

Uncharted Waters: Challenges in the Era of Biologic Therapies for Nasal Polyposis



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Several new, promising, targeted therapies for nasal polyposis are being tested in large-scale clinical trials. These agents target pathways thought to be involved in the disease, including IgE, IL-5, IL-4/IL-13, and others. Designing these trials poses significant challenges: who and when to enroll is not completely clear, optimal dosing is not known, outcome measures are insufficiently robust, there are no validated biomarkers, trial regimens may not comport with how clinicians might use these drugs once approved, and cost-benefit ratios have not been assessed. Thus, there is a need to consider such questions, as trials of these novel treatments continue and these biologics become available. Despite these uncertainties about trial design, there remains a great deal of excitement in the field as we approach the dawn of a new era of therapeutic options for nasal polyposis. In this rostrum, we enumerate these issues and call for a conference that will allow stakeholders in the field to confront them as we enter this new era of opportunity to advance the treatment of nasal polyposis. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:68-70)

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INTRODUCTION

Heterogeneity among patients marks inflammation in nasal polyposis.¹ Indeed, work over the last several decades has identified the presence of multiple inflammatory pathways that contribute to this disease. The fruits of this research have now provided us with humanized mAbs that target novel and specific

components of these pathways.² Pilot studies using these mAbs show impressive reduction in disease markers after treatment, highlighting the importance of certain mediators (eg, IgE, IL-5, and IL-4/IL-13).^{3,4} The current challenge is how to incorporate these biologics into our treatment paradigm. A plan for using these promising therapies offers the chance to usher in a new era in the field. Indeed, this is an exciting time in rhinology.

Currently, we treat large intranasal polyps with oral steroids followed by intranasal steroids. When this fails, we usually perform endoscopic sinus surgery. Because this strategy is unsuccessful in some patients, multiple other remedies have been proposed and tested to some degree. Few, however, have been proven efficacious outside of limited settings (eg, targeting leukotriene pathways and/or aspirin desensitization in aspirin-exacerbated respiratory disease). Intranasal steroids have been approved for treatment, though effect size is relatively modest. Therein lies the key unanswered question in the field today: which individuals who fail our current treatment approaches would benefit from a biologic?

DEFINING FAILURE/CONTROL OF DISEASE

Approaching this conundrum is not straightforward. One barrier is that there is no standard definition of failure of treatment, or, more importantly, control of the disease.⁵ Is failure of treatment defined as the need for surgery or additional courses of oral steroids? To answer this question, we must consider carefully the time interval between surgeries and/or courses of oral steroids. If the need for surgery is every 5 years, is using a biologic regularly for all of those 5 years justified? When do the risks of multiple courses of oral steroids outweigh their benefits and warrant biologics? Once, twice, 3 or 4 times a year? How should we compare the safety of the biologic to the safety of repeated courses of oral steroids and/or surgery? Thus, the basic decisions of when to start biologic therapy and for which patients are complex and unanswered at this time.

DEFINING CANDIDATES FOR TREATMENT

We must also consider patient comorbidities. Severe uncontrolled and aspirin-intolerant asthma frequently coexist in patients with nasal polyps and are major indications for the use of biologics in asthma. Thus, studying the role of biologics in patients with polyps with these diseases might not be as useful or relevant, because these drugs are already indicated to control lower airways disease in these patients. Would it not be more relevant to focus on the patient with nasal polyps who does not qualify for biologic therapy based on the presence of severe asthma? These patients are far more numerous. Another clinical challenge is patients with barriers to standard therapy, for example, the patient with diabetes or insulin dependence who does not tolerate oral steroids and the patient with severe medical

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conditions (eg, severe heart or lung disease) placing them at high risk for anesthesia, or those who require anticoagulant therapy that significantly increases the risk of surgery. These patients, who are at a higher risk for certain medical treatments or surgery, may be ideal candidates for biologic therapy. However, they represent a small percentage of the total number of patients with nasal polyps.

