Current and Future Treatments of Rhinitis and Sinusitis

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Abstract

Advances in understanding the pathogenic mechanisms of both rhinitis and chronic rhinosinusitis have resulted in new treatment options, especially for chronic rhinosinusitis. A review of relevant medical and surgical clinical studies shows that intranasal corticosteroids, antihistamines, and allergen immunotherapy continue to be the best treatments for chronic rhinitis. Dupilumab is the first biologic approved for chronic rhinosinusitis with polyps. Omalizumab, mepolizumab, and benralizumab may have a future role in the treatment of chronic rhinosinusitis. Novel corticosteroid delivery devices such as an exhalation delivery system for fluticasone and bioabsorbable sinus implants provide enhanced and localized distribution of corticosteroids. Surgical management tailored to the underlying disease process improves clinical outcomes in chronic rhinosinusitis with or without nasal polyposis. Advances in the understanding of the heterogeneous nature of rhinitis and rhinosinusitis have resulted in more precise treatments. Improving the understanding of different endotypes should provide better knowledge to determine appropriate current and new therapies to treat these diseases.

Full Text

Introduction

Chronic rhinitis (CR) and chronic rhinosinusitis (CRS) are common inflammatory conditions of the upper airways. These 2 conditions often coexist, negatively impact quality of life (QOL), and are associated with significant health care utilization and economic burden to society.[1-7] Both CR and CRS are particularly relevant because they are comorbidities of severe and difficult-to-control asthma.[8-11] Allergic rhinitis (AR) and nonallergic rhinitis (NAR) were important comorbidities for 30-day hospital readmissions of patients with asthma or chronic obstructive pulmonary disease, emphasizing the importance of correctly diagnosing and treating CR.[12] Rhinosinusitis is associated with frequent asthma exacerbations, and patients with both comorbid CRS and asthma have worse lung function and QOL compared with those with either asthma or CRS alone.[13,14] This article reviews advancements in the management of rhinitis and CRS.

Chronic Rhinitis

CR is classified as AR that is seasonal (seasonal allergic rhinitis [SAR]), perennial (perennial allergic rhinitis [PAR]), localized (localized allergic rhinitis [LAR]), mixed (mixed rhinitis [MR]), or NAR.[15,16] One survey reported that AR, NAR, and MR comprised 43%, 23%, and 34%, respectively, of patients with CR in allergy/immunology practices.[17] A study of 3398 patients with CR found that more than 90% of patients with SAR reported symptoms to at least 1 nonallergic trigger, suggesting that MR is more common than recognized and likely underdiagnosed.[18] Another study, using an objective irritant index questionnaire to quantify subject responses to nonallergic triggers, found that approximately 25% previously diagnosed as AR met MR criteria because of a high total irritant burden response.[19] Reclassification of AR to MR also reveals that patients with MR have more frequent and severe symptoms as well as an increased likelihood of physician-diagnosed asthma compared with patients with AR.[19] Patients with LAR or "entopic" rhinitis experience classic AR symptoms but have negative skin and/or serologic testing results to aeroallergens. Symptoms can be reproduced after nasal provocation to the specific allergen. Rondon et al[20-25] estimate that approximately 26% of patients with CR may have LAR and that more than 47% of patients previously diagnosed with NAR may have LAR.

Patients with NAR versus AR often exhibit similar symptoms. However, patients with NAR often develop symptoms later in life, have no family atopic history or seasonality of symptoms or trouble around furry pets, and experience symptoms around irritants such as perfumes and fragrances.[26] The most common form of NAR is vasomotor rhinitis.[27] Studies suggest that the pathophysiologic mechanism of vasomotor rhinitis involves neurogenic pathways leading to a hypercholinergic response. Stimulation of nasal transient response potential calcium ion channels by nonallergic triggers can activate and depolarize nasal afferent nociceptive nerve fibers. This results in release of neuropeptides (substance P, neurokinin A) and increased central nervous system signaling resulting in overactivity of the parasympathetic nervous system manifested as increased glandular (mucus production) and/or vascular (rhinorrhea, nasal congestion) responses.[28,29] Research indicates that capsaicin nasal spray reduces the expression of transient receptor potential vanilloid 1.[30-32]

