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Subcutaneous Dupilumab and Mometasone Furoate Nasal Spray for Chronic Rhinosinusitis With Polyps

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Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis:

A Randomized Clinical Trial

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IMPORTANCE Dupilumab has demonstrated efficacy in patients with asthma and atopic dermatitis, which are both type 2 helper T-cell-mediated diseases.

OBJECTIVE To assess inhibition of interleukins 4 and 13 with dupilumab in patients with chronic sinusitis and nasal polyposis.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, placebo-controlled parallel-group study conducted at 13 sites in the United States and Europe between August 2013 and August 2014 in 60 adults with chronic sinusitis and nasal polyposis refractory to intranasal corticosteroids with 16 weeks of follow-up.

INTERVENTIONS Subcutaneous dupilumab (a 600 mg loading dose followed by 300 mg weekly; n = 30) or placebo (n = 30) plus mometasone furoate nasal spray for 16 weeks.

MAIN OUTCOMES AND MEASURES Change in endoscopic nasal polyp score (range, 0-8; higher scores indicate worse status) at 16 weeks (primary end point). Secondary end points included Lund-Mackay computed tomography (CT) score (range, 0-24; higher scores indicate worse status), 22-item SinoNasal Outcome Test score (range, 0-110; higher scores indicating worse quality of life; minimal clinically important difference ≥ 8.90), sense of smell assessed using the

University of Pennsylvania Smell Identification Test (UPSIT) score (range, 0-40; higher scores indicate better status), symptoms, and safety.

RESULTS Among the 60 patients who were randomized (mean [SD] age, 48.4 years [9.4 years]; 34 men [56.7%]; 35 with comorbid asthma), 51 completed the study. The least squares (LS) mean change in nasal polyp score was -0.3 (95% CI, -1.0 to 0.4) with placebo and -1.9 (95% CI, -2.5 to -1.2) with dupilumab (LS mean difference, -1.6 [95% CI, -2.4 to -0.7]; $P < .001$). The LS mean difference between the 2 groups for the Lund-Mackay CT total score was -8.8 (95% CI, -11.1 to -6.6; $P < .001$). Significant improvements with dupilumab were also observed for the 22-item SinoNasal Outcome Test (LS mean difference between groups, -18.1 [95% CI, -25.6 to -10.6]; $P < .001$) and sense of smell assessed by UPSIT (LS mean difference, 14.8 [95% CI, 10.9 to 18.7]; $P < .001$). The most common adverse events were nasopharyngitis (33% in the placebo group vs 47% in the dupilumab group), injection site reactions (7% vs 40%, respectively), and headache (17% vs 20%).

CONCLUSIONS AND RELEVANCE Among adults with symptomatic chronic sinusitis and nasal polyposis refractory to intranasal corticosteroids, the addition of subcutaneous dupilumab to mometasone furoate nasal spray compared with mometasone alone reduced endoscopic nasal polyp burden after 16 weeks. Further studies are needed to assess longer treatment duration, larger samples, and direct comparison with other medications.

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Chronic rhinosinusitis with polyps (CRSwP) remains a challenging condition to treat. Patients vary substantially in their responses to existing therapies. Some patients require surgery with minimal post-



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operative medical management, while others require more extensive medical therapy with long-term use of topical and short-course "rescue" oral steroids. Some patients have refractory disease despite aggressive surgical and medical therapies. A recent systematic review¹ of the best evidence regarding medical treatments for CRSwP identified only topical steroids, saline irrigations, and systemic steroids as having American Heart Association A-I level evidence. These medications, however, have no specific targets in the inflammatory pathways of CRSwP.

Many research efforts are directed toward a better understanding of the inflammatory pathways in CRSwP so that more targeted therapies can be developed.² As a result of many of these findings, substantial advances have been made in targeted biologics for inflammatory airway conditions.³ For instance, omalizumab (targeting free IgE), mepolizumab, and reslizumab (targeting interleukin 5 [IL-5]) have been tested in CRSwP with reduction in symptoms and clinical measures of chronic rhinosinusitis (CRS). However, the application of these new targeted biologic medications in CRSwP is just beginning and more studies, including phase 3 trials in patients with CRSwP, are expected.

