

Is Dupilumab Effective in Treating Uncontrolled Moderate-to-Severe Asthma?

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Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

REFERENCE

Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;378:2486-96.

BACKGROUND

In some patients with moderate-to-severe asthma, the disease remains uncontrolled despite standard-of-care controller therapy. Asthma associated with type 2 inflammation is characterized by an increase in T_H2 cells in the airway, which is mediated by cytokines including IL-4, IL-5, and IL-13.¹ With the exception of omalizumab (an anti-IgE mAb), the use of biologics for asthma has been aimed at blocking IL-5: benralizumab (directed against the IL-5 receptor) and mepolizumab and reslizumab (both directed against IL-5).²⁻⁴ Dupilumab was approved in 2017 for patients with moderate-to-severe atopic dermatitis, not adequately controlled with topical prescription therapies. It is an mAb that is directed against the alpha subunit of the IL-4 receptor, which inhibits signaling of both IL-4 and IL-13. This study looks at its use in uncontrolled moderate-to-severe asthma, refractory to standard medical care. This was one of the key studies that led the Food and Drug Administration to recently approve dupilumab (October 2018) as add-on maintenance therapy in patients with moderate-to-severe asthma for patients aged 12 years and older with an eosinophilic phenotype of asthma.

METHODS

This was a phase 3, randomized, double-blind, placebo-controlled, parallel-group trial. A total of 1902 patients were randomized to subcutaneous injections of dupilumab (200 mg or 300 mg) or matched volume placebo in a 2:2:1:1 ratio. The treatment period

was 52 weeks and injections were given every 2 weeks. For study entry, patients were required to have been on a medium-to-high-dose inhaled glucocorticoid and at least 1 other controller (eg, long-acting β_2 agonist or leukotriene receptor antagonist) for at least 3 months. Baseline controllers were continued throughout the study. Patients were also required to have a worsening of asthma in the previous year defined by either hospitalization, emergency medical care, or systemic glucocorticoids.

The primary end points were the rate of severe asthma exacerbations in 1 year and the absolute change in FEV₁ before bronchodilator use, from baseline to week 12. These variables were also looked at in subgroups based on baseline blood eosinophil count and baseline fractional exhaled nitric oxide (FENO). Safety was also evaluated.

RESULTS

The rate of severe asthma exacerbations over 1 year was 47.7% lower among patients assigned to 200 mg of dupilumab compared with those assigned to a matched placebo ($P < .001$). The absolute risk reduction of severe exacerbations in these patients was 0.41, with a number needed to treat of 2.44. Similar results were seen with the higher dose of dupilumab.

At week 12, the absolute change in FEV₁ before bronchodilator use was 0.32 L in patients assigned to 200 mg of dupilumab. There was a difference of 0.14 L compared with placebo ($P < .001$). Similar results were seen with the higher dose.

The efficacy of dupilumab was greater in patients with increasing baseline levels of blood eosinophils. For patients who had an eosinophil count of 300 or more per cubic millimeter, the rate of severe asthma exacerbations was 65.8% lower in the dupilumab 200 mg group when compared with the placebo group. Similar results were observed with the higher dose. The efficacy of dupilumab was greater in patients with higher baseline FENO. For patients with a FENO of greater than or equal to 25 parts per billion (ppb), the rate of severe exacerbations was lower than for patients who had a FENO of less than 25 ppb.

In terms of adverse events, injection-site reactions were more common in those who received dupilumab (16.8%) versus placebo (7.9%). Eosinophilia also occurred more often in those who received dupilumab (4.1%) versus placebo (0.6%). There were 4 patients treated with dupilumab who developed clinical symptoms associated with eosinophilia. Two of these cases were reported as serious adverse events: worsening of hyper-eosinophilia and chronic eosinophilic pneumonia. Both these

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication November 20, 2018; revised January 7, 2019; accepted for publication January 10, 2019.

Available online February 6, 2019.

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2213-2198

<https://doi.org/10.1016/j.jaip.2019.01.013>

patients had been randomized to the 300 mg treatment group and needed to discontinue treatment.

CRITICAL APPRAISAL

The authors conclude that dupilumab reduces severe exacerbations and improves lung function, with greater benefits in patients with increasing baseline eosinophil counts and FENO. However, the study data also show that the exacerbation rate and the change in FEV₁ was similar compared with placebo when looking at patients with lower baseline blood eosinophil counts (<150/mm³). In addition, for patients with baseline eosinophil values of 150 to less than 300/mm³, FEV₁ change was significant compared with placebo in only the 200 mg treatment arm.

FENO has been shown to be a useful measure of disease activity in studies of patients with an eosinophilic phenotype of asthma.⁵⁻⁷

In this study, patients with an FENO value of less than 25 ppb in both dupilumab groups did not show a statistically significant decreased risk of severe asthma exacerbations or change in FEV₁ when compared with placebo.

Baseline blood eosinophil counts may not be as important in patients with corticosteroid-dependent severe asthma. Another recent study showed that patients with oral glucocorticoid-dependent severe asthma were able to decrease oral glucocorticoid dosing and at the same time decrease their rate of severe exacerbations and improve their lung function (FEV₁) after adding dupilumab to their regimen, regardless of the baseline blood eosinophil count.⁸ Patients with higher blood eosinophil counts did do better in that trial, and results may have been confounded by the effect that daily steroids have on baseline blood eosinophil counts.

It is difficult to compare dupilumab to the other biologics because there are no head-to-head studies comparing the efficacy of these studies. A recent meta-analysis concluded that the 3 anti-IL-5 treatments (mepolizumab, reslizumab, and benralizumab) roughly halve the rate of asthma exacerbations in patients with severe eosinophilic asthma and poor control.⁹ Dupilumab in this study decreased the rate of severe asthma exacerbation by around 1/2 (47.7%) when compared with placebo in patients with moderate-to-severe asthma. As an editorial in the *New*

England Journal of Medicine points out, ideally clinical researchers could perform a randomized controlled trial with all 4 of these biologics to truly compare efficacy.¹⁰

RECOMMENDATION

The results of this study support the use of dupilumab as an alternative add-on systemic therapy for patients with moderate-to-severe asthma with baseline eosinophil values of greater than or equal to 150/mm³ or FENO value of greater than or equal to 25 ppb.

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