Pharmacotherapy

Treatment options for AR include allergen avoidance, nasal saline rinses, pharmacotherapy, and allergen immunotherapy (AIT). Allergen avoidance is an important adjunctive therapy but often difficult to achieve. Second-generation oral antihistamines (AHs) are considered first-line treatment for mild SAR and PAR.[33] Intranasal AHs are also recommended for mild AR and NAR.[34] Intranasal AHs can be used as needed because of their relative quick onset of action (30 minutes). Intranasal corticosteroids (INCSs) are considered first-line treatment for moderate to severe AR and are superior to either oral AHs or leukotriene receptor antagonists.[35,36] INCS sprays are most effective if taken daily compared with as-needed use. Combination therapy with intranasal azelastine and fluticasone is more effective than either monotherapy alone and is approved for moderate to severe SAR and PAR.[37] No studies demonstrate that using these 2 agents in combination is better than using a single preparation containing both agents in 1 device. Patients with LAR versus AR respond to similar therapies, including allergen avoidance, INCS, and second-generation AHs.[38,39]

The leukotriene receptor antagonist montelukast is approved for the treatment of SAR and PAR, especially those with mild asthma. Studies demonstrate similar efficacy of montelukast to second-generation oral AHs, but the 2 together may have an additive effect.[33,39-41] As an adjunct treatment, saline irrigation is beneficial in managing AR on the basis of a 2018 meta-analysis.[42]

Intranasal ipratropium bromide 0.03% is approved for the treatment of rhinorrhea associated with PAR, SAR, and NAR, whereas the higher 0.06% concentration is approved for the treatment of rhinorrhea associated with the common cold.[43-45] Use of an intranasal decongestant spray beyond 3 to 5 days is not recommended because of concerns about rebound nasal congestion (aka rhinitis medicamentosa). However, studies indicate that they can be safely used in conjunction with an INCS for adult and adolescent patients with nasal congestion not responsive to INCS alone or in combination with an intranasal AH.[46-48] The longest double-blind randomized trial evaluating an intranasal decongestant in combination with an INCS was 6 weeks and found this combination to be effective and safe without evidence of rhinitis medicamentosa.[49]

Allergen immunotherapy

AIT is the only potential curative therapy for SAR and/or PAR. It should be considered in patients uncontrolled by allergen avoidance measures and regular use of maximum pharmacotherapy or for patients unable to tolerate medications or avoid indoor/outdoor exposures. Patient preference/acceptance, expected adherence, and costs should all be considered when starting AIT.[50]

The mechanism of AIT involves increased production of IgG-blocking antibodies, a shift from T_H2 to T_H1 cytokines, and an increase in regulatory T cells driven by IL-10 and TGF-β cytokines resulting in tolerance.[51] Administration of high doses of allergens is effective in controlling SAR and PAR.[52] Benefits of subcutaneous immunotherapy should be weighed against the potential risks of inducing a systemic allergic reaction, which occurs in approximately 0.1% of injections.[53] AIT has many other benefits including the prevention or progression of allergic asthma and reduction of recurrent sinusitis.[52] Studies suggest that subcutaneous immunotherapy can be used in patients with well-controlled mild to moderate asthma and may be effective for patients with LAR.[54,55]

Sublingual immunotherapy (SLIT) is approved for grass and ragweed SAR and dust mite PAR on the basis of large placebo-controlled clinical trials.[56] Similar to subcutaneous immunotherapy, it has a good safety profile.[57] The most common side effect associated with SLIT is local oral and pharyngeal itching and swelling that begins within days after initiation of therapy. In clinical trials, only rare mild systemic reactions were reported. A sustained therapeutic effect was demonstrated for 2 years after discontinuation after 3 years of continuous SLIT with grass tablets. Advantages of SLIT are no required buildup period and patients can self-administer treatment at home after the first dose is administered in a clinic.[57]

Chronic Rhinosinusitis

CRS is an inflammatory disease of the paranasal sinuses lasting for at least 12 weeks and affecting 6% to 12% of patients in the Western world.[58-60] It is most commonly classified as CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). CRS is a heterogeneous disease and is characterized by type 2 (IL-5 and IL-13) inflammation, but subsets of patients show type 1 (IFN-γ) and type 3 (IL-17A) inflammation.[61-64] The contribution of type 1 and type 3 inflammation to CRS is not understood. Research targeting these mechanisms is lagging, so there is a lack of therapeutic options for these pathways.

