Knowledge Gaps and Research Needs for Biologic Therapy in Rhinology Practice

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KEYWORDS

- Biologic agents • Chronic rhinosinusitis with nasal polyps
- Aspirin-exacerbated respiratory disease

KEY POINTS

- Indications for use of biologic agents in various chronic rhinosinusitis with nasal polyposis (CRSwNP) endotypes need to be clearly defined.
- Biomarkers associated with a clinically meaningful response to biologic therapies are needed to facilitate appropriate patient selection.
- Head-to-head trials will be needed to compare outcomes of various biologic agents for CRSwNP.
- Required duration of biologic therapy needs to be assessed.
- Cost-effectiveness analyses are needed to determine an appropriate treatment algorithm.

INTRODUCTION/HISTORY/DEFINITIONS/BACKGROUND

Chronic rhinosinusitis (CRS) is a form of sinonasal inflammation with unmet needs for patient treatment, especially in those with recalcitrant disease. The prevalence of CRS is between 5% and 16%,[1] with nasal polyps (CRSwNP) occurring in about 25% of cases.[2] The economic burden of CRS treatment is estimated to be approximately $22 billion per year in the United States.[1] CRS patients are a heterogeneous group represented by several inflammatory endotypes. Among these, the most common CRSwNP endotypes are defined by high levels of type-2 inflammatory mediators, including eosinophilic CRSwNP, aspirin-exacerbated respiratory disease (AERD), allergic fungal rhinosinusitis (AFRS), and central compartment atopic disease (CCAD).[3,4] Current treatment options for all CRS endotypes include appropriate medical management with topical saline irrigations and intranasal corticosteroids, as well

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as oral corticosteroids or antibiotics as medically indicated. Endoscopic sinus surgery (ESS) is subsequently considered to remove obstructive tissue and facilitate the postoperative delivery of topical medications. However, despite adherence to contemporary treatment guidelines, the rates of disease recurrence following ESS remains high.[5] Innovative treatment strategies are therefore needed to improve patient care for this recalcitrant disease.

Biologic agents are humanized monoclonal antibodies designed to act upon a specific target, such as specific Th-2 mediators/receptors (eg, immunoglobulin E [IgE], interleukin [IL]-5 and IL-5Rα, IL-4Rα) associated with many forms of CRSwNP.[6] By targeting specific pathways of the inflammatory response, biologic medications have shown promising results for multiple diseases including asthma, atopic dermatitis and CRSwNP.[7] In June 2019, dupilumab was the first biologic approved for use in CRSwNP patients, and omalizumab was approved for use in CRSwNP in December 2020. There are several other biologics currently under investigation for potential approval for the CRSwNP indication in the near future.

NATURE OF THE PROBLEM

Despite studies suggesting multiple objective and patient-reported benefits of biologic agents as an adjunctive treatment for CRSwNP, several unanswered questions remain. These questions are challenging to investigate because of the immunologic complexity and heterogeneity of CRSwNP patients. Additionally, when attempting to compare biologic agents with other management options, blinding patients and physicians becomes nearly impossible, particularly because surgery is a potential treatment for recalcitrant CRSwNP. Nonetheless, research investigating the current gaps in knowledge for biologic agents in a rhinology practice is critical. Overall, the most important research need is to determine the best treatment algorithm for each unique patient. Treatment algorithms should be determined by patient outcomes and cost-effectiveness analyses.

Patients have options regarding their care for CRSwNP and should consider the risks, benefits, and alternatives to all treatment options. At this point, quality-of-life outcomes have not been well studied for comparison of biologic agents with other CRSwNP treatment regimens, such as aspirin desensitization and high-dose maintenance aspirin therapy for AERD. Additionally, the efficacy of various treatment algorithms, including the timing of surgical intervention and biologic agent administration, has not been compared. By furthering these areas of investigation, counseling patients on treatment choices would become supported by evidence-based medicine.

