Relationships among allergic rhinitis, asthma, and chronic rhinosinusitis

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) is a common disease in the United States. There are a significant number of patients with CRS who are refractory to standard medical and surgical therapy. Many of these patients also have comorbid allergic rhinitis (AR) and asthma, although the underlying pathophysiology that connects these three conditions remains unclear.

Objective: The goal of this article is to review the relationships among CRS, AR and asthma.

Methods: Scientific literature that addresses the prevalence of AR and asthma in CRS populations, the effect of AR and asthma on CRS disease severity, and whether treatment of AR and asthma can affect CRS outcomes was reviewed.

Results: The literature supports the relationship between AR and CRS, but there is no direct evidence of causality the between the two conditions. There is a high prevalence of CRS in patients with asthma and the presence of CRS is associated with worse asthma outcomes. There is weak evidence that treatment of CRS may improve asthma outcomes. Targeting type 2 inflammation via biologics is being investigated in the treatment of asthma and CRS.

Conclusion: AR, asthma, and CRS are closely related and understanding the associations among these comorbid diseases will have significant clinical implication.

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Chronic rhinosinusitis (CRS) is a common disease, which impacts ~12 to 14% of the population in the United States.^{1,2} The association among allergic rhinitis (AR), asthma, and CRS has long been observed, but the mechanism remains unclear. The goal of this review was to further examine the connections among these diseases and whether guiding the management accordingly can improve outcomes in patients with CRS.

EPIDEMIOLOGIC CONNECTION

Prevalence of Atopy in CRS

There have been numerous studies that showed that atopy is more prevalent in populations with CRS. The prevalence of positive skin-prick testing results ranges from 50 to 84%.^{3–6} Some studies showed that perennial allergens, including molds, dust mites, and animals, may play a more significant role than seasonal allergens, which indicates that aggressive treatment of these allergies may improve CRS outcomes.⁴ The majority of patients with CRS are sensitized to multiple allergens, which indicates that control of multiple allergy risk factors through environment, pharmacologic, and immunotherapy interventions may improve CRS symptoms.⁷ Other data about patients with CRS refractory to medical management alone showed that there was a high prevalence of atopy but similar to those in the control rhinitis group and that no specific allergen group seemed to predispose patients to CRS.⁵ Moreover, there is no convincing evidence in the literature that atopy is causative in CRS.

Connection between Atopy and Severity of CRS

According to data from Geisinger Clinic primary care patients, patients with CRS had a higher prevalence of premorbid AR and

chronic rhinitis.⁸ Given the high prevalence of atopy in patients with CRS, it has been postulated that atopy and AR contribute to the severity of CRS. In pediatric patients who underwent functional endoscopic sinus surgery, their recovery time after surgery was significantly longer if they had a history of AR compared with those who did not.⁹ When measuring CRS severity by sinus computed tomography (CT), there were mixed results related to atopy. In studies that looked at severe CRS, the extent of disease radiographically was significantly correlated with peripheral eosinophilia and the presence of atopy.^{10,11}

In patients refractory to medical management alone, Batra *et al.*¹² found that those with inhalant allergies had a higher mean Lund-Mackay score than those without inhalant allergies. Ramadan *et al.*¹³ noted similar findings and found that patients with allergy and with CRS had higher CT scores (mean score, 12) when compared with patients without allergy and with CRS (mean score, 6). Robinson *et al.*¹⁴ also found that the mean Lund-Mackay score was higher in those with atopy than in those without atopy, although this difference disappeared when patients were grouped by those with CRS with nasal polyps (CRSwNP) and those with CRS without nasal polyps (CRSsNP). Pearlman *et al.*¹⁵ showed no significant difference between the mean Lund-Mackay score and the presence of atopy when comparing patients with CRSwNP and patients with CRSsNP. Similarly, Tan *et al.*⁵ found that there was no difference in Lund-Mackay scores among patients with atopy and with CRS and patients without atopy with CRS who were undergoing sinus surgery. These studies indicate evidence of an association between allergy and CRS, but there is no direct evidence of causality between the two conditions. The discrepancies among these studies is likely at least partially due to the inaccuracy of the Lund-Mackay scoring system in measuring the extent of sinus disease. A different approach that uses a volumetric scoring system may better reflect the true severity of sinus disease.

Does Treating Allergy Improve Outcomes in CRS?

