Drugs (2017) 77:1713–1721
DOI 10.1007/s40265-017-0803-4

LEADING ARTICLE

Pharmacological Management of Chronic Rhinosinusitis: Current and Evolving Treatments

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Published online: 29 August 2017

Abstract Chronic rhinosinusitis (CRS) is an inflammatory sinonasal condition with multiple etiologic factors that is associated with a vast economic cost. Treatment is most frequently pharmacologic and has centered on agents that ameliorate inflammation, decrease bacterial or pathogen load, and facilitate egress of mucus or purulence from the sinonasal cavity. Nasal saline irrigations, topical nasal steroids, certain antibiotics, and systemic steroids have shown some efficacy in the management of CRS. Recently, biologic therapeutics that target specific inflammatory pathways associated with subsets of CRS have been developed and evaluated. Early data evaluating these biologic treatments suggest a potential role in treating a subset of CRS with refractory, poorly controlled disease. Additional studies are necessary to identify which patients would benefit most from biologic therapies and to assess the cost of these therapies compared with the benefit they provide. This review describes the pathophysiology of CRS and summarizes both established and novel biologic pharmacologic treatments.

Key Points

Chronic rhinosinusitis (CRS) is an inflammatory sinonasal condition with multiple etiologic factors. Pharmacologic treatment is the foundation of management for this condition.

Nasal saline irrigations, topical nasal steroids, certain antibiotics, and systemic steroids have shown some efficacy in the management of CRS.

Novel biologic therapeutics are under evaluation for the treatment of refractory, poorly controlled CRS with nasal polyps.

1 Pathophysiology

Chronic rhinosinusitis (CRS) affects tens of millions of patients worldwide and has an estimated total national healthcare cost of over$8 billion annually in the United States [1]. Multiple etiologic factors have been linked to the development of CRS, including environmental and occupational factors, infection, allergy, disruptions of the sinonasal mucosal epithelial barrier, genetic abnormalities, anatomic variations, inflammation/osteitis, vitamin D status, biofilms, disturbances of the nasal microbiome, immune status, ciliary dysfunction, superantigens, and systemic diseases [2]. In part due to the many etiologic factors, CRS is not a uniform disease, rather it displays significant phenotypic heterogeneity and likely represents a syndrome consisting of many diseases that have yet to be more clearly defined. While commonly considered to be an infectious disease, most CRS appears to have a primarily inflammatory pathophysiology.

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CRS can be grossly divided into disease with (CRSwNP) and without nasal polyposis (CRSsNP), even though there is still significant heterogeneity within these subcatergorizations. Recent evidence supports the presence of distinct underlying endotypes that lead to different disease states, including T helper (Th) 1-driven pathways for CRSsNP and Th2-driven pathways for CRSwNP [3]. The different pathways associated with CRS and molecular mechanisms behind those pathways provide insight into possible new therapeutic targets.

CRSsNP patients typically have an abundance of neutrophils and elevated type 1 cytokines such as interferon (IFN)-γ, while CRSwNP patients have an array of eosinophils, mast cells, basophils, and elevation in type 2 cytokines such as interleukin (IL)-4, IL-5, and IL-13 [4]. IL-5 is essential for the differentiation, survival, and activation of eosinophils, which plays a significant role in not only CRSwNP but also other atopic diseases, including asthma [5]. Nasal polyps are most commonly eosinophilic and are therefore intertwined with IL-5 mechanistically, although a smaller subset of certain neutrophil-expressing polyps demonstrates higher levels of IL-17 and IFN-γ [4, 6]. In the CRSwNP population, IL-4 is a key factor in the underlying immunoglobulin (Ig) E-mediated response [4]. IL-13 and IL-4 suppress bone remodeling, and IL-13 has recently been shown to have a possible association with osteoneogenesis in a subset of patients with CRS [7, 8].

