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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 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 heterogenous nature of rhinitis and rhinosinusitis has 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.

Keywords

chronic rhinitis; chronic rhinosinusitis; nasal polyposis; dupilumab; omalizumab; mepolizumab; EDS-FLU; bioabsorbable sinus implant; sinus surgery

Chronic rhinitis (CR) and chronic rhinosinusitis (CRS) are common inflammatory conditions of the upper airways. These two conditions often coexist, negatively impact quality of life (QOL), and are associated with significant healthcare utilization and economic

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burden to society.[1–7] Both CR and CRS are particularly relevant as they are comorbidities of severe and difficult to control asthma.[8–11] Allergic rhinitis (AR) and non-allergic rhinitis (NAR) were important co-morbidities for 30 day hospital readmissions of patients with asthma or COPD 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 to 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 which is seasonal (SAR), perennial (PAR), localized (LAR), mixed (MR) or NAR.[15, 16] One survey reported AR, NAR and MR comprised 43%, 23%, and 34%, respectively, of CR patients in allergy/immunology practices.[17] A study of 3,398 CR patients found that >90% of patients with SAR reported symptoms to at least one non-allergic 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 non-allergic triggers, found 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 MR patients have more frequent and severe symptoms as well as an increased likelihood of physician diagnosed asthma compared to AR.[19] LAR or “entopic” rhinitis patients experience classic AR symptoms but have negative skin and/or serologic testing to aeroallergens. Symptoms can be reproduced after nasal provocation to the specific allergen. Rondon and colleagues estimate that approximately 26% of CR patients may have LAR and that greater than 47% of patients previously diagnosed with NAR may have LAR.[20–25]

NAR versus AR patients often exhibit similar symptoms. However, NAR patients 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 (VMR).[27] Studies suggest that the pathophysiologic mechanism of VMR involves neurogenic pathways leading to a hypercholinergic response. Stimulation of nasal transient response potential (TRP) calcium ion channels by non-allergic triggers can activate and depolarize nasal afferent nociceptive nerve fibers. This results in release of neuropeptides (substance P, neurokinin A), 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 expression of transient receptor potential vanilloid 1 (TRPV1).[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 antihistamines (INAH) are also recommended for mild AR and NAR.[34] INAH can be used as needed due to their relative quick onset of action (30 minutes). Intranasal corticosteroids (INCS) are considered first line treatment for moderate to severe AR and are superior to either oral AH or leukotriene receptor antagonists (LTRAs).[35, 36] INCS sprays are most effective if taken daily compared to 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 two agents in combination is better than using a single preparation containing both agents in one device. Patients with LAR versus AR respond to similar therapies, including allergen avoidance, INCS and second-generation AHs.[38, 39]

The LTRA, 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 two together may have an additive effect.[33, 39–41] As an adjunct treatment, saline irrigation is beneficial in managing AR based on a 2018 meta-analysis.[42]

Intranasal ipratropium bromide .03% is approved for treatment of rhinorrhea associated with PAR, SAR, and NAR whereas the higher .06% concentration is approved for rhinorrhea associated with the common cold.[43–45] Use of an intranasal decongestant spray beyond 3–5 days is not recommended due to concerns about rebound nasal congestion (a.k.a. rhinitis medicamentosa). However, studies indicate 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 INAH.[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 Th2 to Th1 cytokines and an increase in T regulatory cells driven by IL-10 and TGF-β cytokines resulting in tolerance.[51] Administration of high doses of allergens is effective to control SAR and PAR.[52] Benefits of subcutaneous immunotherapy (SCIT) should be weighed against the potential risks of inducing a systemic allergic reaction which occurs in approximately 0.1 percent 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 SCIT 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 based on large placebo controlled clinical trials.[56] Similar to SCIT, 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 two years following discontinuation after three 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 6–12% 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 are lagging, so there is a lack of therapeutic options for these pathways.

Approximately 85% of CRSwNP and 50% of CRSsNP patients 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, 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 CRS with nasal polyps.

