

RESLIZUMAB: MAINTENANCE TREATMENT FOR EOSINOPHILIC ASTHMA INADEQUATELY CONTROLLED ON CORTICOSTEROIDS

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SUMMARY

The starting point for this drug was the growing realization that eosinophils appeared to be associated with a severe form of asthma in which patients were subject to exacerbations of their condition that could not be adequately managed using inhaled and/or oral corticosteroids. Studies of the pathophysiology of eosinophils revealed that they produce many bioactive compounds that contribute to the pathophysiology of a number of diseases including

asthma. Interleukin-5 (IL-5) in particular is an important factor in some forms of severe asthma. A rat antibody to IL-5 (39D10) was humanized producing the product now know as reslizumab. However, initial studies of this antibody in patients with asthma were unsuccessful. It was only when the importance of the eosinophilic asthma endotype was recognized that reslizumab was found to indeed reduce the severity and exacerbations of asthma in patients who were inadequately treated by inhaled and/or oral corticosteroids. These studies have determined that reslizumab is a valuable drug for the management of such patients provided that they have an eosinophil count of > 400 cells/ μ L. Because a very small percentage of

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patients receiving reslizumab may experience anaphylaxis, reslizumab must be only given in a facility with adequate facilities and by a health professional trained in the management of anaphylaxis.

Key words: Reslizumab – Bronchial asthma – Maintenance treatment – Eosinophils – Interleukin-5 – Anaphylaxis

BACKGROUND

Asthma is a common chronic disease of the airways in which functional, inflammatory and structural changes cause hyper-responsiveness of the bronchi and reversible reduction in expiration. It has become apparent that asthma is not a disease with a uniform etiology but that different asthma phenotypes can be differentiated (1, 2). When a known pathophysiological mechanism is added to a phenotype it is known as endotyping (2). An example of this is in severe asthma when there are recurrent exacerbations despite the use of corticosteroids and some patients have an increased number of eosinophils in the sputum and the blood; this is referred to as eosinophilic asthma or endotype (1, 2). Such patients have severe asthma and are not adequately controlled by long-acting bronchodilators and corticosteroids.

There are fewer than 350 eosinophils per milliliter of blood in a normal blood sample reading. A recent review has detailed advances in the understanding of the contents and the actions of eosinophils in health and disease (3). These cells are packed with a large number of biologically active compounds that are involved in allergic inflammation, fibrosis and thrombosis. Eosinophils also possess a large number of surface receptors including receptors for cytokines, chemoattractants, Fcs and inhibitory compounds, for pattern recognition and adhesion, and for lipid mediators (3). Not surprisingly, they respond to many compounds produced and released by other cells, and also affect the biology of numerous other cells, thus contributing to the pathophysiology of a number of diseases.

Eosinophils not only are a major source of interleukin-5 (IL-5) but they also respond to IL-5 themselves (3). IL-5 has a major role in the differentiation of eosinophils in the bone marrow and in their recruitment and activation at sites of allergic inflammation. There is now considerable evidence that eosinophil-related inflammation characterizes the eosinophilic asthma phenotype, in which patients present severe chronic asthma that is not adequately relieved by corticosteroids. In such patients, the sputum and blood contain an elevated number of

eosinophils (1-3). Because of the importance of IL-5 in the biology of eosinophils, the development of IL-5 monoclonal antibodies presented itself as a likely avenue for the more selective treatment of patients with severe, chronic eosinophilic asthma. This approach has now been extensively reviewed (3-8). It is important to note that genetically manipulated mice that totally lack eosinophils do not display any distinctive syndrome or failure of their health (9). This suggests that IL-5 monoclonal antibodies are unlikely to cause undesired health problems.

PREPARATION OF AN INTERLEUKIN-5 ANTIBODY

IL-5 binds to a heterodimer receptor complex composed of α and β subunits. The α subunit accounts for IL-5 binding, while the β subunit is essential for the formation of the high-affinity receptor complex and for signal transduction. While antibodies can be produced in rats or mice, they have the drawback of potential allergenicity in humans. This possibility can be minimized by the 'humanization' of such antibodies. Cook et al. (10, 11) have described how a rat monoclonal Fab (JES1-39D10) was humanized; to facilitate this effort, they determined the X-ray crystal structure of JES1-39D10. It was found that to maintain high affinity for the IL-5 receptor, four residues had to be preserved as either all human or all animal. 39D10 was humanized using complementarity determining region grafting technology into a human framework with a κ light chain and a $\gamma 4$ constant region. This humanized antibody was shown to retain the potency of 39D10 for blocking the IL-5 receptor and was designated SCH-55700. It was subsequently given the generic name reslizumab, which is indeed a humanized IgG4 κ antibody.

