

Chronic rhinosinusitis management beyond intranasal steroids and saline solution irrigations

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) is a heterogeneous disease with clinical manifestations that are influenced by the presence or absence of nasal polyposis. Understanding of the current and future treatment modalities for CRS is essential in preventing exacerbation and morbidity associated with this chronic condition.

Objective: The aim of this article is to review the evidence behind current medical therapies and potential new treatments for CRS.

Methods: Scientific literature regarding intranasal and systemic antibiotics, intranasal systemic corticosteroids, and monoclonal antibodies as interventions for CRS with and without nasal polyps was reviewed.

Results: The literature supports the use of topical or systemic glucocorticoids in patients with nasal polyps, and there appears to be a role for systemic antibiotics in the treatment of acute exacerbations of CRS with nasal polyps. The response to corticosteroids or antibiotics in the treatment of exacerbations of CRS without nasal polyps is variable. Due to the lack of appropriately designed trials, there is weak evidence for the adjunctive use of immunotherapy at this time. Monoclonal antibodies that target Immunoglobulin E and T helper cell 2 cytokines have been clinically effective in symptom reduction for some patients with CRS with nasal polyps although further studies are needed.

Conclusion: Current therapies used in the treatment of CRS are discussed.

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Chronic rhinosinusitis (CRS), characterized by chronic inflammation of the nasal mucosa and paranasal sinuses, affects >12.5% of the U.S. population.¹ A diagnosis of CRS requires objective evidence of sinus disease, either endoscopically or radiographically, along with at least 12 weeks' duration of two or more of the following symptoms: mucopurulent drainage, nasal obstruction, facial pain, or decreased olfaction.¹ CRS is further categorized into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). Due to the heterogeneity of the disease and variable responses to medical therapies, CRS can often be problematic to treat, cause significant morbidity, and negatively impact quality of life.

There have been new insights into the pathophysiology of CRS, with some distinct differences noted in the mucosal microenvironment that are associated with the formation of nasal polyps. Secondary defects in expression of epithelial junction proteins can lead to compromised barrier function that may allow for epi-

thelial transmigration of foreign particles and microbes that stimulate local mucosal inflammation.² Tieu *et al.*³ demonstrated that anti-inflammatory proteins, *e.g.*, the S100 family of peptides, that are important in barrier defense and innate immunity are reduced in CRS compared with controls without CRS. CRS is often associated with an acquired impairment in sinonasal mucociliary clearance, which may promote bacterial colonization and biofilm formation.⁴ Although the direct role of bacterial infection and superantigen production in triggering chronic sinusitis remains unclear, the important interaction between commensal bacteria and the sinus mucosa has become increasingly evident in modulating mucosal inflammation.⁵ Bachert *et al.*⁶ demonstrated that many patients with CRSwNP are colonized with *Staphylococcus aureus* and that specific Immunoglobulin E (IgE) to *S. aureus* enterotoxins can develop. The specific IgE to *S. aureus* enterotoxins correlate directly to eosinophilic inflammation observed in CRSwNP.

In the case of CRSwNP, typically, there is a skewing toward a T helper cell 2 (Th2)-predominant microenvironment that promotes eosinophilic recruitment and inflammation into mucosal sinus tissue. Classically, CRSwNP is associated with Th2-mediated eosinophilic inflammation associated with high interleukin (IL)-5 and eosinophil cationic protein in the polyp tissue, and CRSsNP has been described as Th1 with increased levels of interferon (IFN)- γ .⁷ However, results of some studies showed that, in contrast to the eosinophilic inflammation characteristic of European patients with

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CRSwNP, nasal polyps in Asian patients showed a different inflammatory pattern with a Th1/Th17 dominance with a lower number of eosinophils. Nasal polyps from southern China demonstrate increased T-bet expression, IFN- γ protein formation, and IL-17 synthesis.⁸ Significantly lower eosinophilia has also been documented in NP tissue from second-generation Asian Americans, which indicates that genetic factors are playing a role in the pathogenesis of noneosinophilic polyps.⁹ There has been a trend toward increasing eosinophilic nasal polyposis in Asian populations recently.^{10,11} Local allergen-specific IgE and Th2 cytokines, such as IL-4, IL-5, and IL-13, have been identified in nasal polyp tissue, which indicates that atopy may further drive polyp formation.¹² Chronic inflammation is heterogeneous in CRS subtypes, including mucosal remodeling. For example, transforming growth factor (TGF)- β 1 and TGF- β 2 protein, and related collagen deposition are upregulated in sinus tissue from patients with CRSsNP and TGF- β 1, and related collagen is downregulated in polyp tissue.¹³