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 which is typical of CRS including eosinophils, group 2 innate lymphoid cells (ILC2s) and Th2 cells as well as partially reversing the secondary epithelial barrier damage.[72] A frequent problem encountered with INCS, however, is the partial or lack of benefit. A contributing factor is low-volume devices (i.e., spray bottles) typically do not spray liquid that penetrate sinuses effectively, including ethmoids which are the target organ in most cases of CRS.[73–75]

Evidence suggests using large-volume devices (i.e., nasal irrigation) or at least consider changing head positioning to maximize penetration for low-volume devices.[73] Use of large volume budesonide or mometasone nasal irrigations improve 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 post-functional endoscopic sinus surgery (FESS).[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 of the drug to be delivered to the target organ. The first-generation product (Propel®; Intersect ENT, Menlo Park, CA) is designed to be used in the immediate post-operative 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 FDA approved for adults ≥18 years of age with CRSwNP or CRSsNP following 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 three times as much corticosteroid eluted over 90 days. A phase III trial established efficacy of these stents for the treatment of recurrent nasal polyps.[82] The second generation corticosteroid-eluting (mometasone furoate) implant (SINUVA®; Intersect ENT, Menlo Park, CA) is FDA approved in adults ≥18 years of age 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.

EDS-FLU: Exhalation Delivery System for Fluticasone

EDS-FLU is a delivery technique using exhalation with a closed palate and improves deposition of INCS throughout the nasal cavity.[83] A single arm study demonstrates efficacy of EDS-FLU versus placebo in both CRSwNP and CRSsNP subjects.[84] Prospective, randomized, phase 3 double-blind studies confirm efficacy in CRSwNP, again versus placebo only.[85, 86] While 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 treatment of CRSwNP in adults ≥18 years of age and is currently being evaluated in subjects with CRSsNP. EDS-FLU is a daily use medication and fills a complimentary role to bioabsorbable corticosteroid implants which are acute, burst products, similar to an extended course of oral prednisone. While both products have FDA approval and are being utilized 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, MA) is a monoclonal anti-IL4Rα antibody that prevents binding of IL-4 and IL-13 to its receptors thereby blocking down-stream signaling for type 2 inflammation (Figure 1). It was FDA approved for 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 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 dupilumab 300 mg every 2 weeks or placebo for 24 weeks. In SINUS-52, subjects were randomized to either 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 significant improvement in both co-primary endpoints with dupilumab every 2 weeks. The nasal polyp score (NPS) least squares (LS) mean difference compared to placebo ($p<0.0001$) 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 ($p<0.0001$) 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 to placebo ($p<0.0001$) with Lund-Mackay (LM) 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 ($p<0.0001$) 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 following 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 show that the use of systemic corticosteroids or nasal polyp surgery were reduced in the treatment group by 76% compared to the subjects treated with 100 mcg nasal mometasone furoate spray twice daily ($P<0.0001$).

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.[90, 91] This knowledge provided impetus for investigating anti-IgE treatment in CRSwNP.

Studies conducted between 2007 to 2013 show mixed results with omalizumab therapy in subjects with CRS. A 2017 meta-analysis comparing anti-IgE therapy to placebo in subjects with CRSwNP (2 randomized control trials and 1 case-control), demonstrates no significant effect difference in NPS between groups ($P=0.22$).[92–97] In a post-hoc analysis of 2 studies in whom subjects had concomitant asthma, omalizumab compared to placebo shows a greater reduction in NPS (standard mean difference of −1.38; 95% CI, −2.22 to −0.55, $P=0.001$). 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 III trials, POLYP 1 and POLYP II, evaluating omalizumab for primary indication of CRSwNP have positive results.[98]

Mepolizumab—Mepolizumab (Nucala®; GlaxoSmithKline, Brentford, United Kingdom) is a monoclonal anti-IL5 antibody that binds to free IL-5, thereby blocking the IL-5 signaling cascade which normally promotes eosinophil activation and recruitment (Figure 1). It was approved by the FDA in 2015 for treatment of severe, refractory eosinophilic asthma and in 2017 for treatment of eosinophilic granulomatosis with polyangiitis (EGPA). The mechanism by which mepolizumab reduces eosinophilic inflammation in eosinophilic asthma may provide similar benefits in eosinophilic-predominant CRSwNP.[99–101] In a small study of 20 subjects with CRSwNP treated with 2 doses of intravenous mepolizumab, 12/20 subjects (60%) in the mepolizumab group had reduced NPS compared to placebo.[102] Despite these findings, symptom scores did not change.