Approximately 85% of patients with CRSwNP and 50% of patients with CRSsNP from the United States exhibit type 2 inflammation, which explains the effectiveness of corticosteroids for CRS and potential benefit of type 2–targeted biologic therapies.[61,65] Sinus surgery is considered for those who fail appropriate medical therapy. This section focuses on the use of topical corticosteroids, monoclonal biologic agents, antibiotics, and sinus surgery, and includes a brief review of aspirin-exacerbated respiratory disease (AERD).

Intranasal corticosteroids

Please refer to Table I for a list of intranasal corticosteroid drugs and routes of delivery used to treat CRSwNP.

The use of corticosteroids for the management of CRS is supported by a high level of evidence, with particularly strong evidence for CRSwNP.[66-71] Mechanistically, corticosteroids are effective at suppressing the type 2 inflammation that is typical of CRS including eosinophils, group 2 innate lymphoid cells, and T_H2 cells as well as partially reversing the secondary epithelial barrier damage.[72] A frequent problem encountered with INCS, however, is the partial benefit or lack of benefit. A contributing factor is that low-volume devices (ie, spray bottles) typically do not spray liquid that penetrates the sinuses effectively, including ethmoids, which are the target organ in most cases of CRS.[73-75]

Evidence suggests using large-volume devices (ie, nasal irrigation) or at least considering changing head positioning to maximize penetration for low-volume devices.[73] Use of large-volume budesonide or mometasone nasal irrigations improves sinusitis nasal symptoms, QOL, and endoscopic and radiographic disease severity.[76,77] Transnasal nebulization of corticosteroids in pilot studies also shows benefit; however, long-term safety needs to be further evaluated using these delivery methods.[78] Despite these small studies, a meta-analysis shows a lack of robust evidence for recommending corticosteroid irrigation versus saline after functional endoscopic sinus surgery.[79]

Bioabsorbable sinus implants

Bioabsorbable sinus implants, which elute corticosteroids, were developed to improve drug delivery to the sinuses. The implants are placed in the sinus cavity, allowing all the drug to be delivered to the target organ. The first-generation product (Propel; Intersect ENT, Menlo Park, Calif) is designed to be used in the immediate postoperative period and demonstrates improved short-term endoscopic outcomes with a reduced need for additional medical and surgical interventions in both CRSsNP and CRSwNP.[80] These implants are placed in the surgically operated ethmoid cavity, releasing drug over the course of approximately 30 days. Implants, modified to be placed in the frontal outflow tract, also demonstrate improved short-term outcomes for frontal sinus surgery.[81] This first-generation stent (mometasone furoate) is Food and Drug Administration (FDA)-approved for adults 18 years or older with CRSwNP or CRSsNP after ethmoid or frontal sinus surgery. Long-term outcome studies have not been performed. Second-generation implants have a similar, albeit thicker, polymer platform. These devices contain 3 times as much corticosteroid eluted over 90 days. A phase 3 trial established the efficacy of these stents for the treatment of recurrent nasal polyps.[82] The second-generation corticosteroid-eluting (mometasone furoate) implant (SINUVA; Intersect ENT) is FDA-approved in adults 18 years or older with CRSwNP who have had ethmoid sinus surgery. It can be placed into the ethmoid cavity in a clinic setting. The goal of these stents is to reduce the need for oral prednisone and revision surgeries.

