

Nasal Polyps and Biomarkers



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Chronic sinusitis with nasal polyps causes significant morbidity and impairment of quality of life, resulting in billions of dollars of health care costs each year. The standard of care for symptomatic nasal polyps focuses on the use of oral and intranasal steroids. Those patients who are refractory to these treatments often undergo functional endoscopic surgery, followed by treatment with intranasal steroids to prevent recurrence.¹ Surgery for nasal polyps occurs more frequently in patients with aspirin-exaggerated respiratory disease, large polyps, and a history of surgery. The costs associated with surgical intervention are the primary driver of individual health care costs.

Eosinophils have long been associated with the vast majority of cases of nasal polyps in Europe and the United States, frequently in the presence of a T_H2 immune response. The purported roles of eosinophils in nasal polyps have ranged from contributing proinflammatory mediators to trapping bacteria and fungi, among others. Responsiveness to corticosteroids has been associated with the presence of tissue eosinophilia in previous studies. This has driven both the idea that eosinophil levels may be a useful biomarker of disease and the attraction to these cells among researchers as a target for therapeutic intervention.

One such target is IL-5, a T_H2 cytokine, which activates eosinophils. Anti-IL-5 mAbs reduce nasal polyp size in some, but not all patients, suggesting a role for eosinophils in chronic rhinosinusitis with nasal polyps. However, eosinophil markers were not predictive of the response to mepolizumab, one such monoclonal therapy (Claus Bachert, MD, PhD, e-mail communication, April 29, 2017). This paradox has driven the search for indicators of which patients will respond to such treatments.

This background sets the context for the work by Steinke et al² who hypothesized that knowing the level of polyp tissue eosinophilia might help direct patient management. This assumption is

likely based on analogy to the lower airway, where pulmonary tissue eosinophilia levels predict response to such treatments in asthma, a related inflammatory disease. Whether nasal polyp eosinophilia predicts response to targeted medications and therefore is useful in directing the course of nasal polyp management remains to be verified, particularly as expensive novel treatments for reducing inflammation in nasal polyps become available.

Steinke et al² tried to use symptoms and medical history to predict the degree of eosinophils in nasal polyps. They evaluated 74 consecutive patients undergoing surgery for nasal polyps. At presentation, the patients completed the Sino-Nasal Outcome Test-22 (SNOT-22), a disease-specific quality-of-life measure. Absolute eosinophil count, total IgE, and the extent of opacification on sinus computed tomography scan were collected. Postoperatively tissue eosinophilia was quantified in 10 random hpfs and data analyzed addressing both peak and average results. The SNOT-22 and medical history of allergic rhinitis, asthma, or aspirin-exacerbated respiratory disease did not predict tissue eosinophilia. An absolute eosinophil count of greater than 300 was associated with nasal polyp tissue eosinophilia, though the magnitude of its predictive value was small. In contrast, neither total IgE nor extent of sinus computed tomography opacification predicted the degree of eosinophilia in nasal polyps. In sum, Steinke et al could not identify a clinical feature or biomarker that robustly predicted the presence of nasal polyp tissue eosinophilia. Furthermore, they questioned the utility of tissue pathology: "Although individuals could be identified who were unambiguously eosinophilic or non-eosinophilic, a large portion of our cohort presented across a continuous spectrum of tissue eosinophil expression, rendering arbitrary any definitive cutoff distinguishing these conditions."

The article raises several interesting issues. When doing clinical studies, we must ask ourselves how relevant is the study population to clinical practice and how relevant is the population to the question addressed by the study. The answer to the first question is easy. Patients in this study all had nasal polyps and failed treatment with oral and intranasal steroids and thus were referred for surgery, the current standard of care. Thus, the study is broadly applicable clinically. How likely would studying these individuals answer the predictive value of clinical and biological markers examined in predicting nasal polyp tissue eosinophilia? Eosinophils are considered sensitive to oral steroids, so the patients in this study represent a mixture of individuals with tissue eosinophils who did not respond to oral steroids as well as patients in whom eosinophils are irrelevant to their nasal polyp pathophysiology. The heterogeneity of the phenotype of chronic sinusitis with nasal polyps has made association studies such as this one difficult to interpret.

The recognition of the molecular heterogeneity of nasal polyps led to emphasis in the field on a search for biomarkers to predict

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the success of treatment, as Steinke et al attempted here. As we enter the era of biologics that target specific pathways suspected to be involved in nasal polyps, desire to identify predictors of response will intensify. For example, the use of dupilumab, an mAb targeting the IL-4 receptor alpha, showed the importance of IL-4 and IL-13 in the inflammatory process associated with nasal polyps in a pilot study.³

How accurate does a biomarker need to be to be clinically useful? A predictive model is a mathematical relationship between disease variables and an outcome variable with the goal of predicting a future outcome on the basis of values of the disease variables in the model. The term biomarker refers to a measurement variable that is associated with disease outcome, either a single measurement or a combination computed from measures of numerous other variables. The accuracy and reproducibility of the assessment of the biomarker should be considered. Steinke et al did not look for combinations of their biomarkers to totally exclude the utility of the data they gathered, but pointed out the shortfall in predicting their single outcome variable.

Demonstrating that a biomarker is predictive of treatment benefit requires biomarker status on all patients and comparison of treated versus untreated, preferably in the context of a randomized study. Steinke et al did not perform a randomized trial, did not include subjects who were not about to undergo surgery (although a different technique for characterizing tissue eosinophilia would have been needed in this group), and did not use a long-term outcome (their prediction of surgical success was the SNOT-22 score at 3 months, a time point that is not sensitive to the success of surgery). Much longer follow-up of the patients undergoing surgery might begin to address this problem. A formal statistical test of the treatment-by-biomarker interaction should also be significant.

Is biomarker strategy the way forward for guiding nasal polyp management? From a theoretical point of view, the answer is yes. However, from a practical position, the answer is maybe. Nasal polyps are benign, unlike cancer where the prognosis is crucial. Indeed, the most frequently used treatment oral and/or intranasal steroids is empiric. Rather, we look for alternative treatments when oral steroids fail. If you consider treatment with oral steroids as a therapeutic trial, then considering biologics for those who fail may be the preferred treatment algorithm until a predictive biomarker is validated.

The introduction of new, expensive biologics into the treatment paradigm of chronic sinusitis with nasal polyps, though not the subject of the article by Steinke et al, needs to be briefly addressed here. The main issues we are facing in using these drugs are which subgroup of patients with nasal polyps should be targeted and how much clinical improvement is important. Which clinical outcomes should be evaluated needs further refinement, but the choices have already been delineated. Another problem is the cost of these treatments. For example, the cost of treatment of nasal polyps with dupilumab at the dosing regimen used in the pilot study and the cost of the medication for its current indication of atopic dermatitis exceeds the cost of treating chronic sinusitis with nasal polyps surgery every 6 months.⁴ Oral steroids, with all their attendant side effects, are cheap. It is our opinion that cost issues should be left to the payers, though we recognize that all will have input and opinions on these complex issues. Instead, clinicians and regulatory agencies should focus on how these new, effective, and safe treatments fit into the overall management strategy described above for nasal polyps, especially as they do not appear to alter the natural history of the disease after cessation of therapy (like immunotherapy does for allergic rhinitis). Our feeling is that mAbs will be useful in patients who have recurrent polyps after surgery and/or the use of oral or intranasal steroids. Steinke et al unfortunately were not able to find a clinically straightforward biomarker of nasal polyps. Until sensitive biomarkers are available to refine this strategy, clinicians will need to use therapeutic trials in individual patients to move forward.

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