

PRACTICE OPTIONS FROM BEYOND OUR PAGES

Dupilumab Therapy in Patients With Nasal Polyposis and Chronic Sinusitis

Erin Willits, MD, and Rohit Divekar, MBBS, PhD Rochester, Minn

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

Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA* 2016;315:469-79.

BACKGROUND

Chronic rhinosinusitis (CRS) consists of persistent inflammation of the paranasal sinuses lasting longer than 8 to 12 weeks.¹ CRS, a heterogeneous entity with nasal polyps being a common finding, is associated with prolonged inflammation in the paranasal sinuses and often coexists with asthma or aspirin sensitivity. Treatments for CRS include topical and systemic therapies mostly with corticosteroids, antibiotics, aspirin desensitization in some instances, or surgery in severe cases. CRS therapies directed at specific immune or cytokine pathways are in various developmental stages and include targeted blockade or modulation of immune pathways, especially T_H2- or eosinophil-related cytokines. Mepolizumab, an anti-IL-5, and omalizumab, an anti-IgE, are effective in CRS with nasal polyps.^{2,3} Another biologic on the horizon for CRS with nasal polyps is an ST2 receptor antagonist, an inhibitor of IL-33 signaling.⁴ The Practice Options from Beyond Our Pages being presented reports the findings of the role of dupilumab, a human mAb to the IL-4 receptor α subunit that inhibits both IL-4 and IL-13 signaling, in the treatment of nasal polyps in patients with sinusitis.⁵ Previous reports document the efficacy of dupilumab in asthma.⁶

METHODS

Patients aged 18 to 65 years with bilateral polyps refractory to intranasal corticosteroid therapy were randomized for 16 weeks to dupilumab (N = 30) or placebo (N = 30), as add-on treatments

to mometasone (100 μ g twice daily to each nostril). Dupilumab subcutaneous dosing was 600 mg loading followed by 15 weekly doses of 300 mg for 15 weeks. Two dupilumab (both adverse events) and 7 placebo (5 adverse events and 2 lack of efficacy) patients withdrew. The primary efficacy outcome was the mean change in bilateral endoscopic nasal polyp score from baseline to week 16. Major secondary outcomes determined were morning peak nasal inspiratory flow; the Lund-Mackay computed tomography score, which evaluates patency of sinuses; the 22-item Sino-Nasal Outcome Test (a validated symptom questionnaire); the University of Pennsylvania Smell Identification Test; and safety.

RESULTS

The mean reduction in nasal polyp score was significantly greater with dupilumab plus mometasone than with placebo plus mometasone, a difference seen as early at 4 weeks and continued until the end of the treatment period at 16 weeks. Improvement of at least 1 point in the polyp score was seen among 70% of the participants in the dupilumab plus mometasone arm but only 20% of the participants in the placebo plus mometasone arm.

The Lund-Mackay computed tomography score and the nasal inspiratory flow measurements significantly improved at 16 weeks in the dupilumab plus mometasone arm compared with the placebo plus mometasone arm. Overall, improvement in the symptom-based subjective assessment was greater in the dupilumab plus mometasone arm (22-item Sino-Nasal Outcome Test score of 12.8 ± 11 at week 16 compared with 30.2 ± 19.6 in the placebo arm). In addition, those on dupilumab reported a significant improvement in posterior rhinorrhea, nasal congestion, and sense of smell. Also, patients with asthma treated with dupilumab plus mometasone showed significant improvements in FEV₁% predicted and in the score of the 5-item version of the Asthma Control Questionnaire than did those treated with placebo plus mometasone and compared with baseline. Sustained improvement in most efficacy outcomes persisted in the dupilumab plus mometasone group after a further 16-week follow-up off dupilumab treatment. Regarding biomarkers, total serum IgE levels and plasma cotaxin levels significantly decreased with dupilumab plus mometasone compared with placebo plus mometasone. Blood eosinophil count and serum thymus and activation-regulated chemokine did not change significantly with treatments. Dupilumab treatment was reported as safe with no serious adverse events related to its use.

Division of Allergic Diseases, Mayo clinic, Rochester, Minn

This work was supported by the Mayo Clinic Foundation.

Conflicts of interest: R. Divekar is employed by Mayo Clinic and has an unrelated

Web blog through Google.com. E. K. Willits declares no relevant conflicts of interest.

Received for publication April 4, 2016; accepted for publication April 8, 2016.

Available online ■ ■

Corresponding author: Rohit Divekar, MBBS, PhD, Division of Allergic Diseases,

Mayo Clinic, Rochester, MN 55905. E-mail: Divekar.Rohit@mayo.edu.

2213-2198

<http://dx.doi.org/10.1016/j.jaip.2016.04.005>

CRITICAL APPRAISAL

The present proof-of-concept study evaluated the efficacy of dual IL-4/IL-13 inhibition in patients with nasal polyps and sinusitis refractory to intranasal corticosteroids. The major limitations of the study were a small sample size with early study withdrawals and only a 16-week treatment period. However, although the study cohort was small, the effect size of dupilumab efficacy was significant and large as evidenced by improvements in many clinically important outcomes including polyp size, nasal inspiratory flow, validated nasal symptom score, olfaction, and lung function in those with asthma. Generalizability is limited to some degree at this time. Patients older than 65 years were excluded, who constitute a population with age-related differences in disease and symptom burden compared with younger patients.^{7,8} Twenty-five percent of the participants reported aspirin sensitivity, but no analyses were performed on this subgroup. Aspirin-sensitive patients may potentially benefit from dupilumab because IL-4 may play a role in aspirin-exacerbated respiratory disease.⁹ The relationship of changes in the biomarkers to treatment effects was not reported, but could provide mechanistic insight. In addition, the effect of dupilumab in patients with nasal polyps and a more severe asthma phenotype was not studied because patients with asthma with FEV₁ value of 60% or less were excluded. The pattern of reduction in serum IgE and eotaxin-3 levels, but not blood eosinophil counts, in the dupilumab plus mometasone group compared with the placebo plus mometasone group was also reported with dupilumab treatment in an asthma trial.⁶

RECOMMENDATION

Dupilumab may be a novel treatment for patients with nasal polyps and CRS refractory to topical corticosteroid therapy.

We await Food and Drug Administration decision on an indication of dupilumab for nasal polyp disease. Dupilumab may be particularly useful for nasal polyp disease with comorbid asthma. Long-term efficacy and safety data are still needed.

REFERENCES

1. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012;50:1-12.
2. Gevaert P, Van Bruene N, Cattaert T, Van Steen K, Van Zele T, Acke F, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol* 2011;128:989-995.e1-8.
3. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, et al. Dupilumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 2013;131:110-6.e1.
4. Clinicaltrials.gov. Available from: <https://clinicaltrials.gov/ct2/home>. Accessed March 21, 2016.
5. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA* 2016;315:469-79.
6. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013;368:2455-66.
7. Cho SH, Hong SJ, Han B, Lee SH, Suh L, Norton J, et al. Age-related differences in the pathogenesis of chronic rhinosinusitis. *J Allergy Clin Immunol* 2012;129:858-860.e2.
8. Lal D, Rounds AB, Divekar R. Gender-specific differences in chronic rhinosinusitis patients electing endoscopic sinus surgery. *Int Forum Allergy Rhinol* 2016;6:278-86.
9. Steinke JW, Payne SC, Borish L. Interleukin-4 in the generation of the AERD phenotype: implications for molecular mechanisms driving therapeutic benefit of aspirin desensitization. *J Allergy* 2012; Article ID: 182090.