Exhalation Delivery System for Fluticasone

Exhalation Delivery System for Fluticasone (EDS-FLU) is a delivery technique using exhalation with a closed palate and improves the deposition of INCS throughout the nasal cavity.[83] A single-arm study demonstrates the efficacy of EDS-FLU versus placebo in both subjects with CRSwNP and subjects with CRSsNP.[84] Prospective, randomized, phase 3 double-blind studies confirm efficacy in subjects with CRSwNP, again versus placebo only.[85,86] Although these results are very encouraging, the absence of a standard INCS arm makes it difficult to compare efficacy and clinical significance to current standard of care.[87] EDS-FLU (Xhance; OptiNose, Yardley, Pa) is FDA-approved for the treatment of CRSwNP in adults 18 years or older and is currently being evaluated in subjects with CRSsNP. EDS-FLU is a daily-use medication and fills a complementary role to bioabsorbable corticosteroid implants, which are acute, burst products, similar to an extended course of oral prednisone. Although both products have FDA approval and are being used with some positive results, the precise indications await further real-world experience and cost analysis.

Monoclonal biologic therapies

Please see Table II for a list of monoclonal biologics approved or currently being studied in CRSwNP.

Dupilumab

Dupilumab (Dupixent; Sanofi and Regeneron, Cambridge, Mass) is a monoclonal anti–IL-4Rα antibody that prevents binding of IL-4 and IL-13 to its receptors, thereby blocking downstream signaling for type 2 inflammation (Figure 1). It was FDA-approved for the treatment of moderate to severe atopic dermatitis in 2017 and moderate to severe refractory eosinophilic or corticosteroid-dependent asthma in 2018. Its use in CRSwNP was examined in phase 2 and phase 3 trials, with positive findings that led to its approval for the treatment of CRSwNP in 2019.[88,89]

Two phase 3 studies, LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52, assessed dupilumab as adjunctive therapy to mometasone furoate nasal spray.[88,89] In SINUS-24, subjects were randomized to either dupilumab 300 mg every 2 weeks or placebo for 24 weeks. In SINUS-52, subjects were randomized to dupilumab 300 mg every 2 weeks for 24 weeks, then every 4 weeks for 28 weeks, dupilumab 300 mg every 2 weeks for 52 weeks, or placebo every 2 weeks for 52 weeks. In both studies combined, 724 subjects with severe CRSwNP (mean polyp size, 5.97, scale 0-8; nasal congestion score, 2.40, scale 0-3) demonstrated a significant improvement in both coprimary end points with dupilumab every 2 weeks. The nasal polyp score (NPS) least squares (LS) mean difference compared with placebo ($P < .0001$) was −2.06 (95% CI, −2.43 to −1.69) in SINUS-24 and −1.80 (95% CI, −2.10 to −1.51) in SINUS-52. The nasal congestion score LS mean difference ($P < .0001$) was −0.89 (95% CI, −1.07 to −0.71) in SINUS-24 and −0.87 (95% CI, −1.03 to −0.71) in SINUS-52. Radiographic findings improved compared with placebo ($P < .0001$), with Lund-Mackay score LS mean difference −7.44 (95% CI, −8.35 to −6.53) and −5.13 (95% CI, −5.80 to −4.46) in SINUS-24 and SINUS-52, respectively. The 22-item Sino-Nasal Outcome Test (SNOT-22) LS mean difference ($P < .0001$) was −21.12 (95% CI, −25.17 to −17.06) in SINUS-24 and −17.36 (95% CI, −20.87 to −13.85) in SINUS-52. In SINUS-24, treatment effects gradually diminished in the 12-week follow-up period after drug discontinuation.[89] In SINUS-52, there was a sustained benefit throughout the treatment duration. A pooled analysis of SINUS-24 and SINUS-52 studies shows that the use of systemic corticosteroids or nasal polyp surgery was reduced in the treatment group by 76% compared with the subjects treated with 100 µg nasal mometasone furoate spray twice daily ($P < .0001$).