Biologic agents, which are currently costly, are likely to be long-term or even lifelong medications. Prior work has suggested that surgery is cost-effective when compared with biologic agents for the initial treatment of CRSwNP.[8] However, cost-effectiveness studies are lacking to evaluate the economic effects of incorporating biologic agents as an option after a patient has failed a primary surgery. Additionally, the heterogeneous group of CRSwNP patients should be assessed to determine which patients, if any, have long-lasting efficacy if biologic agents are stopped. More work is needed to characterize biomarkers to identify patients who will best respond to biologics, making biologic agents a potentially more cost-effective option compared with multiple surgeries and other medical management.[9]

In November 2019, the National Institutes of Health (NIH) hosted a meeting to promote discussion among experts in industry and the fields of rhinology, pulmonary

medicine, allergy/immunology, and statistics. This discussion identified several critical research needs for the study of biologic agents in CRSwNP patients.[10] The group acknowledged that the primary goal of studies moving forward is to determine where biologic agents belong within the treatment algorithm. Several topics of discussion were raised, including how to measure success (through patient-reported outcomes, imaging, endoscopy findings, or biomarkers) and the challenges of inclusion and exclusion criteria when studying a heterogeneous group of patients, while still maintaining generalizability of data.[10]

CURRENT EVIDENCE

The current evidence supporting biologic agents in CRSwNP is discussed in more detail in Ramaswamy and colleagues' article, "Current Evidence for Biologic Therapy in Chronic Rhinosinusitis with Nasal Polyposis," by in this issue. Briefly, dupilumab, which targets the effects of IL-4 and IL-13 by targeting the IL-4 α-receptor shared by these 2 cytokines, was approved for use in CRSwNP patients in 2019. Dupilumab has been shown to improve polyp scores and quality-of-life measures.[11] Omalizumab, an anti-IgE agent, was approved for use in polyp patients in December 2020. Studies suggest improvement of clinical, endoscopic, and quality-of-life measures.[12] There are several other biologic agents approved for use in other Th2-mediated respiratory diseases, such as asthma, as well as newer biologic agents under investigation. Likely, biologic agents with other targets, such IL-5 and its receptor, will become available for the CRSwNP indication.[7]

GUIDANCE FOR TREATMENT

Several documents contain initial guidance for otolaryngologists regarding the use of biologics in CRSwNP. A group of rhinologists and allergists from the United States recently proposed a treatment algorithm for CRSwNP patients after the research-focused NIH discussion revealed little evidence-based guidance for current treatment planning.[13] These experts advocated consideration of biologic agents as a treatment option after a patient fails both medical management and ESS with postoperative oral and topical corticosteroids. The document also stressed the importance of evaluating patients at 4 months for improvement on these medications. This timeline is similar to the evaluation period suggested for biologic agents in asthma patients.[14] Evaluation for initial benefit of biologic therapy in CRSwNP may include nasal endoscopy, investigation of sinonasal quality-of-life measures, and the need for medications for sinus and respiratory symptoms.[13]

European guidance states that biologic agents should be considered for patients who have had surgery and meet any 3 of the following criteria: type 2 inflammation, 2 or more courses of oral steroids within 1 year, impaired quality of life, loss of smell, and comorbid asthma. For patients who have not undergone surgery, 4 or more of the criteria must be met before considering biologic agents for CRSwNP.[15] As more data become available, recommendations for specific patient populations will likely change.

CONTROVERSIES

Controversies regarding the care of CRSwNP patients are primarily focused on delineating the most appropriate treatment algorithm. In present times, proposed treatment algorithms are largely based on expert opinion, and will evolve with emerging evidence and as more biologic agents become US Food and Drug Administration

(FDA) approved for the CRSwNP indication. One area of dispute is if biologic agents should be prescribed to patients before consideration of surgery. Although some advocate for considering biologic agents only after a surgical intervention, there may be some situations in which surgery or anesthesia is not feasible or appropriate. Future evaluation of biologic agents as a postoperative adjuvant therapy for patients with persistent sinonasal inflammation after ESS will add critical information in this regard. Although the concept of a medical polypectomy or use of a biologic agent to comprehensively remove established polyp tissue is not supported by current phase 3 trials, the efficacy of these medications in reversing the early recurrence of disease remains a concept with the potential to greatly decrease the need for revision ESS.