2 Established Treatment Modalities

A variety of pharmacologic treatments focus on ameliorating inflammation, decreasing bacterial or pathogen load, and permitting egress of mucus or purulence from the paranasal sinuses and nasal cavity. These treatments are generally applicable to both CRSsNP and CRSwNP populations, with some exceptions. High-level studies for these interventions are presented below. For a more comprehensive review of established pharmacologic therapies, the reader is directed to the robust International Consensus Statement on Allergy and Rhinology: Rhinosinusitis [2].

2.1 Nasal Saline Irrigation

High-volume (>200 mL) nasal saline irrigation for the treatment of CRS at all stages of disease is supported by high-level evidence. Saline irrigations facilitate the clearance of mucus, improve ciliary beat frequency, enhance removal of biofilms and antigens, and may also contribute to the resolution of intranasal inflammation [9]. A Cochrane systematic review and meta-analysis in 2007 evaluated the use of nasal saline irrigations in eight trials [9]. Analysis included comparisons of saline irrigation versus no treatment or placebo, as an adjunct to intranasal steroids, against intranasal steroids, and comparisons of high-volume hypertonic versus isotonic solutions. Overall, nasal saline irrigations were determined to be effective as both primary and adjunctive treatment for CRS, although nasal saline was found to be less effective than nasal steroids [9]. High-volume saline irrigation is well-tolerated, inexpensive, and does not have major side effects [2, 9, 10]. A comprehensive consensus statement strongly recommended high-volume nasal saline irrigations as an adjunct to therapy for CRS [2].

Conversely, low-volume nasal saline sprays have been shown to be less efficacious for CRS compared with high-volume irrigations. A randomized trial of patients with chronic nasal and sinus symptoms compared high-volume irrigations with low-volume sprays over 8 weeks and demonstrated greater improvement in patient-reported symptom scores in the high-volume irrigation group [11]. A comprehensive consensus statement identified low-volume saline sprays as likely inferior to high-volume saline irrigations [2].

2.2 Intranasal Steroids

Intranasal steroids are widely used for the treatment of both CRSsNP and CRSwNP at all stages of disease to decrease the inflammatory burden. Mometasone furoate is the only US Food and Drug Administration-approved medication for the treatment of CRSwNP, although other topical steroid medications are frequently employed in clinical practice today [12, 13]. Intranasal steroids have been shown to be quite safe. While previous concerns existed about the potential systemic uptake of certain agents, a recent review evaluating a multitude of studies demonstrated no significant impact on the hypothalamic-pituitary-adrenal axis with newer intranasal steroid agents [14].

A Cochrane review published in 2016 analyzed 18 randomized trials evaluating intranasal steroids versus placebo or no treatment, 14 of which included CRSwNP patients and 4 of which included CRSsNP patients [15]. Medications evaluated included fluticasone propionate 400–800 μg/day, with one study additionally including a higher dose treatment arm; beclomethasone propionate 400–800 μg/day; mometasone furoate 100–400 μg/day; and budesonide 128–400 μg/day [15]. There appeared to be improvement for all symptoms (nasal congestion, rhinorrhea, hyposmia/anosmia, facial pain/pressure), with a moderate benefit for nasal congestion and a small benefit for rhinorrhea [15]. A comprehensive consensus statement recommended standard metered dose nasal steroids based on the benefits of improved symptoms and endoscopic

disease severity scores for patients with CRSsNP, and improved symptoms, polyp size, endoscopic appearance, quality of life (QoL) scores, and olfaction metrics for patients with CRSwNP [2]. This consensus statement also concluded that using high-volume steroid irrigations (topical steroid mixed in >200 mL of saline) was an option for CRS due to the benefits of improved QoL metrics, symptoms, and endoscopic appearance postoperatively for CRSsNP, with greater benefit from irrigations anticipated postoperatively given the greater accessibility of the sinus mucosa afforded by the surgically created openings [2].

Another recent Cochrane review evaluated four different intranasal steroids (fluticasone propionate, beclomethasone propionate, mometasone furoate, and budesonide) administered via nasal spray, drops, or actuated inhaler in nine randomized trials of CRS patients and determined there was insufficient evidence to suggest that one type of intranasal steroid was more efficacious than another [16]. Local, intranasal administration enables patients to avoid many of the side effects of systemic steroids. However, it should be noted that the risk of epistaxis is increased with intranasal steroids, although it is possible that small streaks of blood reported in some patients are not particularly clinically relevant [15].