Omalizumab

Omalizumab (Xolair; Novartis AG, Basel, Switzerland) is a monoclonal anti-IgE antibody that binds to circulating IgE (Figure 1). It was approved by the FDA in 2003 as an adjunctive therapy for uncontrolled, moderate to severe persistent allergic asthma. Local IgE is increased in human nasal polyp tissue (independent of atopy status) although its underlying role in CRS pathogenesis is still being elucidated.[96,97] This knowledge provided impetus for investigating anti-IgE treatment in CRSwNP.

Studies conducted between 2007 and 2013 show mixed results with omalizumab therapy in subjects with CRS. A 2017 meta-analysis comparing anti-IgE therapy with placebo in subjects with CRSwNP (2 randomized controlled trials and 1 case-control) demonstrated no significant effect difference in NPS between groups ($P = .22$).[90-92,98-101] In a post hoc analysis of 2 studies in whom subjects had concomitant asthma, omalizumab compared with placebo showed a greater reduction in NPS (standard mean difference of −1.38; 95% CI, −2.22 to −0.55; $P = .001$). A meaningful interpretation, given the limited number of outcome variables analyzed and the total number of studies available, is challenging. Based on these data, there is potential clinical efficacy of omalizumab for CRSwNP, perhaps favoring those with comorbid asthma. Two completed phase 3 trials, POLYP 1 and POLYP II, evaluating omalizumab for primary indication of CRSwNP have positive results.[92]

Mepolizumab

Mepolizumab (Nucala; GlaxoSmithKline, Brentford, United Kingdom) is a monoclonal anti–IL-5 antibody that binds to free IL-5, thereby blocking the IL-5 signaling cascade that normally promotes eosinophil activation and recruitment (Figure 1). It was approved by the FDA in 2015 for the treatment of severe, refractory eosinophilic asthma and in 2017 for the treatment of eosinophilic granulomatosis with polyangiitis. The mechanism by which mepolizumab reduces eosinophilic inflammation in eosinophilic asthma may provide similar benefits in eosinophilic-predominant CRSwNP.[102-104] In a small study of 20 subjects with CRSwNP treated with 2 doses of intravenous mepolizumab, 12 of 20 subjects (60%) in the mepolizumab group had reduced NPS compared with the placebo group.[93] Despite these findings, symptom scores did not change.

A larger multicenter study further supports a role of mepolizumab for CRSwNP.[94] Subjects refractory to standard of care (INCS for ≥3 months or received a short course of oral corticosteroids) with at least 1 previous sinus surgery were randomized to 6 doses of mepolizumab 750 mg intravenously every 4 weeks (n = 54) versus placebo (n = 51) for 25 weeks. Results demonstrate that 30% of the mepolizumab group compared with 10% of the placebo group no longer met criteria for revision surgery ($P = .006$). In addition, SNOT-22 score was reduced with mepolizumab use ($P = .005$). A limitation to these studies is the use of intravenous versus subcutaneous mepolizumab. A phase 3 trial (SYNAPSE [StudY in NAsal Polyps Patients to Assess the Safety and Efficacy of Mepolizumab]) is evaluating subcutaneous mepolizumab as add-on treatment for severe bilateral nasal polyps (NCT03085797).

Benralizumab

There are minimal data available regarding the efficacy of benralizumab (Fasenra; AstraZeneca, Cambridge, United Kingdom), a monoclonal anti–IL-5 receptor antibody (Figure 1), in subjects with CRS. There are ongoing randomized controlled trials for evaluation of benralizumab in subjects with CRSwNP (NCT03450083 and NCT03401229).

There are many unanswered questions in terms of biologic use in patients with CRS. There are no known biomarkers and only dupilumab is approved for the treatment of CRSwNP. Because CRSsNP may have underlying type 2 inflammation, biologics may have a potential role in this disease process.[61] Ongoing studies with other biologics and real-world experience will hopefully guide the selection of patients who are optimal candidates for these therapies because they are very expensive and currently require long-term treatment.