CHOOSING A DRUG

In the coming years, it is likely that several different biologics will have indications for the treatment of nasal polyps. Which ones do we choose? Biomarker-directed selection is the obvious answer, but no biomarker currently predicts successful control of disease.^{4,6} In asthma, patients with high eosinophil counts are more likely to respond to anti-IL-5 mAbs. However, investigations to identify the predictive use of biomarkers for nasal polyposis have been unsuccessful to date because there are no known predictors of successful treatment. Peripheral and intranasal eosinophilia (or markers thereof), computed tomography (CT) imaging stratification, cytokine markers (eg, IL-5) have all been put forward as potential biomarkers.⁴ These and other clinical markers have been used in endotyping to define subcategories of disease that might behave differently, and potentially respond differently to various treatments.^{1,6} These studies are in their infancy, especially as compared with asthma. Most importantly, how predictive does a biomarker need to be to help the clinician choose the correct biologic? Would a therapeutic trial be a more useful strategy? Which biologic do we choose first for a trial? To date, we have no answers to these important questions. Should we also look for biomarkers that predict failure?

DEFINING UTILITY OF TREATMENT

Efficacy for the treatment of nasal polyps has been defined by the Food and Drug Administration (FDA) as a decrease in polyp size and symptom improvement.³ Are these criteria sufficient to define the utility of a biologic treatment for nasal polyps? From an economic standpoint, eliminating the need for surgery would lead to large cost savings (even considering the potential for office-based procedures). To this end, some trials have attempted to set standardized criteria that would lead to an indication for surgery and then used the need for surgery as one of the parameters to help assess the utility of biologics. Nevertheless, the vast majority of surgeries for the treatment of nasal polyps are elective and have a relative indication. The absolute indications for surgery, such as orbital and intracranial complications and mucocoeles, are few. Does a decrease in polyp size or a reduction in symptom score alone define a reduction in the need for surgical intervention? We think not.

DEFINING THE DOSING REGIMEN

There are many questions about the best treatment regimen for the delivery of biologics. In all the pilot studies, efficacy ranged from 60% to 90%. Characterizing successfully treated patients in such studies will be critical. In all trials to date, stopping the biologic led to a recurrence of nasal polyps and recurrence of symptoms. Thus, there might be a need to continue treatment indefinitely, in contrast to immunotherapy for seasonal allergic rhinitis. What treatment regimen works best for which patient is, therefore, a critical question. We need additional clinical trials to address issues of dose, regimen, and timing. However, these trials are expensive and time consuming.

DEFINING THE RIGHT TRIAL OUTCOMES

The developers of biologics for nasal polyps begin with safety studies in man followed by pilot studies in patients with the largest nasal polyps to show efficacy. Large clinical trials to prove efficacy and effectiveness follow to gain an indication for the treatment of nasal polyps from the FDA and analogous agencies worldwide. Although efficacy is important, we must understand where the treatment fits into the existing treatment paradigm. Several issues define the challenges in this arena.

Patients enrolled in current trials have large polyps (eg, involving the nasal airway below the middle turbinate at least on both sides) and are untreated with oral steroids. They may or may not have asthma and may or may not have had prior sinus surgery. Large polyps that contain significant amounts of inflammatory tissue are helpful in that their size allows for the detection of effectiveness of a biologic. The polyp score, then, which is a measure of size, is a primary or coprimary outcome measure.

The polyp score, however, has major flaws in its current format.⁷ First, polyps that are stage 2, the most common size presenting to the clinician, are variable in their burden; that is, decreasing a nasal polyp from a “bulky” 2 to a “slim” 2 may provide tremendous symptomatic improvement for the patient despite no change in the polyp score (and thus lack of efficacy when using this common primary outcome in current trials), whereas changing from a 3 to a 2 may have minimal effect on symptoms (but potentially help show efficacy in current trials). Second, previous surgery compromises the analysis of change in polyp burden. A postop ethmoid cavity has to fill with polyp tissue before the polyp tissue extrudes into the nasal cavity and can be scored in the current system. Thus, these individuals may have more inflammatory tissue than an unoperated patient with large nasal polyps, which can fill only part of the ethmoid sinus before becoming visible to the scoring system. Relying on the current polyp endoscopy scoring systems, therefore, is suboptimal.

