Satellite Symposium : Drug treatments for severe persistent asthma

Targeting the right patient in severe eosinophilic asthma: Reslizumab

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Introduction

Asthma is a complex chronic disease with a heterogeneous presentation. The identification of asthma phenotypes an ongoing process, and it has been proposed that stratifying patients with asthma on the basis of specific phenotypes could result in improved treatment outcomes.[1, 2]

Eosinophils have long been implicated as playing a central role in the pathophysiology of asthma in many patients. Eosinophilic asthma is now recognized as an important asthma phenotype and assessment of eosinophilia in patients with severe asthma is an important tool for monitoring asthma control and guiding therapeutic decisions.[3,4] Although a number of bioactive proteins, including IL3 and granulocyte-macrophage colony stimulating factor, regulate and control the life cycle of eosinophils, eosinophils respond primarily to IL5. Together with its specific receptor (IL5R) on target cells, IL5 has a central role in eosinophil growth, differentiation, recruitment, activation, and survival (Figure 1).[5]

Reslizumab

Reslizumab (CINQAIR®) is a humanized monoclonal (immunoglobulin [Ig] G4/κ) antibody that targets IL5. It is currently available as an intravenous formulation and development of a subcutaneous formulation is ongoing. Reslizumab binds with high affinity to circulating human IL5 and downregulates the IL5 signaling pathway, potentially disrupting maturation and survival of eosinophils. It inhibits the bioactivity of IL5 by blocking its binding to the alpha chain of the IL5R complex expressed on the surface of eosinophils.[6, 7] When characterized in healthy adults, patients with asthma, and other patient populations, the pharmacokinetic profile of reslizumab was similar across groups, with an inter-individual variability in peak and overall exposure of approximately 20-30%.[8]

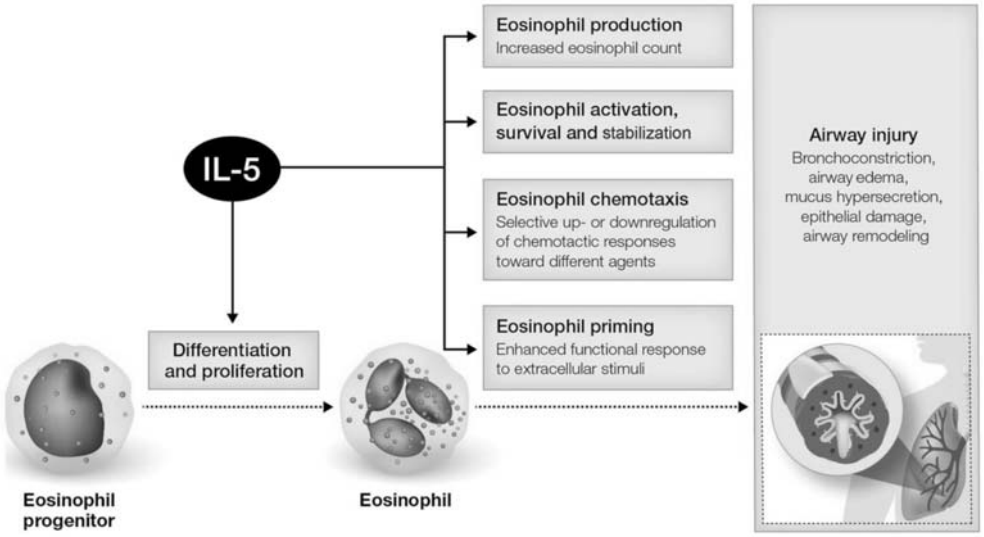

Figure 1. Schematic depicting role of IL5 in promoting eosinophilic asthma. (Adapted from Ref. 8)

Clinical trials of reslizumab in eosinophilic asthma

A lack of patient selection in terms of baseline eosinophilia made initial data from the early stages of the reslizumab clinical development program discouraged. A phase I pilot trial of reslizumab in a small number of patients with severe persistent asthma (n = 26) showed no significant improvement in asthma symptoms and lung function.[9] However, reslizumab dose dependently reduced the circulating blood eosinophil count from baseline, with a significant reduction reported up to day 30. This study highlighted the importance of adequately preselecting patients whose asthma is dependent on the eosinophilic inflammatory pathway, and this led to the incorporation of appropriate patient selection (*i.e.* enrollment of patients with eosinophilia) in the design of phase II/III reslizumab clinical studies.

In the randomized, double-blind, phase II, proof-of-concept study, reslizumab 3 mg/kg IV was compared with placebo administered once every 4 weeks for 15 weeks in adult patients with eosinophilic asthma (n = 106).[10] Eligible patients had confirmed airway hyperreactivity or airway reversibility; had poorly controlled asthma; were receiving high-dose inhaled corticosteroid (ICS); and had induced sputum eosinophils of $\geqslant$3%. In the overall patient population, a significant improvement from baseline was noted in FEV1 with reslizumab versus placebo (0.18 versus -0.08L, respectively; P = 0.0023). In addition, patients in the reslizumab group achieved a significantly greater median percentage reduction from baseline in sputum eosinophil count (-95.4% versus placebo -38.7%; P = 0.0068) and blood eosinophil count (-0.40 versus 0.00 $\times$ 10^3 cells/μL; P <0.0001).