Given the high prevalence of atopy in CRS and the possible association with disease severity, some researchers have started to investigate whether treatment of atopy improves CRS outcomes. Thus far, there are limited data in this area. One of the most effective treatments of AR is immunotherapy. DeYoung *et al.*¹⁶ conducted a systematic review of the efficacy of immunotherapy in CRS. They found that the symptom scores generally improved in patients treated with immunotherapy compared with baseline data and with control patients. Objectively, they looked at endoscopic examination and sinus CT

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scoring before and after immunotherapy, and observed improvement over the short term. They also noted a decreased need for revision surgeries, interventional office visits, and intranasal and oral steroid use. Their conclusions were limited by the amount of data available to analyze, but they concluded that there is weak evidence to support the use of immunotherapy as an adjunctive treatment for patients with CRS. The positive preliminary data from this review should encourage further research in this domain.

ASTHMA AND CRS CONNECTION

Prevalence Studies

The prevalence of asthma has been shown to be increased in patients with CRS. From the Global Allergy and Asthma European Network survey in Europe, the median prevalence of asthma in all 19 centers was 8.6% and ranged from 5.2% to 16.8%, and asthma was found to be less common in the older age group (age, 65–74 years). There was a strong association between asthma and CRS, which was even stronger in those who reported both CRS and AR.¹⁷ Those with CRS without nasal allergies had lower rates of early onset asthma and higher rates of late onset asthma. Likewise, results of studies demonstrated a high prevalence of CRS in patients with asthma. In one study, all the patients with severe asthma had an abnormal sinus CT compared with 88% of the patients with mild-to-moderate asthma. Patients with severe asthma had worse sinus disease both symptomatically and radiographically.¹⁸ Another study of patients with severe asthma showed that 84% of patients with severe asthma had an abnormal sinus CT.¹⁹

Asthma, CRS, and Disease Severity

According to multiple studies, the presence of CRS is associated with worse asthma outcomes. A study by Ek *et al.*²⁰ that used the Global Allergy and Asthma European Network survey data sought to evaluate the impact of CRS on the quality of life of subjects with asthma. The researchers found that those with CRS and asthma had a lower forced expiratory volume in 1 second predicted and percentage forced vital capacity predicted than patients with asthma alone. Patients with CRS and asthma were more likely to have had increased asthma symptoms over the past month and worse quality-of-life scores than those with asthma alone. A study that characterized patients with severe asthma showed that 54% of patients with severe asthma had a history of rhinosinusitis versus 33 to 37% in the non-severe groups.²¹ In addition, there is a direct correlation between CRS severity and asthma severity. Patients with severe nasal sinus disease tend to have more frequent asthma exacerbations.²² Rhinosinusitis is a comorbidity associated with severe asthma, and CRS is one of the factors that is reported significantly more often in patients with moderate and severe asthma who have frequent exacerbations compared with patients with asthma and with fewer exacerbations.^{21,23}

Similarly, the presence of asthma has been associated with worse sinus disease. Compared with patients without asthma, patients with asthma demonstrated significantly higher endoscopy and sinus CT severity scores as well as higher absolute eosinophil counts and total immunoglobulin E levels.¹² Lin *et al.*²⁴ found a strong relationship between asthma severity and advancing radiologic severity of CRS on sinus CT. Those with moderate-to-severe asthma were shown to have worse sinus disease than those with mild asthma, with significantly higher mean Lund-Mackay scores.²⁴ Pearlman *et al.*¹⁵ showed that atopic status does not seem to significantly affect this trend because the mean Lund-Mackay score was shown to be highest in patients without atopy and with asthma, followed by patients with atopy and asthma.

Does Treatment of Sinonasal Disease Improve Asthma Outcomes?

Given the strong association between asthma and CRS, the question is raised of whether treatment of one condition may improve outcomes in the other. The American Lung Association–Asthma Clinical Research Centers' Writing Committee *et al.*²⁵ designed a study to determine whether treatment of sinonasal conditions with nasal steroids improves asthma control. Patients were randomized to nasal mometasone or placebo for a 24-week period, and outcomes were measured in terms of a change in Asthma Control Test score, methacholine reactivity, asthma symptoms and related quality of life, rhinitis and/or sinusitis symptoms and related quality of life, and asthma control. In adults, there was a small decrease in asthma symptoms after using mometasone but no difference in asthma-related quality of life, lung function, or episodes of poorly controlled asthma. They concluded that there was no significant improvement in asthma control from treatment of sinonasal disease with nasal corticosteroids.