It was subsequently found (12) that a small region, ERRR, corresponding to amino acids 89-92 of IL-5, was critical for both SCH-55700 and 39D10 to specifically interact with IL-5. Single mutations of E⁸⁹, R⁹⁰, R⁹¹ or R⁹² to alanine caused a loss of binding to both 39D10 and SCH-55700. E⁸⁹, R⁹⁰ and R⁹¹ were shown to be involved in the interaction between IL-5 and its α subunit. Zhang et al. (12) proposed a model in which several ion pair interactions are involved in the interactions between IL-5 and SCH-55700.

A method was developed to measure the kinetic interactions of SCH-55700 and native human IL-5 using surface plasmon resonance (13). Using this method the association rate constant (k_a) and the dissociation rate constant (k_d) for the first site binding were found to be 2.74×10^5 (M⁻¹ s⁻¹) and 2.26 (s⁻¹), respectively.

PRECLINICAL EFFECTS

In vitro, SCH-55700 had high affinity binding to hIL-5 ($K_d = 20$ pmol/L), inhibited the binding of hIL-5 to Ba/F3 cells ($IC_{50} = 0.5$ nmol/L) and blocked IL-5-mediated proliferation of human erythroleukemic TF-1 cells (14). In allergic mice, SCH-55700 (0.1-10 mg/kg i.p. or i.m.) inhibited the influx of eosinophils in the lungs and had a long duration of activity. Furthermore, the anti-inflammatory activity of this compound was additive to that of oral prednisolone. In allergic guinea pigs, SCH-55700 (0.03-30 mg/kg i.p.) inhibited both the pulmonary eosinophilia and airway hyper-responsiveness, while at 30 mg/kg i.p. it inhibited allergic, but not histamine-induced bronchoconstriction. In allergic rabbits, SCH-55700 blocked cutaneous eosinophilia. The drug (0.1-1 mg/kg i.p.) also blocked the pulmonary eosinophilia and neutrophilia caused by tracheal injection of hIL-5 in guinea pigs. In allergic cynomolgus monkeys, a single dose of SCH-55700 (0.3 mg/kg i.v.) blocked the pulmonary eosinophilia caused by antigen challenge for up to 6 months. SCH-55700 was thus a potent antibody against IL-5 in vitro, and in a variety of species in vivo (4, 14).

HUMAN PHARMACOKINETICS

The pharmacokinetics of reslizumab was similar in healthy adults, in patients with asthma and in other patient populations (15). Peak serum concentrations were usually observed at the end of the infusion; serum concentrations generally declined from the peak in a biphasic manner. Following multiple doses, reslizumab accumulated approximately 1.5- to 1.9-fold. Reslizumab had a volume of distribution of approximately 5 L, suggesting minimal distribution extravascularly. As with other monoclonal antibodies, reslizumab is degraded by enzymatic proteolysis into small peptides and amino acids. Its clearance was approximately 7 mL/h and it has a half-life of about 24 days.

There was no significant effect of age, race or gender on the pharmacokinetics of reslizumab. There were no significant differences in the pharmacokinetics of reslizumab in patients with normal liver function tests and those with mildly increased liver function tests or those with mild or moderate renal impairment. In vitro drug interactions suggested that IL-5 and reslizumab are unlikely to affect CYP1A2, 2B6 or 3A4 enzyme activity.

CLINICAL STUDIES

Inadequately controlled asthma

In a pilot study published in 2003 (16), the effects of reslizumab were studied in patients with severe persistent

asthma that was not adequately controlled by inhaled and/or oral corticosteroids. At doses of 0.3 mg/kg i.v. reslizumab reduced the number of circulating eosinophils and at a dose of 1.0 mg/kg i.v. this reduction was significant up to 30 days after administration. At doses of 0.3 and 1.0 mg/kg i.v. there was a trend towards improvement in forced expiratory volume in 1 second (FEV_1); however, there were no significant changes in other indices of disease activity.

A randomized, placebo-controlled trial of reslizumab was conducted in patients with inadequately controlled asthma with induced sputum eosinophils of 3% or more and published in 2011 by which time there was much more experience in the use of IL-5 antibodies in severe asthma (17). The subjects had a median eosinophil percentage of 10.0% in the induced sputum sample. Reslizumab (3.0 mg/kg i.v. at baseline and after 4, 8 and 12 weeks) caused a pronounced fall in eosinophils that reached 95% after 12 weeks. There was an improvement in airway function in those receiving reslizumab and this was particularly marked in those subjects who also had nasal polyposis. There were also fewer asthma exacerbations in those on reslizumab.