Antibiotics

Antibiotics are often prescribed for the treatment of CRS, especially CRSsNP; however, recommendations for antibiotic use in patients with CRS is controversial given the lack of well-designed trials.[58,105,106] A 2016 Cochrane review of a limited number of placebo-controlled trials shows conflicting evidence on benefits of short- and long-term antibiotic use as primary treatment of CRS.[106] Notably, a randomized controlled trial of 47 subjects showed that 20 days of oral doxycycline had a small but sustained reduction in polyp size compared with 20 days of methylprednisolone taper, which had an immediate larger reduction but it was not sustained at 3 months.[107] Based on this evidence, there could be some benefit of long-term antibiotics as adjunct therapy for CRS. Potentially, those with type 3 inflammation may benefit most with antibiotics. Given limited and inconsistent studies, however, the degree of benefit for antibiotic use is still uncertain and therefore recommendations are lacking.

Recommendations from the 2014 Joint Task Force Practice Parameters state that antibiotics may be most useful in acute exacerbations of CRS (such as presenting with purulent drainage) although rationale for this is based on noncontrolled trials.[105] Sabino et al[108] performed a controlled trial of 37 subjects with acute exacerbation of CRS who were randomized to amoxicillin-clavulanate versus placebo for 2 weeks (all remained on INCS) and observed no significant improvement in symptoms score, total endoscopy score, or microbiological outcomes between the groups. Thus, evidence for a short-term treatment with antibiotics for acute exacerbations and for CRS is lacking and more studies are needed.

Advances in sinus surgery for CRS

Sinus surgery remains an option for CRS after a failure of maximal medical therapy to control symptoms.[109,110] The goals of modern endoscopic sinus surgery (ESS) in the management of CRS include the following: (a) relief from nasal airway and sinus ostial obstruction, (b) debridement of inflamed tissue, and (c) the provision for greater access for topical medications to the sinus mucosa.[111] There is a lack of data on the extent of surgery necessary to meet these 3 goals or whether meeting all the 3 goals is necessary in each patient with CRS. It is now accepted that CRS is a heterogeneous disease with multiple phenotypes and endotypes such that goals of surgery may vary.[61,65] Although never specifically tested in a controlled trial, relief from sinus ostial obstruction is likely more relevant to successful management of CRSsNP, whereas debridement and access for topical medications more closely relate to success with CRSwNP.[112-114] For mild, isolated anterior ethmoid and maxillary CRSsNP secondary to osteomeatal obstruction, balloon sinuplasty—the least invasive surgical treatment for CRS—may be as efficacious, with lower morbidity and lower cost, as standard ESS.[115] For CRSwNP or advanced

CRSsNP, the sparse available evidence suggests that aggressive ESS will offer a greater level of improvement than sinuplasty or limited ESS.[116] The prevailing hypothesis is that these radiologically advanced patients have a primary mucosal disorder, often with a significant component of type 2 inflammation, rather than a simple mechanical obstruction of mucociliary flow.[114] Surgical management consists of a wide maxillary antrostomy, complete spheno-ethmoidectomy, and standard frontal sinusotomy (Draf IIa) with extensive debridement of inflamed mucosal tissue, often termed a "full-house ESS."[117] In cases of type 2 inflammation, which has the highest risk of recurrence, this is combined with high-volume topical corticosteroid irrigations, which have improved access due to wide surgical sinusotomies and debridement of the inflammatory load.[78,118,119] A more aggressive approach to frontal sinusitis is based on the suspected role of frontal sinuses in fostering recurrence after full-house ESS.[120,121] Known as a Draf III procedure (or endoscopic modified Lothrop), this consists of removal of the superior septum and floor of both frontal sinuses, marsupializing these sinuses into the nasal cavity, and more complete penetrance of topical corticosteroid irrigations.[122] Retrospective studies suggest that this aggressive approach significantly reduces clinical recurrence in patients with severe type 2 inflammation.[123,124] These encouraging results have resulted in the use of the Draf III technique as primary surgical therapy for patients at the highest risk of recurrence including those with AERD.[125]