A larger multi-center study further supports a role of mepolizumab for CRSwNP.[103] 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 30% of mepolizumab group compared to 10% of placebo group no longer met criteria for revision surgery (P=0.006). Additionally, SNOT-22 score was reduced with mepolizumab use (P=0.005). A limitation to these studies is the use of intravenous versus subcutaneous mepolizumab. A phase 3 trial (SYNAPSE) is evaluating subcutaneous mepolizumab as add-on treatment for severe bilateral nasal polyps (NCT03085797).

Benralizumab—There are minimal data available regarding efficacy of benralizumab (Fasenra®; AstraZeneca, Cambridge, United Kingdom) in subjects with CRS, a monoclonal anti-IL5 receptor antibody (Figure 1). There are ongoing randomized control 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 selection of patients who are optimal candidates for these therapies as they are very expensive and currently require long-term treatment.

Antibiotics

Antibiotics are often prescribed for treatment of CRS, especially CRSsNP, however, recommendations for antibiotic use in CRS patients is controversial given the lack of well-designed trials.[58, 104, 105] 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.[105] Notably, a randomized control trial of 47 subjects shows that 20 days of oral doxycycline had a small but sustained reduction in polyp size compared to 20 days of methylprednisolone taper, which had an immediate larger reduction but it was not sustained at 3 months.[106] 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 non-controlled trials.[104] Sabino et al performed a controlled trial of 37 subjects with acute exacerbation of CRS who were randomized to amoxicillin-clavulanate vs 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.[107] Thus, evidence for a short-term treatment with antibiotics for acute exacerbations and for CRS are 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.[108, 109] The goals of modern endoscopic sinus surgery (ESS) in the management of CRS include the following: (a) relief of 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.[110] There is a lack of data on the extent of surgery necessary to meet these 3 goals or whether meeting all three is necessary in each CRS patient. 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 of sinus ostial obstruction is likely more relevant to successful management of CRSsNP, while debridement and access for topical medications more closely relates to success with CRSwNP.[111–113] 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.[114] 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.[115] 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.[113] Surgical management consist 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”.[116] 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, 117, 118] A more aggressive approach to frontal sinusitis is based on their suspected role in fostering recurrence after “full-house ESS”.[119, 120] 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.[121] Retrospective studies suggest that this aggressive approach significantly reduces clinical recurrence in patients with severe type 2 inflammation.[122, 123] These encouraging results have resulted in the utilization of the Draf

III technique as primary surgical therapy for patients at the highest risk of recurrence including those with AERD.[124]

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 CRS patients remain uncontrolled at 3–5 years post-surgery.[125] In this study, female gender, aspirin intolerance, and revision surgery were associated with a higher prevalence of uncontrolled CRS. Based on a U.S. study of adult subjects with CRSwNP undergoing sinus surgery, 40% of polyps recurred at 18 months post-FESS.[126] These same authors, however, showed in a 10-year observational, prospective study of adults with CRSwNP and CRSsNP that there is clinically significant improvement in QOL after a mean follow up of 10.9 years following sinus surgery.[127] Overall there was a revision surgery rate of 17% for all CRS subjects, of whom 80% had CRSwNP and 50% had AERD. Generalizability is limited as 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 based on 3 criteria: (1) LM CT score ≥1, (2) adequate pre-operative medical therapy, and (3) SNOT-22 score ≥20 post-medical treatment.[128] In brief, recommended medical therapy consists of INCS for all CRS patients, plus a course of antibiotics for CRSsNP or a short course of oral corticosteroids for CRSwNP. Applying these criteria to a retrospective multi-institutional academic surgical database, 93% were ‘appropriate’ and the ‘inappropriate’ cases noted significantly less improvement following surgery when compared to the ‘appropriate group’. [129] While these criteria are merely rough guidelines, they do indicate that patients with SNOT-22 < 20 are less likely to show significant QOL improvement following surgery.

Aspirin-Exacerbated Respiratory Disease

AERD (a.k.a aspirin triad or Samter’s triad) is characterized by hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), asthma and CRSwNP. AERD is a CRSwNP phenotype subgroup usually refractory to conventional therapies and polyps commonly reoccur following sinus surgery.[130–132] The prevalence of AERD among adult asthma patients ranges between 7%−21% whereas approximately 16% of patients with CRSwNP have AERD.[131, 133] Although the pathophysiology of AERD is still incompletely elucidated, dysregulation of arachidonic acid metabolism (higher production of cysteinyl leukotrienes and prostaglandin D2 (PGD2) with lower levels of prostaglandin E2) and increased activation of type 2 effector immune cells (i.e., eosinophils and mast cells) in addition to genetic and epigenetic factors are involved in both upper and lower airways. [134–136] Other cells, such as epithelial cells, ILC2s, basophils, and platelets, are activated and involved in the pathogenesis of AERD.[137, 138]