2.3 Oral Steroids

Oral steroids, like their topical counterpart, are commonly used pharmacologic agents intended to decrease the inflammation associated with CRS. Robust evidence supports employing short-term courses of oral steroids for CRSwNP, while there is limited evidence to support the routine use of oral steroids in CRSsNP [2]. There are potential significant side effects of oral steroids that must be considered, including hyperglycemia, gastrointestinal ulcers, adrenal suppression, increased bone turnover, and avascular necrosis at higher cumulative doses [2].

A recent Cochrane review evaluated the efficacy of oral steroids in CRSwNP in eight randomized trials [17]. The authors concluded that patients experienced improvements in QoL metrics and symptom severity following a 2- to 3-week course of oral steroid therapy, although this benefit was limited to 3–6 months after therapy. Additionally, side effects, including gastrointestinal disturbances and insomnia, may have been increased during treatment with oral steroids [17]. These conclusions are supported by a recent consensus statement that recommends oral steroids in CRSwNP for short-term management but not long-term or frequent management due to the increased risk of side effects [2]. An evidence-based risk analysis in CRSwNP patients using complication rates from the literature, QoL changes, and US Medicare costs demonstrated that endoscopic sinus surgery (ESS) would be favored over medical management when patients required oral steroids more frequently than once every 2 years [18].

2.4 Antibiotics

Antibiotics are frequently used to mitigate the infectious component of CRS. In addition to standard antimicrobial effects, macrolide antibiotics possess anti-inflammatory and immunomodulatory properties, which may be of additional benefit in treating sinonasal disease [19].

Macrolides have been primarily evaluated in refractory CRSsNP and have been shown to decrease endoscopic disease severity scores and certain symptoms. Based on this evidence, macrolides are a treatment option for CRSsNP, although neither the subgroup of patients who would most likely benefit nor the optimal treatment regimen (dose and length of therapy) has been rigorously studied [2]. Similarly, in CRSwNP, macrolides decrease polyp burden after ESS and reduce symptoms, and may be beneficial postoperatively [2]. A recent Cochrane review on the utility of antibiotics in CRS patients found limited evidence that systemic antibiotics are effective in treating CRS, although there was a moderate, transient QoL improvement in CRSwNP patients receiving 3 months of macrolide antibiotics [20]. Again, this improvement is thought to be due to a combination of anti-inflammatory, immunomodulatory and antibacterial effects [19]. Side effects of macrolides are rare and are usually related to gastrointestinal irritation; very unusual side effects include ototoxicity, liver dysfunction, and the small chance of the cardiac arrhythmia torsades de pointes, which recently prompted an FDA warning cautioning against the use of macrolides in patients with known cardiac risk factors [2, 21].

The use of non-macrolide antibiotics for CRS is more controversial and potential risks and benefits must be evaluated. For the CRSsNP population, evidence for both short- and long-term use of non-macrolide antibiotics is limited, and no recommendation for their use was possible based on an extensive literature review [2]. For the CRSwNP population in a non-acute clinical setting, evidence for the use of short-term non-macrolide antibiotics generally suggests that harms of gastrointestinal upset, the chance of fostering resistant organisms, and the risk of anaphylaxis outweigh the benefits associated with these agents [2]. While controversial, antibiotics are commonly prescribed for CRS; in recent years, provider visits for CRS were among the most frequent reason an antibiotic was prescribed [22]. The potential negative consequences of antibiotic therapy include allergic reactions, cost, adverse effects, and bacterial resistance [22]. Common adverse effects include gastrointestinal irritation, rashes, genitourinary infections, and *Clostridium difficile* colitis [2].

Intravenous antibiotics are not recommended for routine cases of CRS based on the risk-benefit ratio of complications such as thrombophlebitis, neutropenia, venous thromboembolism, rash, and other adverse events compared with a potential reduction in symptoms, although there may be a role for intravenous agents in complicated, extra-paranasal complications of sinusitis [2].

