NEW DRUGS

New drugs

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Benralizumab

Approved indication: asthma

Fasenra (AstraZeneca)
pre-filled syringe containing 30 mg in 1 mL
Australian Medicines Handbook section 19.1.6

Benralizumab is a humanised IgG1 monoclonal antibody. It is indicated as an add-on therapy for people with severe eosinophilic asthma aged 12 years and over. It binds to the interleukin-5 receptor which is expressed on eosinophils and basophils. Antibody binding leads to apoptosis of these cells through cell-mediated cytotoxicity and aims to reduce eosinophilic inflammation.

The approval of benralizumab is based on three main placebo-controlled trials. The SIROCCO[1] and CALIMA[2] trials assessed the effect of benralizumab on asthma exacerbations over 48 and 56 weeks respectively. A third trial – ZONDA[3] – investigated whether benralizumab reduced the need for oral corticosteroids over 28 weeks.

The SIROCCO and CALIMA trials enrolled people (aged 12 and over) who had asthma requiring high-dose inhaled corticosteroids plus long-acting beta agonists (with or without oral corticosteroids). They must have had at least two exacerbations in the previous year requiring systemic corticosteroids or an increase in their usual dose of oral corticosteroids. Participants were given subcutaneous benralizumab 30 mg every four weeks, or every four weeks for the first three doses then every eight weeks, or placebo. The primary outcome was the annual exacerbation rate at the end of treatment. In patients with a baseline blood eosinophil count of at least 300 cells/microlitre (≥0.3 x 10^9/L), both trials found that benralizumab significantly reduced the exacerbation rate and improved the forced expiratory volume in one second (FEV_1) compared to placebo (see Table).[1,2]

In a pooled analysis of the two studies looking at predictors of treatment response, lower baseline blood eosinophil counts (less than 300 cells/microlitre or <0.3 x 10^9/L) and age less than 18 years seemed to be associated with a poorer response to benralizumab treatment.[4]

The ZONDA trial enrolled adults with severe asthma who had been taking high-dose inhaled corticosteroids plus long-acting beta agonists

Table **Efficacy of benralizumab in severe eosinophilic asthma**

Trial (duration)	Annual exacerbation rate	FEV_1 change from baseline (L)
SIROCCO (48 weeks)		
Placebo	1.33 (267 patients)	0.239 (233 patients)
Benralizumab (every 4 weeks)	0.73 (275 patients)	0.345 (236 patients)
Benralizumab (every 8 weeks)	0.65 (267 patients)	0.398 (235 patients)
CALIMA (56 weeks)		
Placebo	0.93 (248 patients)	0.215 (244 patients)
Benralizumab (every 4 weeks)	0.60 (241 patients)	0.340 (238 patients)
Benralizumab (every 8 weeks)	0.66 (239 patients)	0.330 (238 patients)

Subcutaneous injections of benralizumab 30 mg were added to patients' usual therapy of high-dose inhaled corticosteroids plus long-acting beta agonists.
Participants in the analysis had blood eosinophil counts of at least 300 cells/microlitre (≥0.3 x 10^9/L) at baseline. (The normal reference range for blood eosinophils is around 0–0.6 x 10^9/L.)
FEV_1 forced expiratory volume in 1 second
Source: references 1, 2

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

and oral corticosteroids for at least six months.[3] Participants had a median baseline blood eosinophil count of 437–535 cells/microlitre (0.44–0.54 x 10^9/L). As with the other trials, they were randomised to subcutaneous benralizumab 30 mg every four weeks (72 patients) or every four weeks for the first three doses then every eight weeks (73 patients), or placebo (75 patients). The trial period was preceded by an eight-week run-in phase (–8 to 0 weeks) to establish the minimum oral corticosteroid dose for each participant. This was followed by an induction phase of four weeks (0 to 4 weeks) in which patients continued to receive their established corticosteroid dose, then a dose-reduction phase of 20 weeks (4 to 24 weeks) in which the oral corticosteroid dose was gradually reduced at regular intervals. This was followed by a four-week dose maintenance phase (24 to 28 weeks).

At 28 weeks, the median reduction in the oral corticosteroid dose was 75% in those given benralizumab (every 4 or 8 weeks) compared with 25% in those who were given placebo. Of those taking a 12.5 mg daily dose of corticosteroid or less at baseline, more people in the benralizumab groups were able to stop their corticosteroid dose than people in the placebo group: 56% (22/39, 4-weekly dosing) and 52% (22/42, 8-weekly dosing) versus 19% (8/42, placebo). The corresponding annual asthma exacerbation rates at the end of the trial were 0.83 and 0.54 versus 1.83. Improvements in FEV_1 were significantly higher with benralizumab than with placebo at 20 weeks. However, by 28 weeks, there was no significant difference between groups.[3]

The most common adverse events with benralizumab in the exacerbation trials included headache (8.6%), pharyngitis (4%), arthralgia (3.9%) and cough (3.3%). They all occurred more frequently with benralizumab than with placebo. Injection-site reactions were reported in 2.2% of those receiving eight-weekly benralizumab and 1.9% of those receiving placebo. Similar results were seen in the ZONDA trial. Hypersensitivity reactions such as urticaria and rash have occasionally been reported with benralizumab.

In the exacerbation trials, 13% of participants treated with benralizumab developed anti-drug antibodies. High antibody titres were associated with increased clearance of benralizumab, but this did not appear to affect efficacy or safety.

As benralizumab reduces eosinophils, it may impair the immune response to helminth infections. Pre-existing infections should be treated before the start of therapy. If someone develops a helminth infection during therapy and does not respond to antihelmintics, benralizumab should be stopped.

Benralizumab is available as a single-dose pre-filled syringe. The recommended dose is 30 mg given subcutaneously (upper arm, thigh or abdomen) by a health professional every four weeks for the first three doses then every eight weeks. The drug's elimination half-life is around 15.5 days. As it is catabolised, renal and hepatic impairment are not expected to affect clearance. Drug interactions are also not expected.

Although there have been no studies in pregnant women, IgG antibodies can cross the placenta particularly in the third trimester of pregnancy. This could deplete eosinophils in the fetus and poses risks in the newborn. Antibodies can also be excreted in breast milk.

Adding benralizumab to usual treatment seems to reduce exacerbations, improve lung function and decrease the reliance on chronic corticosteroid use in people with poorly controlled asthma and elevated eosinophils. However, its efficacy beyond 56 weeks is unclear. It is not known how benralizumab will compare to mepolizumab, another antibody that targets interleukin-5 in eosinophilic asthma.

TT manufacturer provided additional useful information

REFERENCES

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.