Biologics for the treatment of severe chronic rhinosinusitis with nasal polyps.

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Abstract

Chronic rhinosinusitis is a heterogenous persistent inflammatory disease affecting the nasal and paranasal sinuses. It is classified into chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). CRSwNP is strongly associated with eosinophilic asthma and aspirin exacerbated respiratory disease. CRSwNP is a debilitating disease, with significant clinical burden and contributes significantly to the socioeconomic costs of the health care systems. The comorbidity of CRSwNP and asthma is difficult to treat, because CRSwNP impacts on the severity of asthma. Similarly, asthma contributes to the morbidity and severity of CRSwNP, which may necessitate high-dose intranasal corticosteroids and repeated revision functional endoscopic sinus surgery in patients with CRSwNP. Type 2 helper (Th2) lymphocytes 2 and innate group 2 cells (ILC2s) play a central role in the pathogenesis of both eosinophilic asthma and CRSwNP via secretion of inflammatory cytokines and chemokines. Cytokines secreted by Th2 lymphocytes and ILC2s, such as IL-5, IL-4, IL-13 and epithelial-derived cytokines including IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) play a key role in the pathogenesis of eosinophilic asthma and CRSwNP. Uniform targeted treatment of asthma and CRSwNP may require administration of anti-interleukin biologics. Dupilumab and omalizumab are the only biologics which have been approved for the treatment of both diseases. They have been shown to significantly improve patient-reported nasal congestion scores, nasal polyp scores, Lund-Mackay computed tomography scores, peak nasal inspiratory flow and the Sino-Nasal Outcome Test-22 scores. Mepolizumab, reslizumab and benralizumab (anti-IL-5) and tezepelumab (anti-TSLP) are in phase III clinical trials. They have been shown to be effective and safe; and well tolerated for the treatment of patients with eosinophilic asthma and CRSwNP.

Keywords: Chronic rhinosinusitis, Nasal polyps, Eosinophilic asthma, Biologics, Dupilumab.

Introduction

Chronic rhinosinusitis with nasal polyps

Chronic rhinosinusitis (CRS) is a heterogenous persistent inflammatory disease affecting the nasal and paranasal sinuses. It is usually accompanied by the formation of nasal polyps, synonymously called chronic rhinosinusitis with nasal polyps (CRSwNP). CRSwNP is characterized by nasal obstruction, mucopulurent discharge, facial pain or pressure and hyposmia lasing more than 12 weeks, with corresponding radiologic or endoscopic visualization of inflammation or polyps of the sinuses [1]. CRSwNP is often associated with sleep disturbance, depression and anxiety which affect the patients' health-related quality of life (HLQoL) [2]. CRSwNP is one of the most common chronic diseases, with prevalence of 1.1% in the United States [3] and 2.1% to 4.4% in the European Union [4].

Traditionally, CRS has been classified into CRSwNP and CRSsNP depending on whether the patient has nasal polyps, or not, respectively [5, 6]. However, the distinction is not clear cut and each of these phenotypes can be subdivided into several immunopathological sub-types [7] and a lot of overlap is seen.

CRSwNP can be further sub classified to include aspirin-exacerbated respiratory disease (AERD), a syndrome comprising of chronic rhinosinusitis with recurrent eosinophilic nasal polyposis, eosinophilic asthma and respiratory reactions induced by aspirin or any other NSAIDs that inhibit the cyclooxygenase-1 enzyme [8]. The prevalence of AERD is about 30% in patients with asthma and CRSwNP [9]. The nasal polyps in patients with AERD tend to be large and are recurrent after functional endoscopic sinus surgery (FESS) [10, 11] and concomitantly make CRSwNP and asthma control very difficult.

Most commonly, CRSwNP is associated with allergic diseases, such as eosinophilic asthma, allergic rhinitis (AR) and atopic dermatitis (AD) [4]. The combination of asthma, AR and

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CRSwNP is termed the united airway disease. Patients with CRSwNP and comorbid asthma have a more severe disease, frequent systemic corticosteroid dependence, repeated FESS [10, 11], poor asthma control, frequent asthma exacerbations, resulting in high medical costs and excessive utilization of health care resources [12, 13]. Table 1 shows the associated clinical conditions associated with CRSwNP.