Current therapies for CRS aim at targeting various points of the inflammatory pathway. For decades, the mainstay of treatment of CRSsNPs or CRSwNPs has included saline solution irrigations, intranasal or systemic steroids, or intranasal and systemic antimicrobials. Aeroallergen immunotherapy in patients with atopic CRS and aspirin desensitization in patients with aspirin-exacerbated respiratory disease with nasal polyposis have been used as adjunctive treatments with variable success.^{14,15} Medically, refractory disease often necessitates surgical intervention to facilitate mucociliary clearance and restore patency of sinus drainage tracts, especially in the case of severe nasal polyposis. Despite advances in surgical technique and the use of intranasal steroids after surgery, patients may continue to have recurrence of their sinus disease, and, therefore, new therapeutics are needed to treat these medically and/or surgically refractory patients. Newer monoclonal antibodies that inhibit IgE and specific cytokines implicated in the Th2 mediated pathway of inflammation show promise and may be effective in treating subsets of patients with CRS for whom conventional therapies failed. This review focused on therapeutic options that are available for the treatment of CRS. Intranasal steroids and saline solution sinus rinses are currently indicated for the treatment of CRS and will not be discussed in detail in this article.

CRSsNP

Topical or Oral Steroids

In a Cochrane Review of 10 randomized trials that compared intranasal steroid therapy to placebo or no treatment in CRSsNP, topical intranasal steroids improved symptom scores and had a greater proportion

of responders.¹⁶ Adverse effects of topical steroids were overall minor, and there was increased benefit with steroid delivery *via* direct sinus irrigation over intranasal spray.

Oral steroids appear to provide similar benefit in modulating the inflammation seen in CRS. In particular, a study by Ozturk *et al.*¹⁷ in 2011 evaluated the potential benefit of administering oral corticosteroids and systemic antibiotics for the treatment of CRSsNP. Forty-eight children were randomized to receive either oral methylprednisolone for 15 days and amoxicillin-clavulanate for 30 days or placebo for 15 days and amoxicillin-clavulanate for 30 days. Outcome measurements included symptom score, sinus computed tomography (CT) score, relapse rate, and medication tolerability. After completion of therapy, both the placebo and methylprednisolone treatment groups showed significant radiographic improvement by sinus CT and clinical improvement by mean total symptom score compared with baseline scores.¹⁷ The reduction in sinus CT scores was significantly greater with methylprednisolone compared with placebo, and complete recovery and clinically significant improvement were more frequent in the methylprednisolone group. However, given the lack of large, randomized, placebo-controlled trials, the use of topical or oral corticosteroids has not become standard of care for treatment for CRSsNP and has been implemented on a case-by-case basis by the treating physicians.

Antimicrobials

Randomized studies that evaluated the efficacy of short courses of oral antibiotics on exacerbations of CRSsNP have shown some benefit, although these studies are limited by a lack of a placebo-control arm. In particular, one study showed a clinical response rate of 95% with amoxicillin-clavulanate compared with 88% with cefuroxime when 206 patients with CRS exacerbation were randomized to a 10-day course of either antibiotic therapy; bacteriologic cure rates were 65% and 68%, respectively, in each treatment group.¹⁸ A study by Legent *et al.*¹⁹ showed similar benefit from oral antibiotics when 251 patients with CRSsNP exacerbation were randomized to treatment with either ciprofloxacin or amoxicillin-clavulanate; clinical cure rates were 58% and 51% in each treatment group, respectively, although there was not a statistically significant difference in cure rates between the two groups.¹⁹

In vitro studies also demonstrated the anti-inflammatory and immune-modulatory properties of macrolide antibiotics in influencing neutrophil, eosinophil, and macrophage function.²⁰ A study by Wallwork *et al.*,²¹ in 2006, evaluated the response of CRS in 64 patients to

long-term treatment with roxithromycin 150 mg daily for 12 weeks compared with placebo. Clinical and molecular responses were assessed by using nasal endoscopy, peak nasal inspiratory flow, sino-nasal outcomes test (SNOT)-20 scores, saccharine transit time, and IL-8 levels. There was a favorable response in the roxithromycin treatment group in terms of patient response score (-0.73 points; 1–6 point scale) and a decrease in SNOT-20 scores at the end of treatment compared with placebo.²¹ However, a study published by Videler *et al.*,²² in 2011, did not show a significant response in 60 patients with CRSwNPs and CRSsNPs after treatment with azithromycin for 12 weeks compared with placebo. Due to conflicting results in other studies, according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 document,²³ the strength of recommendation for systemic antibiotic use in the treatment of CRSsNP is C (based on evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case control studies). However, there is stronger evidence for the benefit of macrolide treatment in patients with CRS and normal IgE levels.²⁴

