Introduction

Chronic rhinosinusitis (CRS) represents a common health problem with a worldwide prevalence ranging from 4.3 to 12.5% [1]. Patients with CRS can present with several troubling symptoms, including hyposmia, chronic nasal obstruction, nasal discharge, and recurrent facial pain or pressure, all affecting their quality of life (QOL), causing work absences, requiring frequent hospital visits and medications, and not uncommonly necessitating one or more endoscopic sinus surgery (ESS) [2,3]. The economic effect of CRS in the United States alone, as an example, has been estimated to be in excess of $30 billion annually, including direct and indirect costs [3].

CRS is defined as an inflammation of the nose and paranasal sinuses for more than 3 months and is clinically diagnosed when the patient presents with two or more of the aforementioned symptoms, one of which should be either nasal obstruction/congestion or nasal discharge, along with radiologic and/or endoscopic evidence of paranasal sinus inflammation [2].

There are two major phenotypes of CRS: chronic rhinosinusitis with nasal polypos (CRSsNP) and chronic rhinosinusitis without polypos (CRSwNP) [4]. Several clinical subtypes are also described such as allergic fungal rhinosinusitis and aspirin-exacerbated respiratory disease (AERD) [2,4]. The exact pathophysiologic mechanism of the inflammation in these types and subtypes is not necessarily distinct, as there is an overlap in their mediators and biological markers (endotypes) [5].

Endotypes of chronic rhinosinusitis

Endotypes of CRS are described based on different inflammatory mediators and biomarkers, namely, the type of T-helper (Th) cells involved, level of cytokines such as interleukins (IL), level of immunoglobulin E (IgE), and on the cellular infiltrate [6]. Three main patterns of inflammation have been described [5–8]:

(1) Type 1: mediated by Th1 cells with elevated IL-2, interferon, and tumor necrosis factor alpha and abundance of neutrophils in the tissues

(2) Type 2: mediated by Th2 cells with elevated IL-4, IL-5, and IL-13; high local IgE; elevated periostin and P-glycoprotein levels; and blood and/or tissue eosinophilia

(3) Type 3: mediated by Th-17 cells with elevated IL-6, IL-17, IL-22, and tumor necrosis factor alpha [9].

In United States and Europe, CRSwNP is predominantly driven by Th2 cells (type 2) and is often associated with asthma, inhalant allergy, or aspirin sensitivity, whereas CRSsNP is mainly driven by Th1 cells [10]. However, approximately one-third of CRSsNP are mediated through the Th1 pathway [11]. Type 3 inflammation has been reported in Asian patients with CRSwNP [9]. Indeed, the immune response in different patients can vary based on their racial background [12]. A large study of the pathophysiologic and clinical characteristics of CRS...
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Mediators and biomarkers in type 2 inflammation

Upon exposure to allergens or pathogens, the dendritic cells present the stimulant to Th2 cells, which then release IL-4, IL-5, and IL-13 (adaptive pathway of inflammation). The epithelial cells can also release thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which subsequently act on type 2 innate lymphoid cell to similarly produce IL-5 and IL-13 (innate pathway of inflammation) [19]. Furthermore, TSLP stimulates dendritic cells to help Th2 cell differentiation with an ‘amplified’ type 2 cytokine production. IL-5 in turn promotes eosinophil recruitment, activation, as well as survival. Both IL-4 and IL-13 promote secretion of periostin from epithelial cells, goblet cell hyperplasia and mucous production, fibrosis and remodeling, and activation of B cells, with local production of IgE and even several autoantibodies in severe cases. Abnormal expression of mucin 1 and mucin 4 (MUC1 and MUC2) in epithelia cells may contribute to steroid resistance [19].

Endotype-based versus traditional treatment of chronic rhinosinusitis with nasal polyps

Traditional therapies for CRSwNP such as local and systemic steroids are utilized to suppress or decrease the inflammatory response. Systemic steroids are not without significant adverse effects, including gastric irritation, metabolic derangements, glucose intolerance or even steroid-induced diabetes, weight gain, fat redistribution, and rarely avascular hip necrosis [20].

Leukotriene antagonists have been also tried in CRSwNP as studies have shown elevated levels of leukotrienes and their receptors in nasal polyps [21,22]. Leukotrienes are produced by eosinophils and mast cells, and they promote localized inflammation, mucous secretion, eosinophil infiltration, and release of cytokines [23]. Montelukast is a leukotriene receptor antagonist that can inhibit this process, whereas zileuton can prevent the formation of certain leukotrienes by inhibiting 5-lipoxygenase. However, a randomized controlled trial involving 72 patients operated for their CRSwNP showed that adding montelukast to intranasal steroids after ESS for 1 year did not lead to a significant difference in patients’ symptom score, nasal polyp score (NPS), or computed tomography (CT) Lund–Mackay score [24].