Multiple studies examined whether surgical treatment of CRS can improve symptoms of comorbid lower airway disease.^{26–29} One study looked at 15 patients who required functional endoscopic sinus surgery for CRS and found that they required a decreased number of days and decreased total dosage of prednisone in the postoperative year compared with the preoperative year.²⁷ Another study looked at more objective measures of improvement in lower airway disease after functional endoscopic sinus surgery and showed that patients had improvement in symptoms and a significant increase in their peak expiratory flow after surgery.²⁸ Finally, a prospective randomized study compared medical and surgical therapy for 43 patients with CRS and concomitant asthma by comparing symptoms, control, forced expiratory volume in 1 second, peak flow, exhaled nitric oxide, medication use, and hospitalizations.²⁹ They found that overall asthma control improved significantly after medical and surgical therapies but that response was better maintained after medical therapy.²⁹

Use of Biologics in Treatment of Asthma and CRS

Targeting type 2 inflammation *via* blocking interleukin (IL)-4 or IL-5 signaling pathways is an approach that has been investigated to reduce the eosinophilic inflammation in patients with asthma and CRSwNP. In several placebo-controlled, double-blind studies, mepolizumab, a humanized anti-IL-5 monoclonal antibody, was shown to reduce the risk of asthma exacerbations, reduce sputum and blood eosinophil counts, and improve quality of life in patients with severe eosinophilic asthma.^{30–32} In those with severe nasal polyposis, mepolizumab improved the nasal polyp endoscopy score and showed a significant reduction in nasal polyp size for at least 1 month after dosing.³³ Reslizumab therapy, another humanized anti-IL-5 monoclonal antibody, showed a significant reduction in sputum eosinophils and in the frequency of asthma exacerbations in patients with moderate-to-severe eosinophilic asthma not controlled on inhaled corticosteroids.^{34,35} Reslizumab has also demonstrated reduction in polyp size, after one injection, in 50% of patients with nasal polyps. This effect was greater in those with higher baseline IL-5 concentrations in their nasal secretions.³⁶

Benralizumab, an anti-IL-5 receptor α monoclonal antibody, decreased airway mucosal, sputum, and blood eosinophil counts in a phase 1 study and has been shown to have an acceptable adverse effect profile.^{37,38} In a phase 2b study that looked at patients with uncontrolled asthma on inhaled corticosteroids and long-acting β agonists, those with baseline elevated sputum or blood eosinophils had reduced exacerbation rates with benralizumab compared with placebo.³⁹ Dupilumab, a monoclonal antibody to the α subunit of the IL-4 receptor, demonstrated reduced asthma exacerbations and improved respiratory symptoms and lung function in patients with moderate-to-severe asthma and with elevated eosinophils,⁴⁰ and

sinonasal symptoms also improved in patients on dupilumab compared with placebo in the study. Dupilumab has recently been studied in patients with CRSwNP, although the results have not been published to date. Finally, omalizumab, an anti-immunoglobulin E monoclonal antibody, has shown benefit in patients with CRSwNP. Omalizumab produced a significant decrease in total nasal endoscopic polyp scores after 16 weeks compared with placebo in patients with nasal polyps and comorbid asthma.⁴¹ Omalizumab is currently approved for use in moderate-to-severe asthma; however, the other medications mentioned are not approved at the present time by the U.S. Food and Drug Administration for asthma or CRSwNP.

CONCLUSIONS

AR, asthma, and CRS appear to be strongly connected with each other. Although the findings that concern atopy and CRS severity have been mixed, the preliminary data on immunotherapy seems to show promise in improving outcomes in CRS. Studying CRSwNP and CRSsNP as separate entities may help to elucidate further how AR affects CRS because the underlying disease mechanisms may be different. Asthma and CRS are clearly associated, and studies that showed improved asthma outcomes after treatment of CRS as well as the promise of targeted biologic therapies are encouraging. More research needs to be done to further characterize the complex relationship between upper and lower airway disease.

Recent studies that used anti-IL-5 targeted therapies in asthma showed decreased asthma exacerbations and improved pulmonary function in patients with eosinophilic asthma.^{31–35} Two small pilot studies of anti-IL-5 monoclonal antibodies (mepolizumab and reslizumab) in patients with CRSwNP showed reduced eosinophilic markers in nasal secretions and serum, but clinical efficacy was noted in only 50% of the patients.^{36,37}

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