Another area of controversy to consider is the appropriate prescriber for each indication of biologic agents. As biologic agents have been approved and used for treatment of asthma and other Th-2 mediated processes for several years, allergy, immunology, and pulmonary physicians have extensive experience prescribing these medications. Many CRSwNP patients have a comorbid asthma diagnosis and will be followed by both an otolaryngologist and a medical specialist. As indications for biologic agents expand, there will be a need to closely work together to communicate regarding these complicated patients. Each specialist has expertise in unique diagnostic tools (eg, nasal endoscopy and pulmonary function testing), and while controversies regarding appropriate patient selection for biologic agents may arise, there will be significant benefit from collaboration.

The current Coronavirus disease 2019 (COVID-19) pandemic has also led to questions regarding the safety of biologic agents during these unexpected times. A rare adverse effect of Th2-associated biologic agents is a helminthic infection, and there is a technical possibility of an increased susceptibility to COVID-19 or other respiratory viral pathogens while taking these immune-modulating medications.[16] A recent study has shown a decrease in ACE2 receptors, the site of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) host entry, in polyp tissue compared with sinonasal tissue from patients without CRSwNP.[17] Another recent study suggested that patients on multiple biologics for psoriasis management did show an increased risk of COVID infection but had decreased risk of severe COVID symptoms, potentially because of the effects of biologic agents acting to block a cytokine storm.[18] Compared with surgery, some biologic agents can be administered at home, avoiding contact with others, which may be beneficial during this time. As with most research areas regarding the current pandemic, there is still much to learn about the relationship between biologic agents and COVID-19. Additional work to understand the potential effects of immune modulators on host response to vaccination will also be needed.

DISCUSSION

This section discusses several research needs for biologic therapy in rhinology practice in order to develop evidence-based treatment algorithm recommendations (**Table 1**).

Biomarkers: Identifying the Right Drug, for the Right Patient, at the Right Time

Biomarkers are measurable clinical factors that may aid in disease diagnosis or the prediction of a therapeutic response. Biomarkers are critical to predict the success of biologic therapies in an individual patient with CRS. Uniform and objective measures across studies are needed and may be measurable from any biologic source. Although several biomarkers for the identification of specific CRSwNP endotypes,

Table 1
Research needs

Area of Research	Specific Questions
Biomarkers	• Which biomarkers should be used to define eligibility for biologic agents? • How can success of biologic treatment be measured using biomarkers? • Can biomarkers be used to determine if patients can wean or stop biologic therapy?
Endotype/phenotype	• How do biologic agents perform in nested analyses of CRSwNP subgroups?
Clinical trials – head-to-head comparisons	• How do biologic agents compare to one another in terms of symptom improvement, tolerance, and safety?
CRSsNP	• Are biologic agents efficacious in patients without nasal polyps? • Is biologic efficacy dependent on allergy/atopic state?
Cost-effectiveness	• For which patients are biologics considered cost-effective? • At what point does biologic therapy become cost-effective compared with revision surgery?
AERD	• How does aspirin desensitization compare with biologic agents in AERD patients? • Which treatment option is better tolerated by patients – biologic therapy or maintenance aspirin therapy? • Is there any benefit to combining aspirin therapy with biologic agents for the most recalcitrant patients?

such as AERD, have been described, a predictive biomarker for response to biologic therapies has yet to be described.[19,20] This is a critical need to identify patients with the greatest likelihood of experiencing a clinically important treatment response.