ESS is indicated to remove sinonasal polyps for cases not adequately controlled by medical treatment. ESS also opens paranasal sinus drainage pathways and allows for better access of steroid irrigations and other local treatments to different areas. Failure and recurrence after ESS for CRSwNP is not infrequent. Difficult-to-treat patients are defined as those who are not appropriately controlled despite adequate ESS, intranasal steroid irrigations, and up to two short courses of systemic steroids in the last year [2].

Endotype-based treatment of CRSwNP offers a unique precise way that addresses the underlying pathophysiologic process. Biologics are compounds produced by a biological process in a living system such as microorganism, plant, or animal cells. Many are produced using recombinant DNA technology, and in the context of CRSwNP management, they usually refer to different monoclonal antibodies that target specific inflammatory mediators, their receptors, or certain immune cells in the pathophysiologic pathway [5]. Recent trials on the management of CRS have focused on biologics that target type 2 inflammatory mediators rather than type 1 or Th-17 driven inflammation [5].

Biologic therapies for type 2 inflammation

Anti-interleukin-4 receptor alpha subunit (dupilumab)

Dupilumab (Dupixent, Regeneron Pharmaceuticals, Inc; Tarrytown, NY, USA & Sanofi; Bridgewater, NJ, USA) works by binding to IL-4 receptor alpha subunit shared by IL-4 and IL-13 receptor complexes. This inhibits the actions of both IL-4 and IL-13, thus blocking the advancement of type 2 inflammatory pathway [25]. In June 2019, dupilumab was approved by the Unites States Food and Drug Administration (FDA) as the first biologic with a primary indication to treat CRSwNP [26].

The largest published phase 3 trials confirming the safety and efficacy dupilumab are the multi-institutional, randomized, double-blind, placebo-controlled trials termed SINUS-24 and SINUS-52 [27–29]. Inclusion criteria were bilateral, symptomatic CRSwNP despite intranasal steroids, systemic steroids, and/or prior ESS. SINUS-24 study randomized patients to 24 weeks of either subcutaneous dupilumab 300 mg or placebo injections; the primary end points were change in NPS (0–8 scale) and subjective nasal congestion score (0–3 scale). The SINUS-52 trial had the same primary end points but patients were divided in three groups: the first group received dupilumab injections...
every 2 weeks for 52 weeks; the second group received dupilumab injections every 2 weeks for 24 weeks, and then every 4 weeks for another 28 weeks; and the third group received placebo injections every 2 weeks for 52 weeks.

At week 24 in the SINUS-24 trial, there was a significant decrease in average NPS by 1.89 points, as well as in average nasal congestion score by 1.34 points. At the same time in SINUS-52 study, the decrease in the average NPS was 1.71 points, and the average nasal congestion score dropped by 1.25 points. In both studies, all secondary outcome measures also showed significant improvement, including smell test score using University of Pennsylvania Smell Identification Test, Sinonasal Outcome Test-22 (SNOT-22) score, and the Lund–Mackay CT score. When injections were continued after 24 weeks in the SINUS-52 trial, patients continued to feel improvement, and this was slightly higher in the every-2-week schedule compared with the every-4-week dosing.

In both trials, patients had statistically significant improvement after only 2–4 weeks from the beginning of therapy, and there was also decrease in the nasal and serum IgE over the course of the study. However, in SINUS-24, all primary metrics went back to baseline after stopping dupilumab, indicating that therapy did not cure the underlying type 2 inflammatory, and that the medication needs to be a chronic one.

Laidlaw et al. [30] have also studied a subset of patients with AERD who had worse sinus involvement andolfactory function, and poorer pulmonary function compared with the aspirin-tolerant patients with CRSwNP, and dupilumab showed dramatic improvement in both upper and lower airway outcomes in patients with aspirin intolerance, giving a particular hope for this often difficult-to-treat subgroup of patients [30].

A recent Cochrane review on the use of biologics in CRSwNP including nearly 800 participants has concluded that dupilumab improves disease-specific health-related QOL compared with placebo and reduces the extent of the disease in CT scan with high certainty. The review also reported improvement in the NPS with moderate certainty and that dupilumab can reduce the need for further surgery [5].

**Anti-interleukin-5 and anti-interleukin-5 receptor**

1. Mepolizumab (Nucala) is a humanized anti-IL-5 monoclonal antibody that can decrease blood and tissue eosinophil counts and reduce steroid dependence in patients with asthma, and is approved for treatment of severe eosinophilic asthma [31].

