

From The Medical Letter on Drugs and Therapeutics

Dupilumab (Dupixent) for Asthma

The FDA has approved the subcutaneously injected monoclonal antibody dupilumab (Dupixent – Sanofi/Regeneron) for add-on maintenance treatment of patients ≥ 12 years old with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid-dependent asthma. Dupilumab was approved earlier to treat adults with moderate to severe atopic dermatitis inadequately controlled with topical therapies.¹

Mechanism of Action

Dupilumab, a fully human IgG4 monoclonal antibody, binds to the interleukin (IL)-4 receptor alpha subunit shared by IL-4 and IL-13 receptors, inhibiting the signaling of these cytokines, which are thought to be the drivers of inflammation in atopic dermatitis, asthma, and possibly other allergic diseases.²

Monoclonal Antibodies for Asthma

Asthma patients who do not respond to high doses of inhaled corticosteroids plus a second asthma-controller medication may benefit from a phenotype-targeted approach to treatment. Three monoclonal antibodies that target the IL-5 cytokine – benralizumab (Fasenra),³ mepolizumab (Nucala),⁴ and reslizumab (Cinqair)⁵ – are FDA-approved for add-on maintenance treatment of severe eosinophilic asthma (Table 1). Omalizumab (Xolair), a subcutaneously injected anti-IgE monoclonal antibody, is approved for use in patients ≥ 6 years old with moderate to severe persistent allergic asthma not well controlled on an inhaled corticosteroid.⁶

Clinical Studies

FDA approval of dupilumab for the new indication was based on the results of 3 randomized, double-blind, placebo-controlled

trials in about 2800 patients ≥ 12 years old with uncontrolled persistent asthma.

Trials 1 and 2 enrolled patients who were receiving medium to high doses of inhaled corticosteroids plus 1 or 2 additional asthma-controller medications. Addition of dupilumab was associated with statistically significant increases in FEV₁ and decreases in severe asthma exacerbations compared to placebo. Dupilumab was effective irrespective of baseline blood eosinophil counts, but patients with higher eosinophil counts at baseline improved more.^{7,8} The results are summarized in Table 2.

In trial 3, 210 patients with severe asthma who were being treated with daily oral corticosteroids, high doses of inhaled corticosteroids, and 1 or 2 additional asthma-controller medications were randomized to receive add-on treatment with dupilumab 300 mg (following a loading dose of 600 mg) or placebo every 2 weeks for 24 weeks. Oral corticosteroid doses were reduced every 4 weeks from week 4 to week 20 as long as asthma control was maintained. The mean percentage reduction in the oral corticosteroid dose from baseline to week 24, the primary endpoint, was 70.1% with dupilumab versus 41.9% with placebo, a statistically significant difference. At week 24, 48% of patients in the active treatment group had completely discontinued oral corticosteroids, compared to 25% of those in the placebo group, also a statistically significant difference. Use of dupilumab also decreased severe asthma exacerbations and improved lung function compared to placebo. The benefits were greatest in patients with higher baseline blood eosinophil counts.⁹

Adverse Effects

In asthma clinical trials, the most common adverse effect of either dose of dupilumab was injection-site reactions (14-18%). Transient eosinophilia can occur during treatment; blood eosinophil counts

Table 1. Some Drugs for Eosinophilic Asthma

	Benralizumab (Fasenra)	Mepolizumab (Nucala) ^a	Reslizumab (Cinqair)	Dupilumab (Dupixent) ^b
Mechanism of Action	IL-5 receptor antagonist	IL-5 antagonist	IL-5 antagonist	IL-4 receptor alpha subunit antagonist (inhibits IL-4 and IL-13 signaling)
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	200 mg/1.14 mL, 300 mg/2 mL soln in single-dose prefilled syringes
Dosage	30 mg SC q4 wks $\times$ 3, then q8 wks	100 mg SC q4 wks	3 mg/kg IV q4 wks	400 mg SC ^c then 200 mg q2 wks or 600 mg SC ^c then 300 mg q2 wks ^d
FDA-Approved Age	≥ 12 years	≥ 12 years	≥ 18 years	≥ 12 years
Cost per Dose ^e	\$4752	\$2869	\$2688 ^f	\$1466 ^g

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

^b Dupilumab is also FDA-approved for treatment of adults with moderate to severe atopic dermatitis.

^c The initial loading dose is administered as 2 injections at different sites.

^d The dose for patients with oral corticosteroid-dependent asthma or with comorbid moderate to severe atopic dermatitis is 600 mg SC then 300 mg every 2 weeks.

^e Approximate WAC for a single dose or for a single maintenance dose of dupilumab. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource[®] Monthly. December 5, 2018. Reprinted with permission by First Databank, Inc. All rights reserved. ©2018. www.fdbhealth.com/policies/drug-pricing-policy/.