The comorbidity of CRSwNP with eosinophilic asthma is a very debilitating syndrome and a health burden [14], which is very difficult to treat with the standard of care (SoC). The shared immunopathophysiology has important implications in the treatment of both CRSwNP and eosinophilic asthma [15]. Henceforth, targeting asthma and CRSwNP with one weapon (anti-interleukin biologics) is a precision approach [16].

The pathophysiological mechanisms of CRS are complex and multifactorial and involve genetic, immunological, environmental, epithelial dysfunction, mucociliary impairment and infective causes. Lower airways diseases, such as eosinophilic asthma and upper airway diseases, including CRSwNP share similar immunopathophysiology. Both eosinophilc asthma and CRSwNP are characterized by eosinophilia and elevated local levels of immunoglobulin E (IgE) [15].

Type 2 helper (Th2) lymphocytes, innate type 2 lymphoid cells (ILC2s), mast cells, basophils and eosinophils play an important role in the pathogenesis of CRSwNP [17-19]. Activated Th2 lymphocytes and ILC2 cells secrete several cytokines, such as IL-5, IL-4 and IL-13 and chemokines, adhesion molecules and growth factors [6,19-22], which cause nasosinus epithelial cells injury, inflammation and nasosinus remodeling, with the formation of nasal polyps. Dysfunctional nasosinus epithelial cells secrete alarmin cytokines, such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), which further amplifies, the inflammatory and remodeling process [23-25]. TSLP is a potent stimulant of ILC2 cells and mast cells. It induces secretions of Th2 cytokines, such as IL-5, IL-4 and IL-13, which further orchestrates the inflammatory responses and nasosinus remodeling [17]. Nasosinus mucosal remodelling is characterized by epithelial-mesenchymal transition (EMT), goblet cells hyperplasia, deposition of fibrin and finally formation of grape-like nasal polyps [26].

Treatment of chronic rhinosinusitis with nasal polyps

The primary aim of treatments of CRSwNP is to achieve a state of clinical control in which patients no longer have troublesome symptoms combined with a healthy or almost healthy mucosa on examination and the need for local medication only [5]. The standard of care treatment of CRSwNP is outlined in detail in the European Guidelines on Sinusitis and Nasal Polyposis [5].

Treatment of CRSwNP is challenging, especially when co-existing with eosinophilic asthma. Severe asthma is associated with worse outcomes in the treatment of CRSwNP. Patients with CRSwNP and concomitant asthma may require high-dose intranasal corticosteroids, oral corticosteroids, budesonide nasosinus irrigation, doxycycline and repeated FESS.

In the era of precision medicine, several monoclonal antibody (mAb) targeting IgE and interleukins which are responsible for promoting airway and sinonasal pathway inflammation, airway hyperresponsiveness (AHR) and remodeling have been developed. They include omalizumab (anti-IgE), mepolizumab and reslizumab (anti-IL-5), benralizumab (anti-IL-5Rα), dupilumab (anti-IL-4Rα) and tezepelumab (anti-TSLP). Table 2 depicts the Food and Drug Administration (FDA) approved biologics and their dosages for the treatment of eosinophilic asthma.

Astoundingly, some of these biologics which have been approved for the treatment of asthma have demonstrated therapeutic potential for the treatment of CRSWNP [27]. Currently, the only approved biologics for the treatment of CRSwNP, include dupilumab the first biologic to be approved and omalizumab. Although biologics are mostly administered to postoperative patients after failed FESS, they should also be used to treat properly selected preoperative patients with CRSwNP and other subtypes, including AERD and allergic fungal sinusitis (AFS). Nevertheless, there is still unmet need to develop novel biologics for the treatment of eosinophilic CRSwNP, non-eosinophilic CRSwNP and AERD.