Topical antibiotics, which may locally deliver a high concentration of active agent to diseased sinonasal mucosa, are not recommended for CRS based on a greater extent of side effects (congestion, epistaxis, and irritability) compared with a lack of long-term benefit in randomized trials [2, 23–25]. Although included in the Cochrane review search design, no randomized trials of topical antibiotics were included in the most recent Cochrane review of antibiotics for chronic sinusitis [20].

2.5 Antifungal Agents

Fungal elements may be a contributing etiologic factor in a subset of CRS patients, especially those with eosinophilic disease [26]. However, antifungals have not demonstrated significant benefit in treating CRS. A Cochrane review evaluated six randomized studies of antifungals in the management of CRS and allergic fungal rhinosinusitis, five of which assessed topical antifungals and one of which investigated systemic therapy [27]. Pooled meta-analysis of these studies using original data demonstrated no benefit for either formulation of antifungals over placebo [27]. Other analyses agree with this finding, confirming there is no evidence supporting oral or topical antifungals in the treatment of CRS and recommending against the use of these agents in most cases [2].

2.6 Leukotriene Antagonists

Cysteinyl leukotrienes are mediators of inflammation that originate in eosinophils and mast cells and are closely related to the pathophysiology of CRSwNP and asthma [28, 29]. Leukotriene antagonists (LTAs) function by inhibiting the arachadonic acid inflammatory cascade; montelukast, zarfilukast, and pranlukast inhibit the cysteinyl leukotriene 1 receptor and block downstream effects of this pathway, while zileuton inhibits 5-lipoxygenase and decreases leukotriene synthesis [30].

Overall, studies have demonstrated a mild benefit for LTAs in treating CRSwNP. A systematic review evaluated LTAs in CRSwNP patients among 12 studies, 5 of which were randomized trials [31]. Several of the randomized trials demonstrated improvement in symptom and nasal endoscopy disease severity scores. However, 2 of these 12 studies were combined in a meta-analysis and showed no difference between LTA and intranasal steroid arms when measuring disease severity scores. The authors concluded that LTAs were effective for treating CRSwNP, with limited benefit as adjunctive therapy to intranasal steroids [31]. A separate review of five studies evaluating the utility of montelukast in CRSwNP patients concluded there is moderate evidence that montelukast is an effective adjunct to intranasal or oral steroids [29]. A recent consensus statement describes montelukast as an option for managing CRSwNP patients with or without intranasal steroids [2]; however, a comprehensive European Position Paper from 2012 makes a recommendation to avoid LTAs in CRSwNP [32]. Montelukast has rarely been associated with neuropsychiatric side effects [2], while zileuton has been shown to be effective in patients with asthma-exacerbated respiratory disease but has a less favorable side effect profile than montelukast, including the potential for transaminitis [2, 33].

2.7 Endoscopic Sinus Surgery

Surgical treatment for CRS is indicated when appropriate medical therapy cannot fully control symptoms. While a full discussion of the role and utility of ESS is beyond the scope of this review, the topic is briefly mentioned as ESS is a standard component of treatment for CRS [34–38] and has multiple aims, including the removal of antigenic or inflammatory material, enhancing mucociliary clearance, and facilitating instillation and distribution of topical medications, such as topical steroids, postoperatively [2, 39]. The use of saline irrigations and topical intranasal steroids following ESS reduces symptom severity and improves endoscopic scores. In addition, administration of topical intranasal steroids postoperatively helps decrease the polyp recurrence rate in CRSwNP [40, 41].

3 Biologic Pharmacologic Treatments

Traditional pharmacologic agents and ESS are effective in controlling the symptoms of CRS for the majority of patients; however, a substantial proportion of patients who undergo appropriate medical therapy and ESS have disease recurrence and persistent symptoms. Among CRSwNP patients, those with aspirin-exacerbated respiratory disease, asthma and/or frontal sinus disease are more likely to remain symptomatic and require revision surgery [42]. There is a clear need for additional therapeutic interventions to decrease the inflammatory disease burden in these patients with more complicated disease.