In 2015 a key publication reported the results of two duplicate, double-blind, parallel-group, placebo-controlled phase III trials (18). Patients with asthma inadequately controlled by inhaled corticosteroids who had had one or more exacerbations in the previous years were studied provided that they had a blood eosinophil count of 400 cells/ μ L or higher. Patients received either reslizumab (3.0 mg/kg i.v.) or placebo every 4 weeks for a year. Overall, 489 patients received reslizumab and 464 placebo.

The results of the study are summarized in Table I. The primary outcome of the studies was the annual frequency of clinical asthma exacerbations. This was very significantly reduced by reslizumab in both studies, the risk being reduced by over 50%. There were also very significant improvements in FEV_1 , Asthma Quality of Life Questionnaire (AQLQ) total score, Asthma Control Questionnaire (Questions 1-7; ACQ-7) score, Asthma Symptom Utility Index (ASUI) score and in the blood eosinophil count.

The efficacy of reslizumab was examined in a double-blind phase III study in patients who had asthma inadequately controlled by inhaled corticosteroids (19). Their blood eosinophil counts were not a factor in their selection for the study. There was a 16-week, double-blind treatment period in which patients received either reslizumab (3.0 mg/kg i.v.) or placebo every 4 weeks. This was followed by a 12-week follow-up period.

Table 1. Efficacy endpoints in patients with asthma treated with intravenous reslizumab (3.0 mg/kg) or placebo every 4 weeks for 1 year.

Parameter	Week 16		Week 52	
	Placebo	Reslizumab	Placebo	Reslizumab
Asthma exacerbations			1.81	0.84
Exacerbations requiring systemic corticosteroids			1.54	0.66
Change in FEV ₁ (L)	0.11	0.23	0.12	0.22
Change in AQLQ score	0.83	0.99	0.81	1.08
Change in ACQ-7 score	-0.67	-0.91	-0.77	-1.02
Change in ASUI score	0.10	0.15	0.12	0.17
Change in blood eosinophil count (cells per µL)	-98	-574	-101	-576

Data from Castro et al. (18). All data are pooled data from the two studies, and are “n” unless otherwise specified. FEV₁, forced expiratory volume in 1 second; AQLQ, Asthma Quality of Life Questionnaire; ACQ-7, seven-item Asthma Control Questionnaire; ASUI, Asthma Symptom Utility Index. Values shown are least-squares mean changes over the specified period from baseline. *P* values in all are < 0.001.

The primary outcome was the change in FEV₁ from baseline to week 16 of treatment. After 16 weeks the mean change in FEV₁ was 255 mL in those on reslizumab and 187 mL in those on placebo. This difference was not significant. In patients with an eosinophil count of < 400 cells/µL the effect on FEV₁ was even less marked being 247 mL in those on reslizumab and 215 mL on placebo. However, in patients with an eosinophil count of > 400 cells/µL, reslizumab had a significant effect increasing FEV₁ by 272 mL compared to 2 mL in those on placebo. Treatment with reslizumab had no effect on ACQ-7.

In a randomized, double-blind, placebo-controlled phase III trial the effect of reslizumab was studied in patients with asthma inadequately controlled on inhaled corticosteroids (20). To be included in the study patients had to have an eosinophil count of > 400 cells/µL. There was a 16-week, double-blind treatment period in which patients received either reslizumab (0.3 or 3.0 mg/kg i.v.) or placebo every 4 weeks, followed by a 4-week follow-up period.

The primary endpoint was the change in FEV₁. This was significantly greater than in those on placebo, the increase being 115 mL and 160 mL in those on reslizumab 0.3 and 3.0 mg/kg, respectively. The dose of 3.0 mg/kg reslizumab produced significant changes in forced vital capacity (FVC), ACQ, AQLQ and ASUI and reduced the eosinophil count by 494 cells/µL. The dose of 0.3 mg/kg produced changes in the same direction. However, the

effect was always less marked and did not always reach significance.

The authors pointed out that the increase in FVC produced by reslizumab is indicative of a reduction in air trapping and recruitment of peripheral airways and that it suggests that a higher dose of reslizumab may be needed to treat active eosinophilic inflammation in the peripheral airways. They also point out that the improvement in ACQ-6 was comparable to that in ACQ-7, suggesting that the observed improvements in asthma control were not driven by FEV₁ improvement alone.

The efficacy of reslizumab in inadequately controlled asthma has been studied in patients with eosinophil counts of > 400 cells/µL, the aim being to determine whether the drug was as effective in those over 65 years of age compared to those from 18-64 years of age (21). It was found that reslizumab was in fact more effective in the older age group in terms of asthma exacerbations, FEV₁, ACQ-7 and AQLQ.