Endotype/Phenotype

It is accepted that there are several unique endotypes and phenotypes of CRS.[21] Likely, specific molecular antibody targets are most appropriate for distinct subtypes of CRS. Biomarkers, as discussed previously, will be useful for a deeper understanding of subtypes of disease. Further work investigating the true delineation of CRS patients, beyond CRSwNP and CRSsNP, will also advance the understanding of appropriate biologic therapy for each individual patient.[21] Studies should include all CRSwNP patients, but also be powered for separate analyses of subgroups of patients to understand indications for specific patients. For example, the nested analysis of the dupilumab phase 2a clinical trial (NCT01920893) showed several superior outcomes among subjects with AERD versus those without aspirin sensitivity.[22] Additionally, some nasal polyp endotypes, such as AFRS, have been largely excluded from prior clinical study and require further investigation.[11]

Head-to-Head Trials

Once more biologic options exist for CRSwNP patients, there will be a need to compare options in head-to-head blinded trials. These trials will allow for a direct comparison of biologics options with similar but slightly variable targets within the inflammatory pathway. This work may also allow the identification of patient or polyp characteristics, which respond in a more significant way to a specific biologic agent.

Most work has focused on CRSwNP patients, and biologic agents have not been well studied in patients with CRSsNP.[23] The benefit of biologic agents in these patients is unknown, and the association with allergy and Th-2 mediated disease is less clear.[24]

Cost-Effectiveness

Cost-effectiveness analyses should include direct costs of surgery and medications and indirect costs such as missed work caused by illness or treatment requirements. Quality-of-life measurements and patient preference will also contribute greatly to these analyses.

Treatment Options - Biologic Agents Versus Aspirin Desensitization

Several studies have suggested the benefit of aspirin desensitization in AERD patients regarding subjective quality-of-life improvement and a decrease in polyp burden and need for revision surgery.[25] Maintenance aspirin therapy is a lifelong treatment, and while inexpensive, it is associated with adverse effects.[26] A comparison of aspirin therapy and biologic agents in regards to efficacy and quality-of-life outcomes in AERD patients is warranted. This work will be especially interesting, as these management strategies are both long-term treatment options, but vary greatly in direct costs.

FUTURE DIRECTIONS

There are several ongoing trials to assess various biologics in CRSwNP patients. These studies are assessing both CRSwNP patients in general, and specific subsets of CRSwNP. Given that there is still much to learn regarding endotypes and phenotypes of CRSwNP and biomarkers to predict a clinical response, this area of research will be ongoing for many years. It is particularly challenging to determine the external validity of CRS studies, as CRSwNP patients are known to be heterogeneous regarding biomarkers, allergic status, polyp size, computed tomography findings, and subjective quality of life. On a larger scale, it would be beneficial to consider a multi-institutional registry of CRSwNP patients to include investigation of outcomes and polyp tissue from participants around the world.[10] Ultimately, work in this field will lead to more complete and evidence-based treatment recommendations to guide physicians caring for these complicated patients.

SUMMARY

Biologic agents are an emerging therapeutic option for patients with recalcitrant sinus disease. Although pivotal phase 3 trials consistently demonstrate clinically important differences in several objective and patient reported outcomes following biologic treatment for CRSwNP, additional investigations are needed to define their appropriate use. Future study aimed at discovering predictive biomarkers will greatly aid in patient identification, while evaluation of efficacy in the postoperative setting will further define treatment indications. Finally, evaluation of specific CRSwNP endotypes, such as AFRS, will fill existing gaps in the literature and provide evidence for a greater number of patients with persistent sinonasal disease.

CLINICS CARE POINTS

- Biologic agents have recently become approved for use in CRSwNP patients.
- Biologic agent use in specific CRSwNP endotypes needs to be studied to determine appropriate patient selection.

- Uniform use of biomarkers and clinical outcome measures should be incorporated to study clinical improvement.
- Cost-effectiveness studies are currently a critical unmet need.

DISCLOSURE

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