



Letters

Dupilumab use in recalcitrant allergic fungal rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) has been described as a distinct subtype of chronic rhinosinusitis with nasal polyps (CRSwNP) characterized by eosinophilic (allergic) mucin, type 1 hypersensitivity to fungi and distinct radiologic findings.¹ Allergic fungal rhinosinusitis requires surgical intervention along with adjuvant medical therapy. Topical and oral corticosteroids markedly decrease AFRS recurrence after surgical procedure, but steroid-sparing agents for the refractory disease are lacking. Dupilumab added to intranasal corticosteroids was found to be effective and safe in 2 double-blind, placebo-controlled phase 3 trials in patients with severe CRSwNP that recurred after oral corticosteroids or sinonasal surgical procedures.² These studies specifically excluded patients with fungal rhinosinusitis. Dupilumab blocks interleukin (IL)-4 and IL-13 signaling, which are key components of type 2 inflammation. That AFRS is driven by type 2 inflammation provides a rationale for evaluating dupilumab as a steroid-sparing agent for recalcitrant AFRS. Here, we report the first case, to the best of our knowledge, of dupilumab use in a patient with recalcitrant AFRS.

An 18-year-old man with allergic rhinitis presented with 4 months of progressive left eye bulging. He was afebrile but reported persistent nasal congestion and anosmia. He had no history of unusual or recurrent infections, including sinusitis. Anterior rhinoscopy revealed bilateral inferior turbinate edema and minimal crusting in the right nasal passage, but no purulence bilaterally. Frontal and maxillary sinuses were nontender to palpation. Mild left eye proptosis was noted. Extraocular movements and visual acuity were intact.

Magnetic resonance imaging results revealed complete opacification of the paranasal sinuses with an expansion of the ethmoid, sphenoid, and left maxillary sinuses. There was a mass effect on the left orbit, displacing orbital content outward and inferiorly. Computed tomography (CT) of the sinus was highly suggestive of AFRS and revealed bony dehiscence in the paranasal sinuses. **Figure 1** illustrates the evidence of thinning and dehiscence of the left lamina papyracea. Opacification with high-density material was seen in the frontal, ethmoid, sphenoid, and left maxillary sinuses. There was an expansion of the maxillary sinuses, sphenoid sinuses, and bilateral ethmoid air cells (left greater than right), with associated mass effect on the left extraocular muscles and orbit.

Intraoperative findings included severely swollen mucosa and polyps in all the sinuses. Polyps and allergic fungal mucin were removed. Histologic findings indicated fungal organisms, severe mixed inflammation, and abundant mucin. Fungal culture grew *Bipolaris* and *Curvularia* species. Sinus cultures also grew *Staphylococcus aureus* and *Klebsiella oxytoca*. Serum specific immunoglobulin

E (IgE) levels indicated sensitization to multiple molds, including *Bipolaris* (*Curvularia*) *spicifera*. He was also sensitized to other perennial and seasonal allergens. Total IgE was 865 kU/L (reference range, <100 kU/L). Differential white blood cell count revealed mild absolute eosinophilia of 460/ μ L (reference range, 0–200/ μ L).

Topical steroids, oral steroids, and oral amoxicillin-clavulanate were recommended postoperatively. The patient did not adhere to the complete oral steroid course. Rhinoscopy performed 9 weeks later revealed regrowth of sinus polyps with polypoid lesions in both nasal cavities and sinuses with purulent secretions. He underwent a second polypectomy 4 months after the first procedure and was noted intraoperatively to have diffuse polypoid mucosa and polyps throughout all sinuses. The cultures grew *Bipolaris* species and *Staphylococcus aureus*. Despite the intake of cephalexin with oral and topical steroids, he showed some polypoid regrowth 3 weeks after his operation. Sinus CT at that point showed a marked reduction in sinus opacification compared with the most recent preoperative CT, but because of left-sided residual disease, he underwent a third sinus surgical procedure 3 months after the second procedure.

Given the risks of long-term systemic corticosteroids, we sought a steroid-sparing intervention. The evidence supporting subcutaneous immunotherapy in AFRS is limited with no placebo-controlled studies; however, there are reports of clinical benefits.¹ It was therefore considered, but he was unable to commit to the injection schedule. After considering the evidence base for systemic antifungal therapy, such as itraconazole,³ we turned to dupilumab. Dupilumab was approved by the Food and Drug Administration in June 2019 to treat inadequately controlled CRSwNP. Despite the exclusion of fungal rhinosinusitis from dupilumab trials, we considered it for our patient with AFRS because of eosinophilia and elevated IgE, marking it as a type 2 inflammation.⁴ He was started on dupilumab 5 weeks after his third sinus operation, and 1 month after its initiation, he had no polyps on rhinoscopy and had much improved symptoms. He was on a dose of prednisone 5 mg daily at that time. A total of 3 months postoperatively, he tapered off oral corticosteroids. He has not had any relapse since (9 months after surgical procedure) and has tolerated dupilumab without any adverse effects.