Real-life evidence of benefit from sinus surgery shows mixed results. A study of a European cohort with CRSwNP and CRSsNP, who underwent ESS at an academic center, reports that at least 40% of patients with CRS remain uncontrolled at 3 to 5 years after surgery.[126] In this study, female sex, aspirin intolerance, and revision surgery were associated with a higher prevalence of uncontrolled CRS. Based on a US study of adult subjects with CRSwNP undergoing sinus surgery, 40% of polyps recurred at 18 months after functional ESS.[127] These same authors, however, showed in a 10-year observational, prospective study of adults with CRSwNP and CRSsNP that there is a clinically significant improvement in QOL after a mean follow-up of 10.9 years after sinus surgery.[128] Overall, there was a revision surgery rate of 17% for all subjects with CRS, of whom 80% had CRSwNP and 50% had AERD. Generalizability is limited because it was an observational study from a single academic center with a poor response rate of 38% at 10 years.

An expert panel defined the appropriateness of a surgical recommendation on the basis of 3 criteria: (1) Lund-Mackay computed tomography score of 1 or more, (2) adequate preoperative medical therapy, and (3) SNOT-22 score of 20 or more after medical treatment.[129] In brief, recommended medical therapy consists of INCS for all patients with CRS, plus a course of antibiotics for patients with CRSsNP or a short course of oral corticosteroids for patients with CRSwNP. Applying these criteria to a retrospective multi-institutional academic surgical database, 93% were "appropriate" and the "inappropriate" cases noted significantly less improvement after surgery when compared with the "appropriate group."[130] Although these criteria are merely rough guidelines, they do indicate that patients with SNOT-22 of less than 20 are less likely to show significant QOL improvement after surgery.

Aspirin-exacerbated respiratory disease

AERD (aka aspirin triad or Samter's triad) is characterized by hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs, asthma, and CRSwNP. AERD is a CRSwNP phenotype subgroup usually refractory to conventional therapies and polyps commonly reoccur after sinus surgery.[131-133] The prevalence of AERD among adult patients with asthma ranges between 7% and 21%, whereas approximately 16% of patients with CRSwNP have AERD.[132,134] Although the pathophysiology of AERD is still incompletely elucidated, dysregulation of arachidonic acid metabolism (higher production of cysteinyl leukotrienes and prostaglandin D2 with lower levels of prostaglandin E2) and increased activation of type 2 effector immune cells (ie, eosinophils and mast cells) in addition to genetic and epigenetic factors are involved in both upper and lower airways.[135-137] Other cells, such as epithelial cells, group 2 innate lymphoid cells, basophils, and platelets, are activated and involved in the pathogenesis of AERD.[138,139]

Treatment of AERD includes strict COX-1 inhibitor avoidance, leukotriene modifiers, aspirin desensitization, and sinus surgery. Because patients suffer from cross-reactivity of nonsteroidal anti-inflammatory drugs, all COX-1 inhibitors should be avoided. Pharmacologic treatment of asthma should follow current guidelines with step-up or step-down therapy based on control.[133,140] Biologics are promising treatment options in the management of AERD, especially in patients with moderate to severe asthma, because they target the type 2 inflammation that is characteristic of this disease. Subjects with AERD are included in phase 2 and 3 clinical trials of biologics for asthma and nasal polyposis.[88,89,91,93,141] Subjects with AERD benefited greater than those with aspirin-tolerant CRSwNP in a phase 2 dupilumab study; however, clinical benefits were similar between these groups in larger phase 3 studies.[89,141] A potential target that is being evaluated in subjects with CRSwNP and is of particular interest in subjects with AERD is blockade of the chemoattractant receptor-homologous molecule expressed on T_H2 cells (NCT02874144). Prostaglandin D2 signals via chemoattractant receptor-homologous molecule and mediates chemotaxis of the type 2 inflammatory cells, release of type 2 cytokines by group 2 innate lymphoid cells, and activation of eosinophils and T_H2 cells (Figure 1). This treatment option could decrease type 2 inflammation and shows some benefit in asthma.[142-146]

Aspirin desensitization is another treatment option for patients with AERD.[147] In some patients, it is efficacious only after optimal sinus surgery.[148] Various 1- to 2-day protocols for aspirin desensitization are recommended by US and *European Academy of Allergy and Clinical Immunology* guidelines.[140] A systematic review and meta-analysis provides high and moderate-certainty evidence that aspirin desensitization, compared with placebo, improves sinonasal symptoms and disease-specific QOL, but results in a significant increase in adverse events (major bleeding, gastritis, asthma exacerbation, or rash).[149] Future studies including cost comparison and AERD-specific outcomes will guide treatment selection among the different therapeutic options now available for managing this disease.