Treatment of AERD includes strict COX-1 inhibitor avoidance, leukotriene modifiers, aspirin desensitization, and sinus surgery. As patients suffer from cross-reactivity of NSAIDs, 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.[132, 139] Biologics are promising treatment options in the management of AERD, especially in patients with moderate to severe asthma, as 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, 95, 102, 140] 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, 140] 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 Type 2 helper cells (CRTH2 receptor) (NCT02874144). PGD2 signals via CRTH2 receptor and mediates chemotaxis of the type 2 inflammatory cells, release of type 2 cytokines by ILC2s, and activation of eosinophils and Th2 cells (Figure 1). This treatment option could decrease type 2 inflammation and shows some benefit in asthma.[141–145]

Aspirin desensitization is another treatment option for patients with AERD.[146] In some patients, it is efficacious only after optimal sinus surgery.[147] Various 1–2 day protocols for aspirin desensitization are recommended by U.S. and EAACI guidelines.[139] A systematic review and meta-analysis provides high and moderate-certainty evidence that aspirin desensitization, compared to placebo, improves sinonasal symptoms and disease specific QOL, but results in a significant increase in adverse events (major bleeding, gastritis, asthma exacerbation or rash).[148] Future studies including cost comparison and AERD specific outcomes will guide treatment selection among the different therapeutic options now available for managing this disease.

Conclusion

Advances in diagnostic algorithms, understanding patient phenotypic and endotypic characteristics, and development of novel pharmacological and surgical treatments have significantly improved the management of CR and rhinosinusitis patients. 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.

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Abbreviations

AERD	Aspirin-exacerbated respiratory disease
AIT	Allergen immunotherapy
AR	Allergic rhinitis
CR	Chronic rhinitis
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyposis

CRSwNP	Chronic rhinosinusitis with nasal polyposis
EDS-FLU	Exhalation Delivery System for Fluticasone
FESS	Functional endoscopic sinus surgery
INAH	Intranasal antihistamine
INCS	Intranasal corticosteroid
LAR	Localized allergic rhinitis
MR	Mixed rhinitis
NPS	Nasal polyp score
NAR	Non-allergic rhinitis
PAR	Perennial allergic rhinitis
QOL	Quality of life
SAR	Seasonal allergic rhinitis
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SNOT-22	Sino-nasal outcome test-22
VMR	Vasomotor rhinitis