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

^g The 200-mg and 300-mg syringes cost the same.

Table 2. Dupilumab Clinical Trial Results

	Overall Population ^a		Blood Eosinophils ≥ 300 cells/ μ L	
	Annual Asthma Exacerbation Rate (n) ^{b,c}	FEV ₁ (L) Change from Baseline at Wk 12 ^{b,d}	Annual Asthma Exacerbation Rate (n) ^{b,c}	FEV ₁ (L) Change from Baseline at Wk 12 ^{b,d}
Trial 1 (≥ 18 yrs old, 24 wks)^e				
Dupilumab 200 mg q2 wks ^f	0.27 (150)	0.31	0.30 (65)	0.43
Dupilumab 300 mg q2 wks ^f	0.27 (157)	0.28	0.20 (64)	0.39
Placebo	0.90 (158)	0.12	1.04 (68)	0.18
Trial 2 (≥ 12 yrs old, 52 wks)^g				
Dupilumab 200 mg q2 wks ^f	0.46 (631)	0.32	0.37 (264)	0.43
Placebo	0.87 (317)	0.18	1.08 (148)	0.21
Dupilumab 300 mg q2 wks ^f	0.52 (633)	0.34	0.40 (277)	0.47
Placebo	0.97 (321)	0.21	1.24 (142)	0.22

^a Unrestricted by minimum baseline blood eosinophil count; FEV₁ = forced expiratory volume in 1 second.

^b $P < 0.05$ for all comparisons vs placebo.

^c Annualized rate of severe exacerbation events during 24 weeks (Trial 1) or 52 weeks (Trial 2) of treatment (in Trial 1, primary endpoint in patients with blood eosinophils >300 cells/ μ L and a secondary endpoint in the overall population; in Trial 2, primary endpoint in the overall population and a secondary endpoint in patients with blood eosinophils >300 cells/ μ L). A severe asthma exacerbation was defined as a deterioration of asthma leading to treatment for >3 days with systemic glucocorticoids or hospitalization or an emergency department visit leading to treatment with systemic glucocorticoids.

^d Mean change from baseline in pre-bronchodilator FEV₁ (in Trial 1, primary endpoint in patients with blood eosinophils >300 cells/ μ L and a secondary endpoint in the overall population; in Trial 2, primary endpoint in the overall population and a secondary endpoint in patients with blood eosinophils >300 cells/ μ L).

^e Wenzel S, et al. *Lancet*. 2016;388:31.

^f Following a loading dose of 400 mg (in those receiving a maintenance dose of 200 mg q2 wks) or 600 mg (in those receiving a maintenance dose of 300 mg q2 wks).

^g Castro M, et al. *N Engl J Med*. 2018;378:2486.

≥ 3000 cells/ μ L were reported in 2% of patients treated with dupilumab in trials 1 and 2 and in 13% of those treated with the drug in trial 3 (the higher rate in trial 3 may have been related to oral corticosteroid dose reductions). Eosinophilic pneumonia and vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported in adults receiving dupilumab; a causal relationship has not been established. Conjunctivitis has been reported in patients treated with dupilumab for atopic dermatitis. Anaphylaxis occurred in one patient treated with dupilumab for asthma.

Drug Interactions

Use of live vaccines should be avoided in patients being treated with dupilumab.

Administration

Dupilumab is injected subcutaneously into the thigh, abdomen, or upper arm. Patients or caregivers can be trained to administer the drug at home.

Conclusion

Add-on maintenance treatment with dupilumab (Dupixent) can improve lung function and reduce severe exacerbations and oral corticosteroid use in patients ≥ 12 years old with moderate to severe asthma, particularly those with an eosinophilic phenotype. How dupilumab compares to the other monoclonal antibodies that are approved for treatment of eosinophilic asthma remains to be determined, and its long-term safety is unknown.

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REFERENCES

1. Dupilumab (Dupixent) for moderate to severe atopic dermatitis. *Med Lett Drugs Ther*. 2017;59(1519):64-66.
2. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368(26):2455-2466.
3. Benralizumab (Fasenra) for severe eosinophilic asthma. *Med Lett Drugs Ther*. 2018;60(1541):33-35.
4. Mepolizumab (Nucala) for severe eosinophilic asthma. *Med Lett Drugs Ther*. 2016;58(1486):11-12.
5. Reslizumab (Cinqair) for severe eosinophilic asthma. *Med Lett Drugs Ther*. 2016;58(1497):81-82.
6. Drugs for asthma. *Med Lett Drugs Ther*. 2017;59(1528):139-146.
7. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist. *Lancet*. 2016;388(10039):31-44.
8. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-2496.
9. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475-2485.