

Reply

To the Editor:

We thank you for the opportunity to respond to the correspondence¹ regarding our recently accepted article.² Although the correspondence raises interesting points, we would like to draw attention to several important details.¹

First, the authors' conclusions regarding the effects of biologic medications for patients with asthma and comorbid chronic rhinosinusitis with nasal polyps is based on a comparison of end points from distinct clinical trials of omalizumab and dupilumab.¹ The European Medicines Agency assessment report for omalizumab suggests that this approach is not appropriate, as it states, "The effect level as compared with other biologicals remain uncertain as there are no directly comparing studies. The point estimates of effect appeared higher in dupilumab studies, but these studies had different enrolment criteria with respect to requirement for prior surgeries and systemic steroids, differences in populations enrolled, and differences in study conduct."³

Furthermore, although Nasal Polyp Score is an important research outcome, quality-of-life outcomes, including the Sino-Nasal Outcome Test-22, assess the direct impact of disease and are therefore arguably most important for patients. In the compared trials, Sino-Nasal Outcome Test-22 measures (placebo-adjusted mean change from baseline at week 24) were similar between omalizumab (−15.04 to −16.12) and dupilumab (−17.36 to −20.96).^{2,4}

Third, patients enrolled in dupilumab trials required surgery or systemic corticosteroid (SCS) use within 2 years, whereas omalizumab trials omitted such inclusion criteria and excluded patients with SCS use within 2 months of screening.^{2,4} That approximately 28% of placebo patients required rescue SCS or surgery during the first 24 weeks of the dupilumab trials versus 6.2% in the omalizumab trials itself suggests differences in patient populations and trial conduct.^{2,4} There were also apparent differences in comorbid asthma severity, when present, and in levels of type 2 biomarkers.^{2,4} Importantly, these differences in disease severity and intensity of type 2 inflammation may define clinical response.⁵

Lipworth et al¹ propose a potential mechanistic advantage of dupilumab over omalizumab; however, the cyclical nature of the disease mechanism suggests otherwise. IgE mediates effector pathways that result in disease symptoms. By promoting release of mediators that positively feed back to the inflammatory cascade, IgE perpetuates type 2 inflammation, thereby contributing to disease pathogenesis and progression.⁶ In targeting IgE, omalizumab both inhibits the downstream targets that cause symptoms and blocks the perpetuation of inflammation.

Beyond efficacy outcomes, the reported safety results of omalizumab in the POLYP 1 and POLYP 2 clinical studies attest to the unparalleled safety record of omalizumab, with more than 18 years of real-world experience in severe allergic asthma and more than 1.3 million patient-years of usage in clinical practice.²

Chronic rhinosinusitis is a heterogeneous disease, and no single therapeutic approach is appropriate for all patients. As our understanding of the mechanisms and drivers of disease grows, we will

hopefully identify improved biomarkers and decision-making tools to guide patient-specific therapy. Presently, however, establishing the relative efficacy between omalizumab and dupilumab can only truly be accomplished through a direct-comparison study, because cross-trial comparisons are confounded by differences in patient populations and study design.

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