

From The Medical Letter on Drugs and Therapeutics

Benralizumab (Fasenra) for Severe Eosinophilic Asthma

The FDA has approved benralizumab (Fasenra – AstraZeneca), a humanized monoclonal antibody selective for the interleukin-5 (IL-5) receptor, for add-on maintenance treatment of severe asthma in patients ≥ 12 years old with an eosinophilic phenotype. Benralizumab is the third anti-IL-5 antibody to be approved for treatment of severe eosinophilic asthma; mepolizumab (Nucala) and reslizumab (Cinqair), which target IL-5 itself, were approved earlier.^{1,2}

Pronunciation Key

Benralizumab: ben" ra liz' ue mab

Fasenra: fas en rah

Mechanism of Action

Severe asthma often has an eosinophilic phenotype with elevated blood and lung eosinophil levels.^{3,4} IL-5 is the major cytokine responsible for the growth, differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab and reslizumab, the two previously approved anti-IL-5 antibodies, reduce the production and survival of eosinophils by binding to IL-5, preventing it from binding to its receptors (Table 1). Benralizumab binds directly to the IL-5 receptor, preventing IL-5 binding and causing apoptosis of eosinophils and basophils through cell-mediated cytotoxicity. All three of these agents decrease eosinophilic airway inflammation.

Clinical Studies

Two randomized, double-blind, placebo-controlled, phase 3 trials, SIROCCO (48 weeks) and CALIMA (56 weeks), evaluated the efficacy of add-on therapy with benralizumab 30 mg SC every 4 weeks or every 4 weeks for the first 3 doses and then every 8 weeks in patients 12-75 years old with severe uncontrolled asthma and baseline blood eosinophil counts ≥ 300 cells/ μ L who were taking a high-dose inhaled corticosteroid and a long-acting β_2 -agonist (LABA), with or without additional asthma-controller medications.^{5,6} Patients in both trials must have had ≥ 2 asthma exacerbations requiring either

systemic corticosteroid treatment or a temporary increase in their usual maintenance oral corticosteroid dosage within one year before enrollment. In both trials, benralizumab significantly reduced annual asthma exacerbation rates and improved forced expiratory volume in one second (FEV₁) (Table 2). It also modestly improved patient-reported asthma symptom scores.

A double-blind, 28-week trial (ZONDA) evaluated the oral corticosteroid-sparing effect of benralizumab in 220 adults with severe eosinophilic asthma who were taking a high-dose inhaled corticosteroid plus a LABA, with or without other asthma-controller medications, and had been on oral corticosteroids for at least 6 months prior to enrollment.⁷ Patients were randomized to receive add-on therapy with placebo or benralizumab 30 mg SC every 4 weeks or every 4 weeks for the first 3 doses and then every 8 weeks. The dose of the oral corticosteroid (prednisone or prednisolone) was reduced gradually over a 20-week period by 2.5-5 mg every 4 weeks in patients who met specific criteria for maintenance of asthma control. At 28 weeks, the median reduction in the daily oral corticosteroid dose, the primary endpoint, was significantly greater with benralizumab than with placebo (75% for both benralizumab regimens vs 25% for placebo). The change in FEV₁ from baseline was measured at 4-week intervals; there was a significant increase with both benralizumab regimens compared to placebo from 4 to 20 weeks, but not at 28 weeks. Total asthma symptom scores decreased slightly from baseline to the end of therapy in all groups, and were not significantly different between benralizumab and placebo.

Adverse Effects

In clinical trials, adverse effects were generally reported at similar rates with benralizumab and placebo. Injection-site reactions occurred in 2.2% of patients treated with benralizumab in the SIROCCO and CALIMA trials. Hypersensitivity reactions, including urticaria, angioedema, rash, and anaphylaxis, have occurred rarely with benralizumab. Patients should have an epinephrine auto-injector (Auvi-Q, EpiPen, and others) available and be trained in its use.

Table 1. Anti-Interleukin-5 Antibodies for Eosinophilic Asthma

	Benralizumab (Fasenra)	Mepolizumab (Nucala) ^a	Reslizumab (Cinqair)
Formulation	30 mg/mL soln in single-dose prefilled syringes	100 mg lyophilized powder in single-dose vials	100 mg/10 mL soln in single-use vials
Route	SC	SC	IV
Metabolism	Degradation by proteolytic enzymes	Degradation by proteolytic enzymes	Degradation by proteolytic enzymes
Half-life	~15 days	16-22 days	~24 days
Dosage	30 mg SC q4 wks $\times$ 3, then q8 wks	100 mg SC q4 wks	3 mg/kg IV q4 wks
FDA-approved age	≥ 12 years	≥ 12 years	≥ 18 years
Cost ^b	\$4752	\$2868	\$2580 ^c

^a Mepolizumab is also FDA-approved for treatment of eosinophilic granulomatosis with polyangiitis in adults.

