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# **Anti-IL5 therapies for asthma (Review)**

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#### [Intervention Review]

# Anti-IL5 therapies for asthma

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#### **ABSTRACT**

#### **Background**

This review is the first update of a previously published review in The Cochrane Library (Issue 7, 2015). Interleukin-5 (IL-5) is the main cytokine involved in the activation of eosinophils, which cause airway inflammation and are a classic feature of asthma. Monoclonal antibodies targeting IL-5 or its receptor (IL-5R) have been developed, with recent studies suggesting that they reduce asthma exacerbations, improve health-related quality of life (HRQoL) and lung function. These are being incorporated into asthma guidelines.

### **Objectives**

To compare the effects of therapies targeting IL-5 signalling (anti-IL-5 or anti-IL-5Rα) with placebo on exacerbations, health-related qualify of life (HRQoL) measures, and lung function in adults and children with chronic asthma, and specifically in those with eosinophilic asthma refractory to existing treatments.

#### **Search methods**

We searched the Cochrane Airways Trials Register, clinical trials registries, manufacturers' websites, and reference lists of included studies. The most recent search was March 2017.

#### **Selection criteria**

We included randomised controlled trials comparing mepolizumab, reslizumab and benralizumab versus placebo in adults and children with asthma.

#### **Data collection and analysis**

Two authors independently extracted data and analysed outcomes using a random-effects model. We used standard methods expected by Cochrane.

#### **Main results**

Thirteen studies on 6000 participants met the inclusion criteria. Four used mepolizumab, four used reslizumab, and five used benralizumab. One study in benralizumab was terminated early due to sponsor decision and contributed no data. The studies were predominantly on people with severe eosinophilic asthma, which was similarly but variably defined. Eight included children over 12 years but these results were not reported separately. We deemed the risk of bias to be low, with all studies contributing data being of robust methodology. We considered the quality of the evidence for all comparisons to be high overall using the GRADE scheme, with the exception of intravenous mepolizumab because this is not currently a licensed delivery route.



All of the anti-IL-5 treatments assessed reduced rates of 'clinically significant' asthma exacerbation (defined by treatment with systemic corticosteroids for three days or more) by approximately half in participants with severe eosinophilic asthma on standard of care (at least medium-dose inhaled corticosteroids (ICS)) with poorly controlled disease (either two or more exacerbations in the preceding year or Asthma Control Questionnaire (ACQ) 1.5 or more). Non-eosinophilic participants treated with benralizumab also showed a significant reduction in exacerbation rates, but no data were available for non-eosinophilic participants, and mepolizumab or reslizumab.

We saw modest improvements in validated HRQoL scores with all anti-IL-5 agents in severe eosinophilic asthma. However these did not exceed the minimum clinically important difference for ACQ and Asthma Quality of Life Questionnaire (AQLQ), with St. George's Respiratory Questionnaire (SGRQ) only assessed in two studies. The improvement in HRQoL scores in non-eosinophilic participants treated with benralizumab, the only intervention for which data were available in this subset, was not statistically significant, but the test for subgroup difference was negative.

All anti-IL-5 treatments produced a small but statistically significant improvement in mean pre-bronchodilator forced expiratory flow in one second (FEV<sub>1</sub>) of between 0.08 L and 0.11 L.

There were no excess serious adverse events with any anti-IL-5 treatment, and indeed a reduction in favour of mepolizumab that could be due to a beneficial effect on asthma-related serious adverse events. There was no difference compared to placebo in adverse events leading to discontinuation with mepolizumab or reslizumab, but significantly more discontinued benralizumab than placebo, although the absolute numbers were small (36/1599 benralizumab versus 9/998 placebo).

Mepolizumab, reslizumab and benralizumab all markedly reduced blood eosinophils, but benralizumab resulted in almost complete depletion, whereas a small number remained with mepolizumab and reslizumab. The implications for efficacy and/or adverse events are unclear.

#### **Authors' conclusions**

Overall our study supports the use of anti-IL-5 treatments as an adjunct to standard of care in people with severe eosinophilic asthma and poor control. These treatments roughly halve the rate of asthma exacerbations in this population. There is limited evidence for improved HRQoL scores and lung function, which may not meet clinically detectable levels. There were no safety concerns regarding mepolizumab or reslizumab, and no excess serious adverse events with benralizumab, although there remains a question over adverse events significant enough to prompt discontinuation.

Further research is needed on biomarkers for assessing treatment response, optimal duration and long-term effects of treatment, risk of relapse on withdrawal, non-eosinophilic patients, children (particularly under 12 years), and comparing anti-IL-5 treatments to each other and, in people eligible for both, to anti-immunoglobulin E. For benralizumab, future studies should closely monitor rates of adverse events prompting discontinuation.

# PLAIN LANGUAGE SUMMARY

Mepolizumab, reslizumab or benralizumab for people already taking inhaled steroids and long-acting beta<sub>2</sub>-agonists for their asthma

# **Review question**

We considered in this review whether taking the new drugs mepolizumab, reslizumab or benralizumab in addition to standard treatment (e.g. inhaled steroids and combination inhalers) are better than a placebo for people with asthma.

#### **Background**

Asthma is an inflammatory lung condition characterised by the narrowing of the airways, breathlessness, a tight chest and reduced quality of life. By the year 2025, there may be up to 400 million people with asthma worldwide. Mepolizumab, reslizumab and benralizumab are new 'anti-IL-5' treatments that may help to reduce asthma symptoms.

#### **Study characteristics**

Thirteen studies compared mepolizumab, reslizumab or benralizumab to a placebo in 6000 people with asthma, most with severe disease. We summarised the results as they related to the occurrence of asthma attacks requiring additional treatment, quality of life, breathing tests, effects on a blood biomarker, and side effects.

#### **Key results**

We found that participants with severe asthma, who had high numbers of a certain type of inflammatory cell (eosinophils) in the blood, benefited from taking mepolizumab, reslizumab or benralizumab through reduced asthma attacks. There were small improvements in quality of life and breathing tests, but these may be too small to be detected by patients. We agree with international guidelines that



say that these treatments can be added to standard treatment for people with severe asthma. However, we think that further research is needed to clarify some aspects, such as how to assess treatment response and how long to give treatment for.

# Quality of the evidence

The evidence included in this review is provided by very well-designed studies. We consider these studies to be at low risk of bias in the following important respects: the procedure that determined who received which treatment, the blinding processes and the clarity of detail concerning participants who did not complete the study. Overall the evidence was high to moderate quality.