Although demonstrating the effect of a biologic in patients with massive polyps is good for a proof-of-concept study, it makes recruiting patients for large clinical trials difficult. More importantly, it does not provide germane information that is applicable to the typical patient who is unresponsive to surgery and oral steroids. These are the patients who need better therapies, because the current treatment paradigm does not work well for them.

Other outcomes measures exist, such as the 22-item Sinonasal Outcomes Test (SNOT-22) (a patient-reported outcome measure), smell identification tests, visual analog scales, individual symptom scores, sinus CT scans, and nasal peak inspiratory flow. In those patients with comorbid asthma, we also can evaluate lower airway quality-of-life measures and pulmonary functions tests. All these outcome measures improve with biologics, but all of them have shortfalls. In addition, costs of measuring them vary greatly (imaging, even using limited screening methods, can be relatively expensive in aggregate, especially from a public health point of view) and they add significant expense to clinical trials. None of them help answer the key question: how do we incorporate these biologics into our current treatment paradigm for nasal polyps? To address this question, we must develop new study designs for phase 3 clinical trials of therapies for nasal polyps. These designs must lower the costs of the study, include the typical challenging patients commonly seen in practice, and determine which patients would benefit most.

DEFINING NEW TRIAL DESIGNS

Polyp size is an important outcome, but the current scoring system needs refinement to incorporate the more typical patient whose polyp score does not meet the current study entrance criteria, but whose quality of life is sufficiently impaired. Should the SNOT 22 replace polyp scores as a primary outcome? The SNOT 22 has been used extensively in the study of chronic sinusitis with and without polyps and has a defined, minimal clinically important difference for testing therapies. Using a patient-reported outcome variable in a disease marked by significant morbidity and no mortality seems important, and we believe this would be an appropriate primary outcome. Thus, once a patient completes an appropriate evaluation that includes nasal endoscopy and a sinus CT scan, they could be entered into a phase 3 clinical trial with SNOT 22 as the primary outcome.

What medical therapy should patients fail before entry? Is an intranasal steroid sufficient (all patients should be on this treatment)? Should the patients have recurred within a year of treatment following surgery or oral prednisone?

Although placebo groups are crucial in pilot studies, we believe that the phase 3 studies may not require them, provided groups with different dosing are incorporated. One approach would be to treat patients for a month or two with a biologic and monitor their progress. If there is no response, the patient would be eliminated from the trial and their data analyzed to look for predictors of failure. If there is a positive response, then different dosing regimens should be investigated. These and other clever study designs should be considered, of course with discussion with regulatory agencies that may require comparison.

DEFINING COST-BENEFIT

Cost will play a major role in treatment decisions in the future. The major expense in the current practice paradigm is the cost of surgical intervention.⁸ Other costs to society include presenteeism, doctor visits, and missed work days.⁹ The yearly cost of a biologic, which currently requires continuous treatment, greatly exceeds the cost of surgery, particularly if the average polyp surgery is about once every 5 years.

CONCLUSIONS

An exciting new era in the treatment of nasal polyps is upon us. We will soon have powerful new tools to treat the disease. We must prepare for this by generating sufficient knowledge on how to fit them in their current treatment regimen. Our goals are simple: we want to overcome the ineffectiveness of current treatments and minimize the risk of side effects found with present approaches. Achieving these objectives with the use of biologics is far from simple, especially when the impact of therapy is not curative.

We propose a conference to discuss all these issues and make plans and recommendations for the future. Multiple parties should participate including clinicians who treat nasal polyps, the National Institutes of Health who supports research, the FDA who approves biologics, pharmaceutical companies who develop and finance clinical trials, health care economists, and the payers who will finance these treatments after they are approved for clinical use. Only then can we fully maximize the benefit of these new therapies for our patients.

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