Conclusions

Advances in diagnostic algorithms, understanding patient phenotypic and endotypic characteristics, and development of novel pharmacological and surgical treatments have significantly improved the management of patients with CR and rhinosinusitis. More research is needed to characterize non–type 2 inflammation that is also involved in CR and CRS. Studies are also needed to determine which medications, the route of delivery, and which patient will benefit from various therapeutic options.

Table I

Corticosteroid delivery options for the management of CRSwNP

Devices	FDA approval status for use in nasal polyps	Recommended dose/frequency
Small-volume devices (eg, nasal pump spray and nebulizer)		
Mometasone (Nasonex) nasal pump spray	Approved	2 sprays (50 μg per actuation) in each nostril twice daily
Nebulizer (eg, NasoNeb) with mometasone or budesonide	Not approved*	Recommend similar dosing as used for large-volume device (below)
Large-volume devices (eg, squeeze bottles, neti pot, and pulsatile jets)		
Mometasone	Not approved	0.6 mg in 240 mL isotonic saline irrigation once or twice daily
Budesonide	Not approved	Respules of 0.25-0.5 mg/mL into 240 mL isotonic saline irrigation once or twice daily. Maximum total dose 1 mg daily
Xhance EDS-FLU	Approved	1-2 sprays (93 μg per actuation) in each nostril twice a day. Maximum is 4 actuations in each nostril per day

Devices	FDA approval status for use in nasal polyps	Recommended dose/frequency
Bioabsorbable sinus implants		
Propel (mometasone furoate)	Approved†	370 μg (corticosteroid released over 30 d)
Sinuva (mometasone furoate)	Approved	1350 μg (corticosteroid released over 90 d)

Table II

Biologic medications approved or being evaluated for CRSwNP

	Dupilumab	Omalizumab	Mepolizumab	Benralizumab
Pharmacology	Fully human monoclonal anti–IL-4 receptor alpha subunit antibody	Recombinant humanized monoclonal anti-IgE antibody	Recombinant humanized monoclonal anti–IL-5 antibody	Recombinant humanized monoclonal anti–IL-5 receptor alpha subunit antibody
Indication	Moderate to severe asthma with eosinophilic phenotype or with oral corticosteroid– dependent asthma, atopic dermatitis, CRSwNP	Moderate to severe asthma with positive allergy testing, chronic urticaria	Severe asthma with eosinophilic phenotype, eosinophilic granulomatosis with polyangiitis	Severe asthma with eosinophilic phenotype
Clinical trials to date	Phase 2 and 2 phase 3 trials SINUS-24 and SINUS-52 observed reduced NP size, improved symptoms including nasal congestion, smell, and SNOT-22[88,89]	2 RCTs observed decreased polyp size, improved symptoms in those with comorbid asthma.[90,91] Phase 3 trials POLYP1 and POLYP2 observed reduced NP size, improved symptoms including nasal congestion, smell, and SNOT-22[92]	2 RCTs observed decreased polyp size, improved smell and SNOT-22, and reduced need for surgery.[93,94] Phase 3 studies ongoing	Phase 3 studies pending

Details

Subject
Allergens;
Asthma;
Fluticasone;
Immunotherapy;
Surgery;
Sinus;
Rhinitis;
Sinuses;
Monoclonal antibodies;
Cytokines;
Clinical trials;
Allergies;
Antihistamines;
Immunoglobulin E;
Nervous system;
Inflammation;
Sinusitis;
Polyposis;
Corticoids;
Rhinosinusitis;
Polyps;
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