As our understanding of the pathophysiology of CRS endotypes progresses, a personalized treatment approach targeted to the specific molecular pathways involved will be possible. These evolving biologic treatments often

Table 1 Biologic therapeutics under evaluation for the treatment of CRS

Drug	Mechanism	Current US FDA-approved indication(s)	Initial FDA approval date	Completed trials for CRS[a]	Ongoing trials for CRS[a]
Omalizumab	Anti IgE	Moderate to severe refractory allergic asthma; chronic idiopathic urticaria	2003	2	1
Mepolizumab	Anti IL-5	Severe refractory asthma	2015	1	2
Reslizumab	Anti IL-5	Severe refractory asthma	2016	1	1
Benralizumab	Anti IL-5	Pending		0	1
Dupilumab	Anti IL-4 and IL-13	Moderate to severe eczema (atopic dermatitis)	2017	1	2

CRS chronic rhinosinusitis, *Ig* immunoglobulin, *IL* interleukin

[a] Based on ClinicalTrials.gov. Completed refers to peer-reviewed, published results

originated as treatments for patients with asthma or atopic diseases, including allergic rhinitis, food allergy, atopic dermatitis, and urticaria. Many patients with these diseases display a similar inflammatory profile as patients with CRSwNP, including elevated Th2 cytokines IL-4, IL-5, and IL-13 [43–45]. Table 1 lists the current biologic agents being evaluated for the treatment of CRS.

3.1 The Anti-Immunoglobulin E Pathway: Omalizumab and Ligelizumab

Omalizumab, a recombinant humanized monoclonal antibody previously approved for patients with refractory allergic asthma [46], has recently been studied in the CRSwNP population. Asthma and CRSwNP often occur simultaneously and both diseases have been shown to share similar inflammatory mediators [2]. IgE leads to allergic symptoms via binding with a specific high-affinity receptor via the Fc region on mast cells and basophils, subsequently promoting degranulation and allowing the release of inflammatory mediators [47]. Omalizumab complexes with free circulating IgE, which leads to lower expression of IgE on effector cells and subsequently inhibits the stimulation of these cells [4]. The selective binding to IgE also disrupts the binding of IgE to the high-affinity IgE receptor [4, 47]. Omalizumab does not complex with IgE molecules that are already bound to cells, and therefore does not promote mast cell crosslinking and degranulation [47].

Following success in treating asthmatics, controlled studies in the early 2000s demonstrated a benefit for omalizumab in treating patients with allergic rhinitis [48, 49]. Later that decade, case reports posited a potential benefit for symptom reduction for asthmatic CRS patients [50, 51]. These reports were followed by a small retrospective pilot study undertaken in CRSwNP asthmatic patients that demonstrated an improvement in endoscopic nasal polyp scores after treatment with omalizumab compared with a control group who did not receive omalizumab, without improvement in computed tomography (CT) disease severity scores [52].

An initial randomized, double-blind, placebo-controlled trial of omalizumab for CRS was published in 2010 [53]. This study had recruitment challenges and did not distinguish between CRSwNP and CRSsNP, although 12 of 14 patients had CRSwNP and all had failed prior ESS. After subcutaneous injection of omalizumab or placebo every 4 weeks for 6 months, treatment with omalizumab decreased CT disease severity scores (the primary outcome measure) in a non-significant fashion. Secondary outcomes, such as general and disease-specific QoL outcomes, olfactory testing, nasal endoscopic disease severity scores, nasal peak inspiratory flow, and eosinophil count in nasal lavage also did not show differences between the omalizumab and placebo groups. The authors concluded that IgE plays a small role in CRS mucosal inflammation, and suggested that larger controlled studies were necessary to assess the size of any effect [53].