In JAMA, Bachert et al⁴ report their findings of a double-blind, placebo-controlled randomized study of dupilumab, which inhibits binding of IL-4 and IL-13 to IL-4Ra. The authors found that subcutaneous weekly administration of dupilumab for 16 weeks was asso-

ciated with significant improvement in endoscopic scoring of polyp burden, computed tomography (CT) sinus findings, and patient quality-of-life scores, among others, over placebo. Of note, no serious adverse events occurred related to dupilumab therapy.

The authors chose an extensive list of variables to study, including physician assessment of disease, symptom scores, and biologic data.⁴ Thus, this study is robust in the assessment of a novel treatment for CRSwP. Changes in patient-reported measures including the 22-item Sino-Nasal Outcome Test (SNOT-22) and symptom Visual Analog Scale (VAS) demonstrated statistically and clinically significant improvement in the dupilumab group compared with placebo. In addition, significant changes were seen in some serum inflammatory markers, specifically IgE and plasma eotaxin-3 levels. However, in their discussion of study limitations, the authors acknowledge that their nasal polyp score based on endoscopy has no well-established minimally clinically important difference. Because this was their main outcome, the changes observed in polyp burden may be less clinically meaningful than stated.

These results point out a particular challenge in research regarding biologic therapies for CRSwP. The outcomes of interest in treating CRSwP have traditionally been clinical, either symptom control or clinical variables such as endoscopy and CT scores. Whereas most variables chosen for this study appear to have been affected positively by the administration of dupilumab, further research must be careful to examine variables that are both clinically meaningful and biologically appropriate for the targeted therapy. Ideally, correlation between clinical variables and biologic markers should be sought to demonstrate a causative pathway in the use of targeted therapy. As these pathways are studied, such research represents a growing opportunity for further identification of phenotypes and endotypes of CRSwP.⁵

As the biologics continue to gain purchase as viable therapies for CRSwP and other inflammatory airway disease, further endotyping of CRS will inform the clinician as to the applicability of any given biologic therapy.² This is the hope and promise of personalized medicine.⁶ The number of implicated cytokines and chemokines in CRS continues to increase, and their relative roles in any 1 patient's disease process may improve endotype identification.⁷ Targeted biologic therapy is promising, but targeting of a single com-

ponent in the inflammatory cascade may have variable effects depending on the endotype profile. Effective targeted therapy will likely benefit from individual patient profiling, both clinically and biologically. New research, using cluster analysis⁸ and other techniques, will help clinicians identify distinct clinical and pathologic endotypes of CRSwP and apply these therapies robustly.

Whereas these biologic therapies have clinical promise, their cost-effectiveness has not been established. As noted by Bachert et al,⁴ patients required weekly in-clinic injections of dupilumab, which in a noninvestigative environment would potentially represent a substantial time investment for patients. Patient monetary cost also may inhibit broad application of these therapies. Of the biologics, Xolair (omalizumab) was the first commercially available therapy and it has been estimated that for patients with asthma, the annual cost of Xolair is between \$6600 and \$33 000.⁹ We should expect similar costs for newer biologics. This cost and time investment is significantly more than that required with current medical treatments, where patients typically manage their therapy at home and costs are much smaller and often defrayed by insurance coverage. Future studies in comparative effectiveness will be necessary.

A further challenge in applying dupilumab and other biologics to patients with CRSwP is the unknown efficacy beyond treatment termination. Bachert et al⁴ acknowledge that the effect beyond 16 weeks of treatment remains unknown. Chronic rhinosinusitis with polyps is a chronic disease, and the optimal time course of treatment remains unknown for many therapies currently used, including topical steroid therapy. Given the future of endotyping of CRSwP, duration of treatment will need to be studied to better give patients realistic expectations about treatment requirements. Further studies will also be needed to assess whether the biologics function simply to control inflammation or reduce it in an effort to cure, as this will also inform patients regarding duration of treatment.

In this "proof of concept" article, the authors⁴ have added to an exciting literature investigating targeted biologic therapies for CRSwP. While the monetary and time costs require further research, we are getting closer to improved therapies for this life-altering disease. Hopefully, as our understanding of endotypes within CRSwP expands, otolaryngologists will have increased ability to target unique inflammatory factors for more specific groups of patients.

ARTICLE INFORMATION

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