Three of the phase III reslizumab studies were conducted in patients with elevated eosinophil counts and one study enrolled patients unselected for baseline blood eosinophil levels. The first study evaluated two

different doses of reslizumab in patients (n = 315) aged 12–75 years with asthma inadequately controlled by at least a medium-dose ICS and a blood eosinophil count of ⩾400 cells/μl.[11] Patients were randomized to receive reslizumab 0.3 or 3 mg/kg or placebo once every 4 weeks for 16 weeks. Reslizumab 0.3 and 3 mg/kg significantly improved FEV1 over 16 weeks (primary efficacy endpoint) by 0.115 L (P = 0.0237) and 0.160 L (P = 0.0018), respectively, compared with placebo. Significant reductions in blood eosinophil concentrations from baseline were observed for both the 0.3 mg/kg and 3 mg/kg reslizumab doses compared with placebo and were greatest with reslizumab 3 mg/kg (difference -323 cells/μL and -494 cells/μL, respectively; both P < 0.0001 versus placebo). Castro and colleagues subsequently conducted two identical phase III trials using the same design in patients aged ⩾12 years (n = 953) with inadequately controlled asthma, elevated blood eosinophils (⩾400 cells/μL) and a history of asthma exacerbation (⩾1 exacerbation during the previous year).[12] Patients were randomized to receive reslizumab 3 mg/kg IV or placebo every 4 weeks for 1 year. In both studies patients treated with reslizumab experienced a significant reduction in clinical asthma exacerbations (primary endpoint) compared with patients receiving placebo and this effect was independent of which concomitant drug treatments were being received at baseline. Significant improvements in FEV1, AQLQ score, and ACQ-7 score were also observed at week 16 and week 52 in favor of reslizumab (Figure 2). Indirect confirmation of the efficacy of reslizumab was provided by a fourth

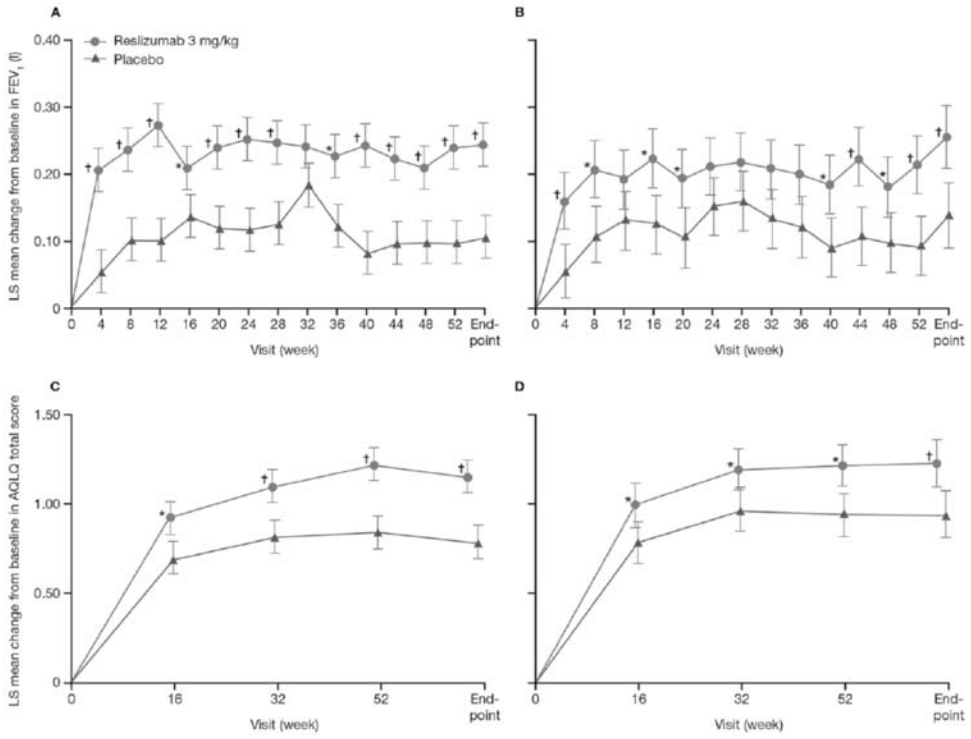

Figure 2. Changes in FEV1 and AQLQ over 52 weeks in patients receiving reslizumab or placebo in the identical phase III Study 1 (A, C) and in the identical phase III Study 2 (B, D). (Adopted from Ref. 12)

phase III study in which patients aged ⩾18 years (n = 491) with poorly controlled asthma who were unselected for eosinophil count were randomized to treatment with IV reslizumab 3 mg/kg or to placebo every 4 weeks for 16 weeks.[13] Predictably, because of the lack of patient selection in terms of baseline eosinophilia, reslizumab did not achieve statistically significant improvements in endpoints. However, in a subgroup of patients with blood eosinophils ⩾400 cells/μL at baseline (n = 96) reslizumab achieved a significantly greater improvement in FEV1 compared with placebo (0.272 versus 0.002 L, respectively; P = 0.0436).