Subsequent high-level evidence demonstrated a greater benefit for treating CRSwNP patients with omalizumab. In a randomized, double-blind, placebo-controlled trial of allergic and non-allergic patients with nasal polyps ($N = 24$), patients treated with four to eight subcutaneous omalizumab injections ($n = 16$) experienced an improvement in nasal polyp scores, the primary outcome, compared with the control group ($n = 8$), starting 8 weeks after treatment and persisting through 16 weeks [54]. The treatment group also demonstrated improvements in CT disease severity scores, most nasal and asthma symptoms, the Short-Form Health Questionnaire (SF-36) general QoL scores, and the sleep and general symptoms domains of the 31-item Rhinosinusitis Outcome Measure instrument (RSOM-31). While the authors acknowledge these benefits, they suggested that due to high costs, omalizumab should

be reserved for asthmatic CRSwNP patients who have recalcitrant symptoms despite ESS [54].

A randomized, phase II trial of 27 patients evaluating the utility of subcutaneous omalizumab for the treatment of nasal polyposis has recently been completed; however, full results are not yet available [55]. A recent retrospective chart review in patients with CRS and asthma who received omalizumab demonstrated a decrease in antibiotic prescriptions following omalizumab treatment compared with the period prior to anti-IgE treatment; post-omalizumab steroid use trended toward declining but was not significant [56].

Ligelizumab (QGE031) is a new, investigational anti-IgE antibody with a higher binding affinity to IgE compared with omalizumab. Early-stage testing demonstrated superior pharmacologic effects in atopic and asthmatic patients compared with omalizumab [57, 58]. The role of this agent in treating CRS remains to be discerned.

3.2 The Anti-Interleukin-5 Pathway: Reslizumab, Mepolizumab and Benralizumab

The majority of CRSwNP patients have a Th2 inflammatory profile with significant tissue eosinophilia and IL-5 expression [59], although there is geographic/ethnic variability associated with nasal polyposis and Asian patients have been shown to have a greater propensity toward Th1 profiles compared with Caucasians [60]. IL-5 is one of the most important and specific factors for eosinophil growth, differentiation, and survival [4, 61]. In vitro work has demonstrated that IL-5 localizes to eosinophils, as well as mast cells and lymphocytes, in nasal polyp tissue, and that treatment with an anti-IL-5 antibody led to increased eosinophil apoptosis and mitigated tissue eosinophila [62].

Reslizumab, a humanized monoclonal antibody to IL-5, was the first anti-IL-5 antibody evaluated clinically for the treatment of sinonasal disease, and is currently approved for the treatment of severe asthma [63]. Reslizumab was tested in a randomized, double-blind, placebo-controlled trial in which 24 CRSwNP subjects received a single intravenous infusion of reslizumab 3 mg/kg ($n = 8$), reslizumab 1 mg/kg ($n = 8$), or placebo ($n = 8$) [64]. The primary outcome, nasal polyp severity score, was improved in approximately half of the treated patients for 4 weeks. On post hoc analysis, patients with elevated baseline nasal secretion IL-5 levels (>40 pg/mL) were found to be more likely to respond to anti-IL-5 treatment. Both treatment groups experienced a decrease in blood eosphinophil count within 1 day of dosing that was sustained for 8 weeks. A randomized, double-blind, phase III study evaluating the utility of reslizumab in treating CRS is underway [65].

Mepolizumab, a humanized anti-IL-5 antibody currently approved for severe asthma [66], was subsequently assessed in a randomized controlled trial of 30 patients with advanced nasal polyps in which patients received either two intravenous infusions of mepolizumab 28 days apart ($n = 20$) or placebo ($n = 10$) [67]. Compared with the placebo group, mepolizumab-treated patients had improved nasal polyp severity scores 8 weeks after the first treatment, the primary outcome. CT severity scores 8 weeks after treatment improved in the majority of the mepolizumab-treated group, compared with less than one-fifth of the placebo group. There were no significant changes in symptom scores and, unlike the aforementioned reslizumab study [64], there was no difference in baseline nasal IL-5 levels between mepolizumab responders and non-responders [67].