***Table 1**. Clinical conditions associated with chronic rhinosinusitis and nasal polyps.*

Allergic rhinitis
Eosinophilic asthma
Allergic fungal sinusitis
Aspirin exacerbated respiratory disease
Atopic dermatitis
Hyposomia
Sleep disturbance
Anxiety
Depression

***Table 2.** Dosages of approved biologics by the food and drug administration for the treatment of eosinophilic asthma, and CRSwNP*

Omalizumab	75-375 mg SC	Reduces exacerbations (47-53%)
Mepolizumab	100 mg SC	Reduces exacerbations (50-60%)
Reslizumab	3 mg/Kg IV	Reduces exacerbations (34-75%)
Benralizumab	30 mg SC	Reduces exacerbations (25-60%)
Dupilumab	200 mg or 300 mg SC	Reduces exacerbations (50-60%)
Tezepelumab	210 mg SC	Reduces exacerbations (60-80%)

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Omalizumab

Omalizumab (Xolair®) was the first biologic to be approved by the FDA in 2003 for the treatment of severe eosinophilic asthma. Omalizumab is an advanced humanized IgG1 monoclonal antibody (mAb) which specifically bids to the Fc portion of unbound IgE forming omalizumab: IgE complexes. This reduces free IgE levels and prevents IgE binding to FCεR1 on effector cells [28]. Therefore, preventing activation and degranulation of mast cells, basophils and eosinophils and preventing release of inflammatory mediators implicated in the pathogenesis of allergic respiratory diseases, such as eosinophilic asthma and CRSwNP [29, 30].

The efficacy and safety of omalizumab in the treatment of adults and children aged 6 years and above is very well established. Omalizumab has been shown to improve asthma control, reduce exacerbations and emergency medical visits; improve lung function and health-related quality of life (HLQoL) in adults [31-33] and children with severe eosinophilic asthma [34, 35]. Furthermore, omalizumab has been demonstrated to allow patients wean or even discontinue corticosteroid treatment [31]. Thus, avoiding the serious adverse effects from high doses and prolonged glucocorticoid therapy.

Several clinical trials, including POLYPS 1 and POLYP 2 have evaluated the efficacy of omalizumab in the treatment or CRSwNP with or without asthma. Xolair® has been reported to significantly reduce the nasal congestion scores (NCS), nasal polyp scores (NPS), Sino-Nasal Outcome Test (SNOT-22) and the Lund-Mackay sinus opacification scores [36]. Encouraging results from the POLYPS 1 and POLYP 2 studies earned omalizumab's approval by the FDA on December 1, 2020.

Dupilumab

The twin cytokines, IL-4 and IL-13 and their shared receptor (IL-4Rα) play an important role in the pathogenesis of CRSwNP [6, 37, 38] and other allergic diseases, such as eosinophilic asthma, atopic dermatitis and eosinophilic esophagitis. Dupilumab is atop of the biologics hierarchy. It is the only interleukin antagonist which has been approved by the FDA and the European Medicines Agency (EMA) for the treatment of severe esosinophilic asthma, AR, AD and eosinophilic esophagitis.

Dupilumab (Dupixent®) is a fully human VelocImmune®-derived IgG4 monoclonal antibody co-developed by Regeneron Pharmaceutical and Sanofi, Inc. Tarrytown, New York [39]. Dupilumab is directed against the alpha subunit of IL-4 receptor (IL-4Rα) that blocks signaling of both IL-4 and IL-13, thus preventing their immunopathological effects [40-42]. Interleukin-4 and IL-13 are the key drivers of type 2 eosinophilic inflammation [43, 44]. Therefore, blocking both cytokines may be more effective in the treatment of allergic diseases, such as eosinophilic asthma and CRSwNP [45, 46].