For CRSwNP, Gevaert et al. [32] have conducted a randomized double-blind placebo-controlled trial including 30 patients, with a mean NPS of 5 or more, refractory to corticosteroid therapy. Overall, 75% had previous sinus surgery, 50% had comorbid asthma, and 25% were diagnosed with AERD. Mepolizumab 750 mg was administered intravenously at 4-week interval for two doses. Patients were assessed at 8 weeks, and there was a decrease by 1 score point or more in 60% of the mepolizumab group versus 10% in placebo group; CT scan also confirmed this response, along with decrease in blood eosinophil count [32].

A second controlled trial investigating mepolizumab in CRSwNP included 107 patients receiving the medication in the aforementioned dose for a total of six doses [33]. Included patients were refractory to standard steroid therapy and have undergone at least one previous ESS and were eligible for another surgery. The mean NPS was greater than 6, and 80% had comorbid asthma. At week 25, 30% in the mepolizumab group no longer required surgery compared with 10% in the placebo group (P < 0.006). There was significant improvement in NPS (50 vs. 27% decreased by at least one point), and in the SNOT-22 score (a mean change of 23 vs. 11) in the mepolizumab group compared with the placebo group, respectively [33].

Chan et al. [34] studied a series of patients with severe eosinophilic asthma in whom subcutaneous mepolizumab 100 mg every 4 weeks improved asthma control while decreasing blood eosinophils from an average of 1393 to 120 cells/mL. In contrast, in these patients, mepolizumab had no effect on CRSwNP exacerbations requiring systemic steroids, endoscopic NPS, Lund–Mackay score, or anosmia. For this reason, we await with interest the results of the completed phase 3 trial studying the effect of mepolizumab in CRSwNP using 100-mg subcutaneous dosage (NCT03085797; SYNAPSE: StudY in NA sal Polyps Patients to Assess the Safety and Efficacy of Mepolizumab) [35]. The results of the latter study will support or refute the effectiveness of mepolizumab in these patients. Indeed, it should be remembered that earlier anti-eosinophil trials have not shown great success for CRSwNP [36].

2. Reslizumab, another anti-IL-5 monoclonal antibody, has been studied in 24 patients with CRSwNP who were randomized to receive a single intravenous infusion of the drug or placebo [37]. Reslizumab reduced NPS for 4 weeks in ~50% of the patients after single administration, along with reduction in the blood eosinophil count, but with no significant effect on patients’ symptoms.
Currently, there are no further known trials for reslizumab in CRSwNP [38].

(3) Benralizumab is an IL-5 receptor antagonist, and its efficacy and safety in severe eosinophilic asthma have been demonstrated in a couple of phase 3 studies [39,40]. Currently, there are two phase 3 studies ongoing in severe CRSwNP: the ORCHID and the OSTRO studies [41,42]. In these studies, benralizumab 30 mg is injected subcutaneously every 4 weeks for three doses, and then every 8 weeks, with a total of eight doses. Results are expected by the end of 2020 or early 2021 [38].

Anti-immunoglobulin E

Omalizumab (Xolair) binds free IgE and thus prevents the interaction between IgE and its receptors on mast cells and was indeed the earliest monoclonal antibody to be approved in treatment of allergic asthma in 2003 [43,44]. Gevaert et al. [45] have conducted a proof-of-concept study on patients with CRSwNP, where all included patients experienced comorbid asthma, 50% had AERD, and ~80% had previous ESS. A total of 24 patients were randomized to receive four to eight subcutaneous doses of either omalizumab or placebo. The primary end point was the decrease in NPS after 16 weeks. Omalizumab-treated group had a statistically significant reduction in the NPS by 22.67 points, whereas the placebo group showed almost no change (P < 0.001). There was also improvement in lower and upper airway symptoms, including olfaction, as well as reduction in CT sinus Lund–Mackay score and improvement in asthma QOL scores.

Two phase 3 randomized controlled trials, POLYP 1 (138 patients) and POLYP 2 (127 patients), have been recently conducted to study the safety and efficacy of omalizumab in patients with CRSwNP [46]. Patients were randomized to receive either omalizumab or placebo for 24 weeks. Included patients had NPS above 6 and a SNOT-22 score above or equal to 60. More than 50% experienced comorbid asthma, 27% had AERD, and 60% had previous ESS. In both studies, at week 24, NPS reduction of one or more was observed in 56% of patients receiving omalizumab, and a reduction of two or more points was observed in 31% of them. There was also significant improvement in nasal symptoms including sense of smell, nasal discharge, SNOT-22 score, as well as asthma-related QOL. On August 6, 2020, Novartis announced that the European Commission has approved omalizumab as an add-on therapy with intranasal steroids for management of adult patients with CRSwNP in whom treatment with intranasal steroids does not provide adequate control [47].