Adverse reaction

Eligible patients who had participated in one of the phase III reslizumab studies were given the option to enter a long-term, open-label extension study in which they received reslizumab 3 mg/kg IV once every 4 weeks for up to 2 years. Of the 1,052 patients who were enrolled in the study, overall 237 patients received ⩾24 months of reslizumab treatment. Long-term (up to 24 months) safety data indicated that reslizumab was generally well tolerated by patients with asthma. The most common AEs (occurring in >5% of patients) were nasopharyngitis, URTI, sinusitis, bronchitis, and headache. SAEs were reported in 7% of prior reslizumab-naïve and 7% of prior reslizumab-experienced patients; study withdrawal due to an AE occurred in 1% and 2% of patients, respectively. Headache was the only AE assessed by investigators to be treatment related that occurred in >1% of patients (incidence 2%). Three deaths were reported during the study but all were considered unrelated to study treatment.[14]

Predicting response to reslizumab

Among patients with eosinophilic asthma there are some specific subgroups in whom reslizumab has been shown to be particularly effective and for whom reslizumab may be considered as the preferred add-on option, based on response rates in clinical trials.

IL-5 is the predominant cytokine in nasal polyposis associated with tissue eosinophilia, promoting the activation and prolonged survival of eosinophils.[15] Nasal polyposis is a hallmark of eosinophilic disease in patients with asthma, and available evidence suggests that the presence of nasal polyps may aid identification of a subset of patients with uncontrolled, eosinophilic asthma who are highly likely to benefit from anti-IL-5 therapy. A *post-hoc* analysis to evaluate the effect of reslizumab on clinical asthma exacerbations in patients with chronic sinusitis with or without nasal polyps enrolled in two of the phase III reslizumab studies.[16] Reslizumab therapy was associated with a reduction of 83% in the annual rate of clinical asthma exacerbations versus placebo in patients with nasal polyps [RR 0.17 (95% CI, 0.10, 0.32); P = 0.0002] and a reduction of 70% in patients with CS without nasal polyps [RR 0.30 (95% CI, 0.20, 0.44);

P = 0.0103].

Asthma severity as defined by Global Initiative for Asthma (GINA) guidelines17 may also be a predictor of response to reslizumab. Preliminary data from post-hoc subgroup analyses of data from patients enrolled in the phase III studies have reported a highly beneficial effect of reslizumab in terms of improvement compared with placebo in asthma exacerbation rate, lung function, asthma symptoms, and patient-reported asthma control and quality of life in subgroups of patients with GINA Step 4 and Step 5 categories of asthma severity.[18]

Older age may also be a predictor of good response. In another analysis of the pooled data, Bernstein and colleagues evaluated the efficacy of reslizumab in older (age ⩾65 years, n = 77) versus younger adults (age 18-64 years, n = 851). Reductions in the frequency of asthma exacerbations per patient during the treatment period were numerically larger with reslizumab versus placebo in older compared with younger adults [older: 67% reduction (RR 0.33, 95% CI, 0.15, 0.71); younger: 53% reduction (RR 0.47, 95% CI, 0.36, 0.60)], with similar findings also reported for other endpoints, including FEV1.[19]

Preliminary data presented recently from a further *post-hoc* analysis of the phase III trials also provide potential opportunities for the development of strategies to enable early prediction of the long-term beneficial effect of reslizumab therapy. This analysis investigated the rate of asthma exacerbations in patients who demonstrated an early FEV1 response (defined as ⩾100 ml) or early ACQ response up to week 16 (n = 953). In this population, patients who demonstrated a response to reslizumab before 16 weeks (FEV1 and/or ACQ) had a greater improvement in clinical asthma exacerbation rate relative to placebo after 52 weeks than patients who did not respond according to either criterion by week 16 (59–76% versus 26–31% reduction relative to placebo).[20] An algorithm using changes in clinical variables from baseline to week 16 of reslizumab treatment has been developed recently to predict response at week 52 and guide the continuation of therapy for patients with inadequately controlled eosinophilic asthma.[21]

Conclusions

The introduction to the clinic of anti-IL5 treatments represents a new direction in asthma treatment, with reslizumab demonstrating good efficacy and safety profiles in appropriately selected patient populations. Strategies to enable identification of patients most responsive to IL5 pathway inhibitors, and thereby ensuring assignment of treatment to the correct patients, are highly dependent on the validation of existing biomarkers, and also the development of new biomarkers for the IL5 pathway. Important questions that are still unanswered at present include time to relapse, optimal duration of treatment, effects on airway remodeling, and clinical profile in children and teenagers with asthma. Continued investigations over the next few years will be needed to provide answers to at least some of these questions.

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