Antibiotic rinses by nasal lavage have garnered modest support with open-label studies that showed a response rate that ranged from 40 to 80%. In a 3-week study of 16 patients with surgically recalcitrant CRS, treatment with mupirocin 100 mg in 200 mL of 0.05% saline solution *via* nasal lavage led to an improvement in nasal endoscopy scores and a significant decrease in sinus symptoms by visual analog score in 15 of 16 patients and SNOT-20 score in 13 of 16 patients. Twelve of 16 patients had negative subsequent bacterial sinus cultures after treatment.²⁵ Overall, there remains insufficient evidence for the efficacy of antibiotic sinus rinses for treatment of CRSsNP.

CRSwNP

Topical or Oral Steroids

For patients with CRSwNP, there have been convincing data to support the use of intranasal steroids to improve nasal symptoms in patients treated with medical management alone or after sinus surgery. A Cochrane Database Review from 2012 concluded that topical steroids are beneficial in the treatment of CRSwNP and that the adverse effects are minor.²⁶ They improved symptoms, reduced polyp size, and prevented polyp recurrence after surgery.²⁶ This was confirmed by a grade A recommendation for the use of intranasal steroids for the treatment of CRSwNP by the EPOS in 2012.²³ In fact, a double-blind, placebo-controlled study by Aukema *et al.*²⁷ in 2005, showed that intranasal fluticasone 400 mcg daily over the course of 12 weeks resulted in 13 of 27 patients with CRSwNP (48%) not needing sinus surgery who previously had

an indication for sinus surgery compared with 6 of 27 (22%) in the placebo group.²⁷ Oral steroids are often used in the treatment of nasal polyps. A Cochrane Database Review based on three studies concluded that short-term use of oral steroids improved quality of life and nasal symptom scores, and reduced polyp size after 2 to 4 weeks of treatment with oral steroids compared with no steroids.²⁸

The efficacy of sinus rinses that contain topical budesonide has also been supported by a study conducted by Steinke *et al.*,²⁹ in 2009. In this study, eight patients with CRSwNP, four of whom carried a diagnosis of aspirin-exacerbated respiratory disease, showed improvement on radiography in sinus disease (median decrease in CT score from 15 to 5) and a significant improvement in sinus symptoms (mean symptom score decrease from 43 to 20) after treatment with rinses of budesonide 500 μ g mixed in >100 mL saline solution twice daily for 3 months.²⁹ The study was limited by a lack of a placebo group. There has been no head-to-head study that compared the benefit of oral corticosteroids versus topical intranasal steroids for the treatment of nasal polyposis.

Antimicrobials

The efficacy of antibiotic therapy, either by oral or intranasal administration, in patients with CRSwNP has not been fully established. In one study, doxycycline has been proposed to exert beneficial effects by anti-inflammatory mechanisms that have not been fully elucidated. In a study by Van Zele *et al.*,³⁰ in 2010, 47 patients with CRSwNP were randomized to receive a 20-day course of either oral methylprednisolone, doxycycline, or placebo, followed by a 12-week monitoring period. After 90 days, polyp size by a change in total nasal polyp score compared with the baseline was significantly reduced in both the methylprednisolone and doxycycline treatment groups compared with placebo; however, the efficacy was much stronger with methylprednisolone.³⁰ In randomized studies of CRS, topical or oral antifungals were not shown to be more effective than placebo and led to more adverse events.³¹ Unfortunately, obtaining definitive evidence of benefit of antimicrobials in the treatment of CRSwNP has been hampered by the heterogeneity of the study populations, differences in route of medication delivery, and lack of culture-guided antibiotic and/or antifungal therapy.

Immunotherapy

In a systematic review of seven studies of aeroallergen immunotherapy in patients who were atopic and with CRS, the immunotherapy treatment group showed improvement in symptom scores, endoscopic findings, and radiographic sinus disease. These patients also showed a

decrease in a need for revision sinus surgery and in oral and intranasal therapy.³² Unfortunately, all of these studies were limited by a lack of randomization and a control group for comparison, and a paucity of data for treating CRS-specific outcome measurements. Therefore, there remains weak evidence to support the use of immunotherapy as an adjunctive treatment in CRS.