^b Approximate WAC for a single dose. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalog or list price and may not represent an actual

transactional price. Source: AnalySource® Monthly. February 5, 2018. Reprinted with permission by First Databank, Inc. All rights reserved. ©2018. www.fdbhealth.com/policies/drug-pricing-policy/.

^c Cost for a 70-kg patient (3 vials).

Table 2. Benralizumab Phase 3 Clinical Trials

Study	Annual Asthma Exacerbation Rate (n) ^a	FEV ₁ (L) Change from Baseline (n) ^b
SIROCCO^c (48 wks)		
Benralizumab ^d	0.65 (267) ^e	0.398 (235) ^f
Placebo	1.33 (267)	0.239 (233)
CALIMA^g (56 wks)		
Benralizumab ^d	0.66 (239) ^e	0.330 (211) ^f
Placebo	0.93 (248)	0.215 (221)

FEV₁ = forced expiratory volume in 1 second.

^a In patients with baseline blood eosinophil counts ≥ 300 cells/ μ L who were taking a high-dose inhaled corticosteroid plus a LABA (primary endpoint). An exacerbation was defined as a worsening of asthma that required use of systemic corticosteroids, or a temporary increase in a stable oral corticosteroid background dosage for at least 3 days, or a single injectable dose of corticosteroids; or emergency department or urgent care visit < 24 hours; or inpatient hospital stay > 24 hours.

^b Least squares mean change from baseline in prebronchodilator FEV₁ (secondary endpoint).

^c Bleecker ER, et al. *Lancet*. 2016;388:2115.

^d Data for patients given benralizumab 30 mg SC every 4 weeks for the first 3 doses and then every 8 weeks.

^e Statistically significant reduction vs placebo (rate ratio 0.49, $P < .001$ in SIROCCO; 0.72, $P = .019$ in CALIMA).

^f Statistically significant increase vs placebo (0.159 L, $P = .0006$ in SIROCCO; 0.116 L, $P = .0102$ in CALIMA).

^g FitzGerald JM, et al. *Lancet*. 2016;388:2128.

Antibodies to benralizumab developed in 13% of patients; they did not appear to affect the efficacy or safety of the drug, but high anti-drug antibody titers were associated with increased clearance of benralizumab and higher blood eosinophil levels.

Pregnancy and Lactation

There are no adequate studies of benralizumab use in pregnant women. Monoclonal antibodies such as benralizumab can cross the placenta during the third trimester. In one study, cynomolgus monkeys were given IV benralizumab every 2 weeks throughout pregnancy in doses that produced exposures up to 310 times those achieved with the maximum recommended human dose. No harmful effects were observed on the fetus or on neonatal growth up to 6.5 months after birth.

There are no data on the presence of benralizumab in human breast milk or on its effects on the breastfed infant or on milk production.

Dosage and Administration

Fasenra is available in single-dose, prefilled syringes containing 30 mg of benralizumab. The recommended dosage is 30 mg injected subcutaneously into the upper arm, thigh, or abdomen every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. The optimal duration of treatment is unclear. Patients should be monitored for adverse effects after each dose. Hypersensitivity reactions can occur hours or days after administration of the drug.

Conclusion

The anti-interleukin-5 (IL-5) monoclonal antibody benralizumab (Fasenra) can reduce asthma exacerbations and improve lung function in patients with poorly controlled severe asthma and elevated eosinophil levels. No head-to-head trials comparing benralizumab with the anti-IL-5 antibodies mepolizumab (Nucala) and reslizumab (Cinqair) are available. Benralizumab is given about half as often as mepolizumab and reslizumab, but costs about twice as much per dose, so treatment costs are similarly high with all three drugs.

ARTICLE INFORMATION

Once a month, *The Medical Letter* provides a previously published article to JAMA to be republished.

Previous Publication: This article was published in *The Medical Letter on Drugs and Therapeutics*. February 26, 2018;60(1541):33-34. It is reprinted here with permission from ©The Medical Letter Inc.

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