Benralizumab for the treatment of severe eosinophilic asthma

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Benralizumab (Fasenra) is a new anti-interleukin-5 monoclonal antibody therapy for the management of severe uncontrolled eosinophilic asthma. This article discusses its properties, clinical trial efficacy and adverse effects.

NICE recommends two interleukin-5 (IL-5) inhibitors – mepolizumab and reslizumab – to add to optimised standard therapy for treating severe eosinophilic asthma in adults. Treatment criteria are slightly different, probably reflecting clinical trial methodology and licensed indications rather than clinical practice.

Mepolizumab is an option as add-on therapy for severe refractory eosinophilic asthma in adults if the blood eosinophil count is ≥300 cells/µl in the previous 12 months and the person has adhered to an optimised standard treatment plan and has had four or more exacerbations needing systemic corticosteroids in the previous 12 months or continuous oral corticosteroids equivalent to prednisolone ≥5mg daily over the previous 6 months. Reslizumab is recommended as add-on therapy for severe eosinophilic asthma if the blood eosinophil count has been recorded as ≥400 cells/µl and asthma control is inadequate despite maintenance therapy with high-dose inhaled corticosteroids plus another drug, and the person has had three or more severe exacerbations needing systemic corticosteroids in the past 12 months.

Like its predecessors, benralizumab (Fasenra) is a monoclonal antibody targeted against IL-5 receptors, which are expressed by eosinophils and basophils. It interrupts IL-5 signalling and promotes apoptosis, depleting eosinophils in the blood and airways mucosa. It is licensed as an add-on maintenance treatment in adults with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists. NICE is currently consulting on the use of benralizumab for the treatment of severe eosinophilic asthma, with final guidance expected in December 2018.

**Administration**

Benralizumab is administered by subcutaneous injection at a dose of 30mg every four weeks for the first three doses, then every eight weeks thereafter. This contrasts with mepolizumab (subcutaneous injection every four weeks) and reslizumab (IV infusion every four weeks). Benralizumab requires no dose adjustment for older people or patients with impaired renal or hepatic function; there is no experience of treating children.

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**KEY POINTS**

- Benralizumab is a monoclonal antibody targeted against IL-5 receptors that depletes eosinophils in the blood and airways
- It is licensed as an add-on maintenance treatment in adults with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists
- It is administered by subcutaneous injection at a dose of 30mg every four weeks for three doses, then every eight weeks
- In clinical trials in patients with severe uncontrolled asthma, benralizumab significantly reduced the annual exacerbation rate compared with placebo, and improved lung function and asthma symptoms
- In patients on long-term oral corticosteroids, it allows a median reduction in steroid dose of 75%
- Treatment is generally well tolerated, with headache, pyrexia and fatigue being the most common adverse effects
- Benralizumab costs £1955 per 30mg prefilled syringe
under 12 years old and efficacy in adolescents has not been established.

**Efficacy**

The efficacy of benralizumab in reducing asthma exacerbation has been evaluated in two similar phase 3 trials – the 48-week SIROCCO (n=1205, of whom 809 had eosinophil count ≥300 cells/µl) and the 56-week CALIMA (n=1306, 728 with ≥300 cells/µl). Its steroid-sparing effect was evaluated in a third trial, ZONDA (n=220). In SIROCCO and CALIMA, patients (mean age 49 years) had severe asthma despite using medium- to high-dose inhaled corticosteroids and a long-acting beta₂-agonist, and a history of at least two exacerbations in the previous year. They were randomised to receive, in addition to standard therapy, placebo or benralizumab 30mg subcutaneously either every four weeks or every eight weeks (after the first three doses every four weeks). The primary endpoint was the annualised exacerbation rate (AER) in patients with a baseline eosinophil count of ≥300 cells/µl. An exacerbation was defined as asthma requiring emergency care with systemic steroid treatment or hospital admission.

The (subsequently licensed) eight-week regimen significantly reduced AER compared with placebo in SIROCCO (0.74 vs 1.52; rate ratio 0.49, 95% CI 0.37–0.64, p<0.0001) and CALIMA (0.73 vs 1.01; rate ratio 0.72, 95% CI 0.54–0.95; p=0.0188). This was associated with significant improvements in lung function (pre-bronchodilator FEV₁ increased by a mean of 0.159L and 0.116L respectively) and asthma symptoms. Efficacy was greater among the subgroup of patients experiencing at least three exacerbations per year. Quality of life scores improved with benralizumab in both trials but the increase did not reach the threshold for clinical importance.

In ZONDA, patients taking oral corticosteroids for at least six months were randomised to receive placebo or benralizumab 30mg every four weeks or every eight weeks (with the first three doses every four weeks). The primary endpoint was the reduction in oral steroid dose after 28 weeks while asthma control was maintained. The median reduction in oral steroid dose was 75% with both benralizumab dosage regimens and 25% with placebo (p<0.001). Oral corticosteroids were completely discontinued by 56% and 52% of patients treated with the benralizumab four-weekly and eight-week regimens respectively and by 19% of those assigned to placebo. Benralizumab was associated with a significantly longer time to first exacerbation compared with placebo (hazard ratio for the eight-week regimen 0.32, 95% CI 0.17–0.57; p<0.001).

**Adverse effects**

In SIROCCO and CALIMA, the most frequent adverse events attributed to benralizumab were headache (1.6%), pyrexia (1.0%) and fatigue (0.9%). The incidence of any severe treatment-emergent adverse events, which included asthma and pneumonia, was 10.1% with eight-weekly benralizumab and 10.7% with placebo. The incidence of hypersensitivity reactions was similar in all treatment arms; injection site reactions were slightly more frequent with eight-weekly benralizumab than placebo (2.2% vs 1.9%). In ZONDA, the incidence of serious adverse events was 10% with both benralizumab regimens and 19% with placebo.5

**References**


**Declaration of interests**

None to declare.

Steve Chaplin is a medical writer specialising in therapeutics.