A multicenter, randomized, double-blind trial comparing mepolizumab with placebo as a means to reduce the potential need for surgery in patients with severe nasal polyps has recently been completed [68]. Patients received up to six doses of mepolizumab or placebo at 4-week intervals; however, the results have not yet been published. A separate clinical trial evaluating the effect of mepolizumab for severe bilateral nasal polyps is ongoing [69].

Benralizumab is a humanized monoclonal antibody that binds the IL-5 receptor alpha subunit with high affinity and inhibits IL-5 binding, which leads to eosinophil and basophil apoptosis via antibody-dependent cellular toxicity [70, 71]. While benralizumab has shown utility in treating severe asthma [72], a role in the management of CRSwNP remains to be specifically elucidated. A phase II clinical trial of benralizumab for the treatment of patients with eosinophilic CRS is ongoing [73].

3.3 The Anti-IL-4/IL-13 Pathway: Dupilumab

IL-4 and IL-13 are inflammatory Th2 cytokines with overlapping effects, and therefore an intervention that blocks the downstream effects of both of these molecules could have therapeutic promise [74]. While two different receptors are involved in the pathways of IL-4 and IL-13 signaling, receptors in both pathways include the alpha subunit of the IL-4 receptor [59]. Dupilumab is a fully human monoclonal antibody against the alpha subunit of the IL-4 receptor and thus inhibits the downstream effects from both IL-4 and IL-13 [75]. Dupilumab is currently approved for the treatment of severe atopic dermatitis [76].

In a multinational, randomized, double-blind trial, dupilumab was assessed in 60 patients with CRSwNP refractory to intranasal corticosteroids [77]. Patients received subcutaneous dupilumab (initial 600 mg dose followed by fifteen 300 mg weekly doses; $n = 30$) or placebo ($n = 30$); mometasone furoate nasal spray was continued for the treatment period. The change in nasal polyp severity scores, the primary study outcome, was

significantly improved in the dupilumab-treated group. Multiple secondary outcomes also showed benefit for dupilumab treatment, including improvement in CT disease severity score, peak nasal inspiratory flow, SNOT-22 scores, olfactory testing, symptom scores, and total serum IgE. Blood eosinophil count showed no difference between groups. The most common adverse events reported were nasopharyngitis, reactions at the injection site, and headache [77]. Additional studies of dupilumab for CRS were recently described at a national European meeting in 2016 but have not yet been published [78]. Furthermore, two phase III trials evaluating the use of dupilumab in the treatment of CRSwNP are ongoing [79, 80]. Other IL-13 inhibitors such as tralokinumab, lebrikizumab, and anrukinzumab have been described as potential targets for asthma but have not been evaluated for CRS [81].

4 Conclusions

Pharmacologic treatment is the foundation of management for CRS. Nasal saline irrigations, topical nasal steroids, certain antibiotics, and systemic steroids have shown some efficacy in the management of CRS. There is no meaningful evidence to support the use of antifungal therapy in the routine management of CRS. Nasal polyposis is a phenotypic subset of CRS that is often associated with specific inflammatory mediators, including cysteinyl leukotrienes, IL-4, IL-5, and IL-13. Antileukotriene therapy has shown mixed results, with modest benefit in some patients with CRSwNP. Recently, novel biologic therapeutics have been evaluated for the management of refractory CRSwNP with severe, poorly controlled disease. Further studies of these novel treatments are warranted, including identifying which subset of CRSwNP patients would most benefit from these therapies and assessing the cost of these treatments compared with the benefits provided.

Compliance with Ethical Standards

Funding No sources of funding were directly used for this project.

Conflict of interest Timothy L. Smith was previously a consultant for Intersect ENT. This relationship ended in 2015. He is supported by a grant for this investigation from the National Institute on Deafness and Other Communication Disorders (NIDCD), one of the National Institutes of Health, Bethesda, MD, USA (R01 DC005805; PI/PD: TL Smith). Public clinical trial registration (http://www.clinicaltrials.gov) ID: NCT01332136. This funding organization did not contribute to the design or conduct of this study; collection, management, analysis, or interpretation of the data; and preparation, review, approval or decision to submit this manuscript for publication.

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