Hypereosinophilic syndrome

In 2003, four patients with hypereosinophilic syndrome who were refractory to conventional treatment were treated with a single 1.0 mg/kg i.v. dose of reslizumab (22). Two patients experienced a fall in their eosinophilia and a marked improvement in their clinical signs and symptoms. Their eosinophil counts remained suppressed for up to 12 weeks. Subsequent monthly treatment with reslizumab resulted in decreased eosinophilia and some

improvement in their signs and symptoms though less marked than the response to the first dose of reslizumab.

Eosinophilic esophagitis

A study was conducted in patients aged 5 to 18 years with active eosinophilic esophagitis with documented biopsy evidence showing at least 24 eosinophils in 1 high-power field (hpf) (23). Eligible patients could continue the treatment they were already taking and were given intravenous infusions of 1.0, 2.0 or 3.0 mg/kg reslizumab or placebo every 28 ± 7 days for a total of four doses. For the overall group of 226 patients the median number of eosinophils was 80.0/hpf. All three doses of reslizumab reduced the esophageal eosinophil count. However, there was no difference in the response to therapy as judged by the physician's eosinophilic esophagitis global assessment scores. There were also no significant differences between the reslizumab and placebo groups in the predominant symptom assessment scores or the Children's Health Questionnaire.

ADVERSE EVENTS

Data on adverse events are taken from the manufacturer's Prescribing Information (15). Overall, 2,195 subjects received at least 1 dose of reslizumab. The data reported by the manufacturer reflect exposure to reslizumab in 1,611 patients with asthma.

Anaphylaxis to reslizumab was reported in 0.3% of asthma patients in placebo-controlled clinical studies. These events were observed during or within 20 minutes after completion of the infusion of reslizumab and were reported as early as the second dose of reslizumab.

In placebo-controlled clinical studies, 0.6% of patients receiving 3 mg/kg reslizumab had at least one malignant neoplasm reported compared to 0.3% of patients in the placebo group. The observed malignancies in reslizumab-treated patients were diverse in nature and without clustering of any particular tissue type.

Because eosinophils may be involved in the immunological response to some helminth infections, patients with known parasitic infections were excluded from participation in clinical studies. It is unknown if reslizumab will influence the immune response against parasitic infections.

Adverse reactions that occurred at a greater than or equal to 2% incidence and more commonly than in the placebo group included oropharyngeal pain (2.6 vs. 2.2%). Transient creatine phosphokinase (CPK) elevations in

patients with normal baseline CPK values were observed more frequently with reslizumab (20%) than placebo (18%) during routine laboratory assessments. CPK elevations $> 10 \times$ ULN, regardless of baseline CPK value, were 0.8% in the reslizumab group compared to 0.4% in the placebo group. These elevations were asymptomatic and did not lead to treatment discontinuation. Myalgia was reported in 1% of patients receiving reslizumab compared to 0.5% receiving the placebo.

A treatment-emergent anti-reslizumab antibody response developed in 5.4% of reslizumab-treated patients. There was no detectable impact of the antibodies on the clinical pharmacokinetics, pharmacodynamics, clinical efficacy and safety of reslizumab.

PRECAUTIONS WHEN ADMINISTERING RESLIZUMAB

Anaphylaxis to reslizumab was reported in 0.3% of asthma patients in placebo-controlled clinical studies. These events were observed during or within 20 minutes after completion of an infusion of reslizumab and occurred as early as the second dose. Because anaphylaxis can be life-threatening, reslizumab should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis, and patients should be observed for an appropriate period of time after administration of the drug (15).

RESLIZUMAB APPROVAL

The U.S. Food and Drug Administration approved reslizumab on March 23, 2016, for use in patients aged 18 years and older who have a history of severe asthma attacks or exacerbations despite receiving their current asthma medicines (24). In the United Kingdom reslizumab is available only to registered users. The European Medicines Agency's Committee for Medicinal Products for Human Use recently issued a positive opinion recommending approval of reslizumab (25).

CONCLUSIONS

Reslizumab is clearly a valuable drug for those patients who are inadequately treated by the combination of inhaled bronchodilators and corticosteroids taken either by inhalation or orally. However, the drug should only be expected to be effective in such patients who also have the eosinophilic endotype as demonstrated by an eosinophil count of not less than 400 cells/ μ L.

The drug must also always be administered by a health professional with the necessary facilities and with training in the provision of emergency treatment of anaphylaxis should this be required. Apart from the possibility of a severe allergic response, other adverse events are not common.

DISCLOSURES

The author states no conflicts of interest.

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