Biologics

Since the advent of using biologics for the treatment of inflammatory disease states, there has been marked interest in the therapeutic role of monoclonal antibodies in the treatment of CRS with nasal polyps. Blocking pathways of Th2-mediated inflammation that propagate nasal polyp formation *via* monoclonal antibodies has shown promise in randomized-controlled studies.

In a small study conducted by Gevaert *et al.*³³ in 2013, 24 patients with allergy and patients without allergy, and both groups with nasal polyps and comorbid asthma, were randomized to receive four to eight subcutaneous doses of an anti-IgE monoclonal antibody (omalizumab) or placebo. After 16 weeks, the omalizumab treatment group had a significant decrease in polyp burden both endoscopically and radiographically compared with placebo. The treatment group also had increased quality-of-life scores and a significant improvement in nasal congestion, rhinorrhea, olfaction, wheeze, and dyspnea. Interestingly, study patients without allergy and with nasal polyposis benefitted significantly from omalizumab administration in both upper and lower airways symptoms, which indicates that local IgE production in the sinonasal mucosa may modulate polyp formation.³³ To date, omalizumab has only been approved by the U.S. Food and Drug Administration for the indication of moderate-to-severe allergic asthma and chronic spontaneous urticaria. There is clear evidence of benefit of omalizumab in the severe asthmatic population, but larger-scale studies will need to be performed to determine if the benefits extend to patients with CRSwNP without comorbid asthma.

The Th2 cytokine, IL-5, is a key promoter of the differentiation and survival of eosinophils, which play a prominent role in the pathophysiology of nasal polyp formation in non-Asian populations. Administration of mepolizumab or reslizumab, which neutralizes anti-IL-5 monoclonal antibodies, therefore, would act by inhibiting a key arm of this inflammatory eosinophil-driven disease. In a randomized, double-blind, placebo-controlled trial of 30 patients with severe nasal polyposis, 12 of 20 patients who received mepolizumab in two doses showed radiographic and endoscopic improvement in nasal polyp burden compared with 1 of 10 patients in the placebo arm after 8 weeks of treatment. Although mepolizumab led to a reduction in loss

of smell, postnasal drip, and nasal congestion, these results did not reach statistical significance, and the benefit in nasal symptoms normalized after a period of time, except for improvement in olfaction.³⁴ Interestingly, the response to mepolizumab did not correlate with concentrations of IL-5 in nasal secretions at baseline. A single injection of reslizumab, another anti-IL-5 monoclonal antibody, improved nasal polyp scores in 50% of patients with CRSwNP, and nasal IL-5 levels predicted the response to treatment.³⁵ These studies support that a select population of patients with severe nasal polyposis may benefit from anti-IL-5 therapy, although, once again, larger studies are needed to corroborate these findings. A randomized, double-blind, placebo-controlled, multicenter clinical trial is currently underway to investigate the use of mepolizumab in reducing the need for surgery in subjects with severe bilateral nasal polyposis.

Other monoclonal antibodies to relevant Th2-mediated cytokines, such as IL-4 and IL-13, have been investigated for use in subgroups of patients with asthma and are undergoing investigation in nasal polyposis. Dupilumab, an anti-IL-4R α /IL-13R monoclonal antibody, has been studied in patients with persistent moderate-severe asthma with baseline elevated blood eosinophilia. Treatment with dupilumab was associated with a decrease in asthma exacerbations after withdrawal of inhaled corticosteroids and/or long-acting beta agonists, improvement in lung function, and reduction in Th2-associated cytokines.³⁶ As a secondary end point, the dupilumab treatment group also had a significant improvement in SNOT-22 scores compared with baseline (-8.49 ; $p = 0.003$). Analysis of these results indicate that dupilumab may be effective in the treatment of CRSwNP, although it is unclear if these effects are primarily mediated by blockade of IL-4 or IL-13 signaling. A randomized, double-blind, phase 2, placebo-controlled clinical trial is currently underway to evaluate dupilumab in patients with CRSwNP, with a primary outcome measurement of change from baseline in endoscopic nasal polyp score after treatment.

CONCLUSIONS

This study highlights the numerous treatment modalities beyond traditional saline solution irrigations that may provide benefit to patients with CRSwNP and those with CRSsNP. Although the mainstay of current medical treatment for CRS remains oral or topical antibiotics and corticosteroids, newer therapeutics, such as monoclonal antibodies, are emerging that target specific cytokines implicated in mediating sinus inflammation. Further large randomized placebo-controlled studies will need to be performed to determine the efficacy of these medications in patients with more-

severe subtypes of CRS. Due to the inherent heterogeneity of the disease, CRS will continue to require an individualized treatment plan tailored to each patient's symptomatology, clinical severity, and response to therapy.

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