Risks and adverse effects of biologics

To date, known adverse effects of biologics are generally mild and well-tolerated such as headache, nasopharyngitis, and reaction at the injection site [44]. One of the most common adverse effects of dupilumab is conjunctivitis, which was reported in ~8% of patients in a recent meta-analysis [48], and a postmarketing study showed an even higher incidence of up to 38% [49]. Dupilumab may be associated with risk of transient hyper-eosinophilia, and there were few reported cases of eosinophilic granulomatous polyangiitis (Churg–Strauss Syndrome) and eosinophilia associated with arthralgia [29,49,50]; however, the number of cases is too small to draw definite conclusions [44].

Risk of malignancy is another theoretical issue with biologics. Initial studies on mepolizumab showed possible slight increase of malignancy compared with placebo [44]; yet, a postmarking analysis did not find a higher malignancy risk [51]. There is a reported case of T-cell lymphoma in a patient treated with dupilumab [49]; however, it is not possible to draw a definite causality relationship.

One study on mepolizumab showed increased incidence of thromboembolic events [52], but this may be related to the severity of asthma in the treated patients. The bottom line is biologics are new, and it is too early to have a definite conclusion about the adverse effects that may be associated with their manipulation of the immune system, particularly with chronic use. Indeed, patient monitoring, appropriate reporting of side effects, future research studies, and continuous postmarketing analysis are all required to help educate the medical community about the safety of biologics on the long term [44].

Cost-effectiveness of biologics in treatment of chronic rhinosinusitis with nasal polyps

A number of researchers have investigated the cost-efficiency of mepolizumab, omalizumab, and reslizumab in treatment of allergic asthma [53–56]. Studies have shown that for such currently expensive biologics to be cost-effective they need to be reserved for severe asthma cases not responding to standard medical therapy [53,55]. Some have also shown that a reduction of the current prices by ~60–80% is required to improve their cost-effectiveness [44]. As dupilumab has been approved by FDA for treatment of CRSwNP, there is a real need for studies that address its cost-efficiency in treatment of those patients. Currently, in United States, it is estimated that the annual cost of using dupilumab in CRSwNP treatment for a single patient...
is $\sim$36,000, assuming the biweekly dosing schedule without insurance coverage [57]. Although biologics can hold a great hope for treatment of CRSwNP, their cost has to be significantly addressed as well.

**Current indications for biologics in treatment of chronic rhinosinusitis with nasal polyps**

Following FDA approval of dupilumab for management of CRSwNP, significant modifications have been made in the management algorithm of these patients. The steering group of the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS2020) currently recommends biologics for patients with CRSwNP who have had previous ESS (or who are unfit for surgery) and who also have three of the following five criteria [2]:

1. Evidence of type 2 inflammation (blood eosinophils \(\geq 250\), tissue eosinophils \(\geq 10/\text{HPF}\), or total IgE \(\geq 100\)).
2. Require at least two courses of systemic steroids per year, or need continuous use of low dose systemic steroids (>3 months), or have contraindication to systemic steroids.
3. Significantly impaired QOL (SNOT-22 \(\geq 40\)).
4. Anosmic on smell test.
5. Comorbid asthma needing regular inhaled steroids.

The EPOS2020 also recommends monitoring response to biological treatment by evaluating the following five criteria after 16 weeks, and to continue treatment to 1 year only if there is at least partial response in all of these criteria:

1. Reduction of polyp size.
2. Reduced need for systemic steroids.
3. Improved SNOT-22 score.
4. Improvement of smell function.
5. Decreased effect of comorbidities (asthma).

**Future perspectives and research**

Despite the progress made in investigating the underlying pathogenesis of CRSwNP and the role of different biological therapies, there are still a plethora of queries and open research questions to be answered. Further categorizing of endotypes is expected as we better understand the underlying pathophysiologic processes. Meanwhile, more monoclonal antibodies will be developed as new targets are discovered. Although type 2 inflammation has been well-described in the United States and European patients, it is still unclear if patients in Arab and Middle East countries share the same endotypes.

We lack data directly comparing biologics to surgery. It would be of great help if we can categorize patients who can benefit from biologics earlier in the treatment algorithm without waiting for failures. It is still unclear how to accurately identify patients who will respond to treatment. Moreover, should we combine biologics with surgery for better outcome? Can we use another biologic after failure of the first one?

There are no known clinical trials investigating biologics in allergic fungal rhinosinusitis. Moreover, anti-IL-13 and anti-TSLP may offer help for certain CRSwNP cases [58]. It is currently unknown if biologics can help patients with neutrophilic CRSwNP. Are biologics targeting Th1 and Th-17 inflammatory pathways helpful in the corresponding conditions?

The cost of biological treatment is obviously a limiting factor, and studies are required to investigate the cost-effectiveness of using biologics in CRSwNP at different levels of the treatment algorithm. Moreover, understanding risks and adverse effects of long-term use of different biologics is still in its infancy.

Although some indications have been suggested for biologics in treatment of CRSwNP, we expect significant changes in the current care pathways as many of the aforementioned questions are being answered.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

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