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Reslizumab in the treatment of severe eosinophilic asthma: an update

Garry M Walsh*,¹

¹School of Medicine, Medical Sciences & Nutrition, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK

*Author for correspondence: Tel.: +44 (0) 774 776 1204; g.m.walsh@abdn.ac.uk

A marked heterogeneity is exhibited by asthma both clinically and at the molecular level with different phenotypes driven by diverse mechanistic pathways that require specifically targeted treatments. Biologics aimed at IL-4/13, IL-5 or IgE are proven or potentially effective treatments for patients with difficult to treat eosinophilic asthma. Importantly, it is now widely accepted that biologic-based therapies give significant clinical improvements in those patient populations where asthma phenotypes are taken into account. Such asthma phenotypes have been identified by reproducible and straightforward discriminatory biomarkers. This short review discusses recent studies of the effectiveness of the anti-IL-5 reslizumab in relation to the use of simple reproducible biomarkers in eosinophilic asthma.

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Asthma is a chronic inflammatory airways disorder that represents a major cause of ill-health worldwide [1] characterized by patterns of clinical severity from very mild and occasional symptoms to recurrent significant exacerbations that, in a small number of patients, can result in a fatal or near-fatal outcome. Severe or refractory disease is seen in approximately 5% of asthmatic subjects who fail to achieve satisfactory symptom control despite adherence to high-dose inhaled glucocorticoid therapies giving rise to significant morbidity, quality of life issues and health cost implications [2], representing a clear unmet medical need. Our understanding of the processes that underlie asthma is now considerable, involving diverse patterns of cytokine-based inflammatory processes controlling the recruitment and function of T cells, B cells, mast cells, eosinophils, basophils, neutrophils and dendritic cells, with significant contributions from structural cells such as epithelial, smooth muscle and mesenchymal cells. Such knowledge has informed the development of antibody-based biological therapies that target the type 2 cytokines IL-4, IL-5 and IL-13, all of which play key roles in the inflammatory processes underlying asthma [3]. It is increasingly accepted that significant clinical effects with anticytokine-based biologic therapies are more likely in carefully selected patient populations that take asthma phenotypes into account that in turn rely on straightforward discriminatory biomarkers, such as an elevated blood eosinophilia, targeting those most likely to benefit from treatment with these expensive interventions [4–6].

There is a long-recognized association between asthma pathogenesis and eosinophils. The latter can release their arsenal of diverse pro-inflammatory mediators that include granule-derived basic proteins, lipid mediators, cytokines and chemokines. These potentiate airway inflammation and contribute to lung tissue remodeling characterized by airway thickening, fibrosis and angiogenesis [7,8]. Approximately half of patients with asthma exhibit evidence of eosinophilic inflammation [9,10]. Compared with patients with non-eosinophilic asthma, those patients with severe disease and an eosinophilic phenotype suffer increased rates of disease exacerbation, impaired lung function, poorer symptom control and lower quality of life. Importantly, increased frequency and severity of clinical asthma exacerbations and unsatisfactory control of symptoms have a proven association with blood eosinophil counts ≥ 400 cells/ml [11]. IL-5 is central to the maturation and release of eosinophils from the bone marrow and their accumulation, activation and persistence in the tissues, thereby providing a rational target to prevent or blunt eosinophil-mediated inflammation. A number of anti-IL-5 biologics have been developed, namely mepolizumab (Nucala[®]) [12,13] and reslizumab (Cinqaero[®]) [14,15] together with benralizumab, an mAb against human IL-

5R α [16,17]. These all target eosinophilic inflammation, and when used as adjunctive therapy to glucocorticoids have proven beneficial effects in patients with severe or refractory disease, further supporting an important role for eosinophils in the pathology of asthma. This review is based on recent English-language original articles in Pub Med or MedLine that reported recent significant clinical findings with reslizumab in the treatment of severe disease with an eosinophilic phenotype.