Several clinical trials have documented the efficacy and safety of dupilumab in patients with moderate-to-severe eosinophilic asthma. Dupilumab has been shown to improve asthma control, decrease severe exacerbations, hospitalizations and emergency medical visits. Additionally, dupilumab has been demonstrated to improve lung function, HLQoL and to allow patients taper or discontinue corticosteroid therapy [43, 44-47].

Clinical trials investigating the efficacy of dupilumab in the treatment of severe asthma, have reported concomitant improvement in nasal symptoms in patients with CRSwNP [47-50]. In patients with CRSwNP with or without comorbid eosinophilic asthma, Dupixent® has been shown to significantly improve patient-reported nasal congestion scores, nasal polyp scores, Lund Mackay computed tomography scores, peak nasal inspiratory flow and the Sino-Nasal Outcome Test-22 (SNOT-22) scores [47-51]. Dupilumab has also been shown to improve sleep architecture, hyposmia and HLQoL [51]. Dupixent® was the first approved biologic for the treatment of CRSwNP by the FDA and the EMA in March 2019.

Other biologics for the treatment of CRSwNP

Three anti-IL-5 biologics, mepolizumab [52, 53], reslizumab [54] and benralizumab [55]; and tezepelumab (anti-TSLP) are in phase III clinical trials and have demonstrated to be effective and safe for the treatment of CRSwNP.

Mepolizumab (Nucala®) is a humanized monoclonal antibody targeting IL-5 and inhibiting its downstream signaling and its eosinophilic inflammatory responses. Mepolizumab has been reported to significantly improve nasal symptoms, SNOT-22, hyposmia and HLQoL [52, 53]; and reduce the need for repeated FESS.

Benralizumab (FasenraTM) is an afucosylated mAb that specifically target the alpha chain of IL-5 (IL-5Rα), thus preventing IL-5 binding to its receptor and preventing the immunopathological effects of IL-5. Additionally, benralizumab has a strong apoptotic effects on eosinophil's [59]. Benralizumab demonstrated statistically significant reduction in the endoscopic total nasal polyps scores (NPS), nasal blockage scores (NBS) and the Lund-Mackay scores [55, 56].

Tezepelumab is a humanized mAb (IgG2λ) that specifically binds to TSLP and prevents it interacting with its heterodimeric receptor (TSLPR). Apart from significantly reducing the annualized asthma exacerbation rates, tezepelumab has been show to significantly improve nasal symptoms in patients with severe asthma and comorbid CRSwNP [56]. Table 2 shows the approved biologics and their dosages for the treatment of eosinophilic asthma. Dupilumab and omalizumab are approved for the treatment of both eosinophilic asthma and CRSwNP.

Conclusion

Chronic rhinosinusitis is a persistent inflammatory disease affecting the nasal and Para nasal sinuses. It is usually accompanied by the formation of nasal polyps, synonymously called chronic rhinosinusitis with nasal polyps. CRSwNP is strongly associated with eosinophilic asthma and AERD. It contributes to significant clinical burden and socioeconomic costs. The comorbidity of CRSwNP and asthma is difficult to treat, because CRSwNP impacts on the severity of asthma.

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Similarly, asthma contributes to the morbidity and severity of CRSwNP, which may necessitate high-dose intranasal corticosteroids and repeated revision FESS in patients with CRSwNP. Th2 lymphocytes and ILC2 cells play a key role in the pathogenesis of both eosinophilic asthma and CRSwNP via secretion of inflammatory cytokines and chemokines. Uniform targeted treatment of asthma and CRSwNP may require administration of biologics. Dupilumab and omalizumab are the only biologics which have been approved for the treatment of both diseases. They have been shown to significantly improve patient-reported nasal congestion scores, nasal polyp scores, Lund-Mackay computed tomography scores, peak nasal inspiratory flow and the Sino-Nasal Outcome Test-22 scores. Reslizumab and benralizumab (anti-IL-5) and tezepelumab (anti-TSLP) are in phase III clinical trials. They have shown to be effective and safe and well tolerated for the treatment of patients with eosinophilic asthma and CRSwNP.

Conflict of interest

The author declares that the publication was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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