 months for 249 patients. The most common AEs were worsening of asthma and nasopharyngitis. Serious AEs affected 78 of 1,051 (7%) patients; 18 of 1,051 (2%) discontinued treatment because of AEs; and there were 3 deaths (all non-treatment-related). Fifteen adult patients (15 of 1,023; 1%) had

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Abbreviations used
ACQ- Asthma Control Questionnaire
ADA- Antidrug antibody
AE- Adverse event
ASUI- Asthma Symptom Utility Index
AQLQ- Asthma Quality of Life Questionnaire
CI- Confidence interval
FEF_{25-75}- Forced expiratory flow at 25% to 75% of the FVC
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
GI- Gastrointestinal
ICS- Inhaled corticosteroid
IL-5- Interleukin-5
IV- Intravenous
QoL- Quality of life
SABA- Short-acting β-agonist
SD- Standard deviation

malignancies of diverse tissue types. Reslizumab-experienced patients maintained improved lung function and asthma control; reslizumab-naïve patients had improvements in these measures throughout open-label treatment. Blood eosinophil counts appeared to be returning to baseline after reslizumab discontinuation.

CONCLUSIONS: In patients with moderate-to-severe eosinophilic asthma, intravenous reslizumab 3.0 mg/kg displays favorable long-term safety and sustained long-term efficacy. Initial improvements in lung function and asthma control were maintained for up to 2 years. These findings substantially add to our understanding of the long-term safety and efficacy of anti-IL-5 strategies. **(J Allergy Clin Immunol Pract 2017;5:1572-81)**

Key words: *Reslizumab; Asthma; Eosinophil; Anti-IL-5; Long-term safety; Open-label extension study*

Recent advances in the treatment of patients with inadequately controlled asthma have focused on targeting inflammatory pathways that contribute to the heterogeneity and severity of the disease. Eosinophils play key roles in the promotion and maintenance of airway inflammation and are associated with remodeling.[1-3] The presence of elevated eosinophils in the blood and sputum has been associated with asthma severity and increased risk of asthma exacerbations.[4-9] Indeed, the blood eosinophil level is a useful biomarker to help identify patients with severe eosinophilic asthma who may be responsive to anti-IL-5 antibody therapy.[10-12] Reslizumab is an IgG4/κ humanized monoclonal antibody that targets IL-5 (a key factor in eosinophil viability), thereby disrupting the maturation, activation, and survival of eosinophils.[13,14] Intravenous (IV) reslizumab was recently approved in the USA, EU, and Canada as an add-on maintenance treatment of patients with severe asthma aged ≥18 years and with an eosinophilic phenotype. The phase III BREATH clinical program in asthma consisted of 4 completed placebo-controlled safety and efficacy studies in patients with asthma uncontrolled on at least a medium-dose inhaled corticosteroid (ICS) with or without another asthma controller. Three of the studies (1 lung function 16-week study and 2 exacerbation 52-week studies) were in patients aged ≥12 years with eosinophilic asthma (screening blood eosinophil count ≥400/μL)[15,16] and the fourth was a placebo-controlled lung-function study in patients unselected for eosinophilic asthma (adults only).[11] The overall results from the placebo-controlled trials showed that reslizumab IV significantly reduced exacerbations, relieved asthma symptoms, and improved asthma-related quality of life (QoL) and lung function in patients with eosinophilic asthma whose symptoms were inadequately controlled on an ICS-based treatment regimen. For example, in the 2 phase III 52-week studies in patients with eosinophilic asthma, the relative risks of asthma exacerbations with reslizumab IV versus placebo were 0.5 (95% confidence interval [CI]: 0.37-0.67) and 0.41 (0.28-0.59), both $P < .0001$.[16]

After participation in any of the phase III placebo-controlled trials in eosinophilic asthma, patients treated with either reslizumab IV or placebo were eligible to enter an open-label extension study of reslizumab for up to 2 additional years, the results of which are presented here. The primary objective of this study was to obtain long-term safety data for reslizumab IV 3.0 mg/kg administered once every 4 weeks for up to an additional 2 years in adolescent and adult patients with moderate-to-severe eosinophilic asthma. Efficacy assessments, including lung function and patient-reported measures of asthma control and QoL, were also assessed.

METHODS

Study design

This was an international multicenter, nonrandomized, open-label extension study designed to assess the long-term safety and efficacy of treatment with reslizumab IV (NCT01290887). The study consisted of a baseline visit (end-of-treatment visit for the prior placebo-controlled studies) followed by clinical visits every 4 weeks during the open-label treatment period, an end-of-treatment visit conducted 4 weeks after the last dose of reslizumab, and a final follow-up evaluation conducted 90 days (±7 days) after the end-of-treatment visit.

Patients

Eligible patients must have completed treatment in a preceding randomized (reslizumab vs placebo), double-blind asthma exacerbation study or received ≥2 doses of reslizumab in a pulmonary function study.[15,16] Patients enrolled in the previous studies were aged 12-77 years with inadequately controlled asthma (Asthma Control Questionnaire [ACQ] score ≥1.5) and elevated blood eosinophils (≥400 cells/μL) and were receiving at least a medium dose of ICS (fluticasone propionate ≥440 μg/day, or equivalent) with or without another controller.[15,16]

Patients were excluded from the open-label study if they had a clinically meaningful comorbidity that would interfere with the study schedule or procedures, or compromise the patient's safety; had another confounding underlying lung disorder; or had any aggravating factors that were inadequately controlled. Patients were also excluded if they had a current infection or disease that might have precluded assessment of asthma or were a current smoker. Patients were restricted from taking concurrent immunomodulatory or investigational medications. Patients were not excluded if they were receiving systemic corticosteroids (up to 10 mg/day) for asthma.

The study was conducted in accordance with the Declaration of Helsinki, local laws, and the International Conference on