In addition to CRSwNP, dupilumab has indicated clinical efficacy in other disorders characterized by type 2 inflammation, including asthma and atopic dermatitis.^{5,6} More recently, a phase 2 trial reported a reduction of esophageal intraepithelial eosinophils in patients with eosinophilic esophagitis after 12 weeks.⁷

Distinguishing among the subtypes of fungal rhinosinusitis clarifies which subtypes may benefit from targeting type 2 inflammation. Notably, AFRS is a localized hypersensitivity response to fungal colonization without tissue invasion in immunocompetent patients. Fungal balls arise from local hyphal occupation of sinuses without invasion, whereas invasive fungal sinusitis is a highly morbid

Disclosures: The authors have no conflicts of interest to report.

Funding: Dr. Lo is supported as a Tashia and John Morgridge Endowed Postdoctoral Fellow by the Stanford Maternal and Child Health Research Institute. The remaining authors have no funding sources to report.

<https://doi.org/10.1016/j.anai.2020.07.014>

1081-1206/© 2020 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.



Figure 1. Axial CT exhibits thinning and dehiscence of the left lamina papyracea (yellow arrow), opacification with high-density material in the sinuses (blue arrows), and mass effect on the left extraocular muscles causing proptosis. CT, computed tomography.

angioinvasive infection primarily occurring in immunosuppressed patients; neither involves type 2 inflammation.

The optimal duration of dupilumab in CRSwNP and in our patient with AFRS is unknown. Effects of dupilumab receded on discontinuation at 24 weeks in 1 of the aforementioned clinical trials,² suggesting that continuation may be needed for sustained disease control. Patients with AFRS tend to be younger than patients with CRSwNP overall, with potential implications for longer treatment; 1 study noted average ages of 44 years and 29 years among patients with CRSwNP and AFRS, respectively, at the time of presentation.⁸

Fungal infections were not increased in dupilumab clinical trials. It is unclear what effect dupilumab has on fungal infections. Interestingly, the combination of interferon gamma and dupilumab was recently reported to treat a pediatric patient with disseminated coccidioidomycosis with T_H2 skewing; dupilumab was added under the premise that increased production of IL-4 may decrease the antifungal activity of phagocytes and suppress T_H1 development.⁹

This medication has been well tolerated in our patient and likely improved his condition. Dupilumab may be beneficial in patients

with refractory AFRS. Further studies should be performed to evaluate the safety and efficacy of dupilumab in AFRS and to evaluate for the possible biomarkers to determine its optimal duration.

Acknowledgments

We would like to thank Rosa Madera for her invaluable assistance in this work.

Rachelle M. Lo, MD*

Anne Y. Liu, MD*,†

Tulio A. Valdez, MD, MSc‡

Yael Gernez, MD, PhD*

*Division of Allergy, Immunology, and Rheumatology
Department of Pediatrics

Stanford University School of Medicine
Stanford, California

†Division of Infectious Diseases
Department of Medicine

Stanford University School of Medicine
Stanford, California

‡Department of Otolaryngology, Head and Neck Surgery
Stanford University School of Medicine
Stanford, California
rachellelo@stanford.edu

References

1. Dykewicz MS, Rodrigues JM, Slavin RG. Allergic fungal rhinosinusitis. *J Allergy Clin Immunol*. 2018;142(2):341–351.
2. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019;394(10209):1638–1650.
3. Head K, Sharp S, Chong LY, Hopkins C, Philpott C. Topical and systemic antifungal therapy for chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2018;9(9):CD012453.
4. Bachert C, Marple B, Hosemann W, Cavaliere C, Wen W, Zhang N. Endotypes of chronic rhinosinusitis with nasal polyps: pathology and possible therapeutic implications. *J Allergy Clin Immunol Pract*. 2020;8(5):1514–1519.
5. 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.
6. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol*. 2019;156(1):44–56.
7. Hirano I, Dellon ES, Hamilton JD, et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis. *Gastroenterology*. 2020;158(1):111–122.e10.
8. Lu-Myers Y, Deal AM, Miller JD, et al. Comparison of socioeconomic and demographic factors in patients with chronic rhinosinusitis and allergic fungal rhinosinusitis. *Otolaryngol Head Neck Surg*. 2015;153(1):137–143.
9. Tsai M, Thauland TJ, Huang AY, et al. Disseminated coccidioidomycosis treated with interferon-gamma and dupilumab. *N Engl J Med*. 2020;382(24):2337–2343.