Reslizumab

Reslizumab is an IL-5 neutralizing IgG4K mAb humanized from a rat anti-IL-5 antibody (JES1-39D10), approved for use as add on maintenance therapy for adults with severe eosinophilic asthma [14,15]. In early preclinical studies, reslizumab was reported to be effective in a number of animal models that featured eosinophilic inflammation [18,19]. One early Phase II, multicenter, randomized, placebo-controlled trial [20] in patients with poorly controlled eosinophilic asthma reported significant improvements in asthma symptoms in a subgroup of patients with concomitant nasal polyposis, a hallmark of eosinophilic disease in patients with asthma [21]. Two parallel large multicenter, double-blind Phase III trials found that reslizumab treatment reduced exacerbations, improved FEV1, forced vital capacity, the 7-item Asthma Control Questionnaire and use of rescue short-acting β 2-agonists in subjects with poorly controlled disease who had one or more exacerbations treated with systemic glucocorticoids during the previous year together with a blood eosinophil count greater than 400 cells/ml [22]. Similar findings were reported in a Phase III study [23] with 492 patients with poorly controlled asthma treated with 3.0 mg/kg of intravenous reslizumab every 4 weeks a period of 16 weeks ($n = 395$) or placebo ($n = 97$). In those patients with eosinophil counts greater than 400 cells/ml, reslizumab treatment significantly increased mean FEV1. Another study [24] assessed the effects of two doses of reslizumab (0.3 and 3.0 mg/kg for 16 weeks) in 311 patients with persistent asthma not adequately controlled by inhaled glucocorticoids with levels of blood eosinophils ≥ 400 cells/ml. In contrast, there was no significant improvement in FEV1 in patients with fewer than 400 eosinophils/ml. Both dosages of reslizumab improved symptom control evaluated through Asthma Control Questionnaire score and decreased use of inhaled rescue medications with significant reductions in blood eosinophil counts.

The development of late-onset asthma in adulthood is considered to be a particularly difficult-to-treat subgroup of the severe asthma population and it has distinctive biological and phenotypic characteristics compared with the early onset asthma that develops in childhood [25]. A *post hoc* analysis evaluated reslizumab in patients with late-onset eosinophilic asthma and poorly controlled symptoms. These authors reported [26] that reslizumab treatment (3 mg/kg every 4 weeks) gave significantly greater reductions in asthma exacerbations and superior improvements in lung function in patients with late-onset asthma (reslizumab, $n = 143$, placebo, $n = 130$) compared with early-onset asthma (reslizumab, $n = 322$, placebo, $n = 336$). They concluded that this approach seemed to identify a reslizumab-responsive late-onset asthma subgroup from the overall population, although they also acknowledged that prospective controlled studies are required to confirm their observations.

Another important issue relates to optimal duration and long-term effects of treatment with reslizumab. A recent international, multi-center, nonrandomized open-label extension study obtained long-term safety data for reslizumab (3.0 mg/kg IV) administered once every 4 weeks for up to an additional 2 years in adolescent and adult patients with moderate-to-severe eosinophilic asthma [27]. The positive treatment effects of reslizumab on lung function and asthma control reported in previous clinical studies were sustained for up to an additional 2 years in subjects previously treated with reslizumab. At the first on-treatment assessment at 4 weeks, a significant improvement in FEV1 was seen in the reslizumab-naïve group that was sustained over 96 weeks. The FEV1 improvement observed in the reslizumab-experienced patients during previous double-blind treatment was maintained throughout the open-label period with similar trends observed in FVC and FEF25–75 over 96 weeks.

There were no significant concerns, including incidents of anaphylaxis, associated with prolonged reslizumab treatment, further supporting the use of this biologic for long-term control of moderate-to-severe asthma in patients with an eosinophilic phenotype.

Conclusion

Overall the evidence summarized above supports the use of anti-IL5 treatments as an adjunct therapy to standard of care in patients with severe eosinophilic asthma who experience poor control of their symptoms. In terms of efficacy, reslizumab treatment roughly halved the rate of asthma exacerbations with some evidence for improved HR quality of life scores and lung function. To date, there appear to be no significant safety concerns regarding reslizumab use compared with placebo [28].

Future perspective

Biologic therapies aimed at reducing blood and tissue eosinophils, such as mepolizumab, reslizumab and benralizumab may benefit patients with severe eosinophilic asthma. The main limitations of asthma treatment with these biologics are high costs together with crossover and overlap of the different pathways in asthma pathogenesis, thus the complete success of treatment with these therapies remains questionable. To date there is a lack of studies comparing different anti-IL-5 treatments to each other and with the anti-IgE biologic omalizumab. Finally, more studies are required to more clearly identify the ideal target patient population to receive these biologic drugs.

Executive summary

Efficacy

- Reslizumab is efficacious in patients with specific phenotypes of severe asthma characterized by persistent, glucocorticoid-resistant eosinophilia receiving therapy according to GINA Step 4 and 5.
- Reslizumab reduces exacerbation rates and improves lung function and patient-reported outcomes.
- There is a requirement for further research on biomarkers that would aid the assessment of response to reslizumab treatment.

Safety

- There appear to be no significant safety concerns regarding reslizumab treatment.

Conclusion

- Real world information is required on optimal duration and long-term effects of treatment together with the risk of relapse on withdrawal.
- There is a paucity of information on the use of reslizumab in children with asthma under 12 years.

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Company review

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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