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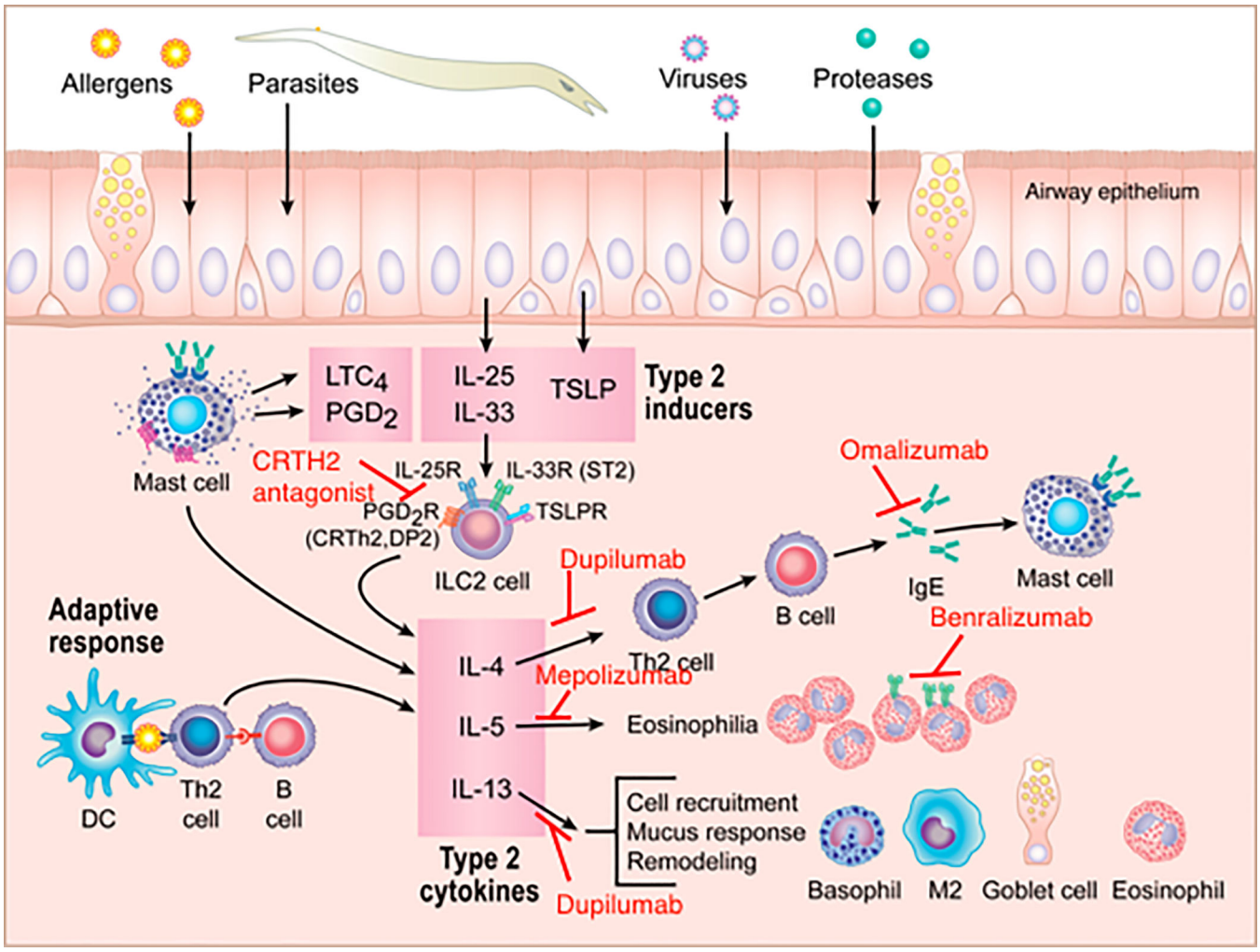

Figure 1.

Inflammatory type 2 pathway is the principle mechanism involved in chronic rhinosinusitis with nasal polyposis (CRSwNP) pathogenesis and targets of pharmacotherapy. Adapted from “Pathogenesis of nasal polyposis” by Hulse et al. 2015. Clin Exp Allergy 45(2), 341. Illustration courtesy of Dr. Robert Schleimer.

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 (e.g. nasal pump spray, nebulizer)		
Mometasone (Nasonex®) nasal pump spray	Approved	2 sprays (50 mcg per actuation) in each nostril twice daily.
Nebulizer (e.g. NasoNeb™) with mometasone or budesonide	Not approved *	Recommend similar dosing as used for large volume device (below).
Large volume devices (e.g. squeeze bottles, neti pot, pulsatile jets)		
Mometasone	Not approved	0.6 mg in 240 mL isotonic saline irrigation once or twice daily.
Budesonide	Not approved	Respules of 0.25-0.5mg/mL into 240 mL isotonic saline irrigation once or twice daily. Maximum total dose 1 mg daily.
Xhance™ Exhalation Delivery System with Fluticasone (EDS-FLU)	Approved	1-2 sprays (93 mcg per actuation) in each nostril BID. Maximum is 4 actuations in each nostril/day.
Bioabsorbable sinus implants		
Propel® (mometasone furoate)	Approved **	370 mcg (corticosteroid released over 30 days)
Sinuva® (mometasone furoate)	Approved	1350 mcg (corticosteroid released over 90 days)

* NasoNeb™ is FDA approved as a medical device but its specific use as a treatment for CRSwNP has not been established

** Also approved for chronic rhinosinusitis without nasal polyps

Table II –

Biologic Medications Approved or Being Evaluated for CRSwNP

	Dupilumab	**Omalizumab**	**Mepolizumab**	**Benralizumab**
Pharmacology	Fully human monoclonal anti-IL-4 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 two 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.[94, 95] Phase 3 trials POLYP1 and POLYP2 observed reduced NP size, improved symptoms including nasal congestion, smell, and SNOT-22.[98]	2 RCTs observed decreased polyp size, improved, smell and SNOT22, and reduced need for surgery.[102, 103] Phase 3 studies ongoing.	Phase 3 studies pending.

RCT - Randomized Control Trial