Updates on current evidence for biologics in chronic rhinosinusitis

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Purpose of review
The purpose of this review is to present the most important recent developments concerning biologics as a therapeutic option for chronic rhinosinusitis (CRS).

Recent findings
mAb anti-IL-4 receptor α (Dupilumab) was recently approved by Food and Drug Administration (FDA) for patients with CRSwNP and four other biologics are under investigation, with promising preliminary results.

Summary
CRS is a disease associated with a significant symptom burden and high-indirect costs. Despite recent advances in combined approaches, persistent symptoms or recurrences are not uncommon. Monoclonal antibodies, used mainly to treat asthma, have recently been shown to have a positive impact on controlling the symptoms of CRS and reducing the need for endoscopic sinus surgery. Dupilumab, mepolizumab, reslizumab, benralizumab and omalizumab are discussed and their mechanism of action, risk and current evidence on efficacy are presented. Preliminary studies show encouraging results with relatively few side effects. Once the high cost of such therapies is addressed, they could prove an important adjuvant therapy for patients with CRS. Large-scale clinical trials designed to evaluate them are called for.

Keywords
biologics, chronic rhinosinusitis, dupilumab, monoclonal antibodies, nasal polyps

INTRODUCTION

Chronic rhinosinusitis (CRS) is a multifactorial inflammatory disease of the paranasal sinuses which affects 5–12% of adults worldwide [1]. It can have significant adverse effects on quality of life [2]. CRS can be divided into two phenotypic subtypes, with and without nasal polyps (CRSwNP or CRSsNP, respectively) [3,7]. However, the high rate of polyp recurrence after conventional treatment combined with better knowledge and understanding of this complex disease has led to the discovery of new effective treatments. Biological therapies have been approved for patients with eosinophilic asthma for 15 years [4,5]. Asthmatic patients have a higher rhinosinusitis severity score than nonasthmatic ones and higher incidence of nasal polyps [5]. The strong connection between nasal polyposis and asthma combined with the encouraging results of biological treatment in patients suffering from asthma has led to the use of monoclonal antibodies in a subgroup of patients suffering from CRSwNP [6]. In general, CRSsNP is characterized by predominantly neutrophilic inflammation with elevated levels of Th1 cytokines, whereas CRSwNP is an eosinophilic inflammation with increased levels of Th2 cytokines [7–9] (Fig. 1).

PATHOPHYSIOLOGY-ENDOTYPES

The underlying pathophysiology which leads to the chronic sinonasal inflammation in CRSwNP is not fully understood. It is hypothesized that inhaled pathogens, antigens and particulates stimulate an immunologic response that promotes chronic inflammation [9]. Dysfunctional and inflamed mucosa in the paranasal sinuses may derive from epithelial dysfunction that entails a low-host defense and reduced tolerance to microbial antigens. Cytokines and chemokines of the epithelium conduct T-cells, B-cells, mast cells and lymphoid-cells to immune response [10–12]. In CRS, three main inflammatory pathways-endotypes have been identified. T-helper cells (especially Th-1, Th-2 and

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Curr Opin Otolaryngol Head Neck Surg 2019, 27:000–000
DOI:10.1097/MOO.0000000000000594

KEY POINTS

- Biologic therapy should be considered as a treatment option for CRS, since mAb anti-IL-4 receptor α (Dupilumab) was recently approved by Food and Drug Administration (FDA) for patients with CRSwNP.
- More monoclonal antibodies have shown promising results in a number of clinical trials.
- Further research is urgently needed concerning responder identification criteria, cost-effectiveness, correlation to surgery and long-term risks of biologics.

Th-17) advance the production of specific cytokines, which can lead to a permanent inflammatory state [13]. Th1-driven inflammation is relevant to CRSsNP and is mainly characterized by high levels of neutrophils, which is associated with myeloperoxidase, increased levels of IFN-c, IL-2 and TNF-a [14,15]. Th2-driven inflammation is associated with CRSwNP in white patients. Uncontrolled CRSwNP is often associated with other Type 2 allergic inflammatory diseases, such as asthma, atopic dermatitis, allergic rhinitis, eosinophilic esophagitis and food allergies [13,16]. The disease is characterized by an imbalance or hyperactivity of certain immune cells,

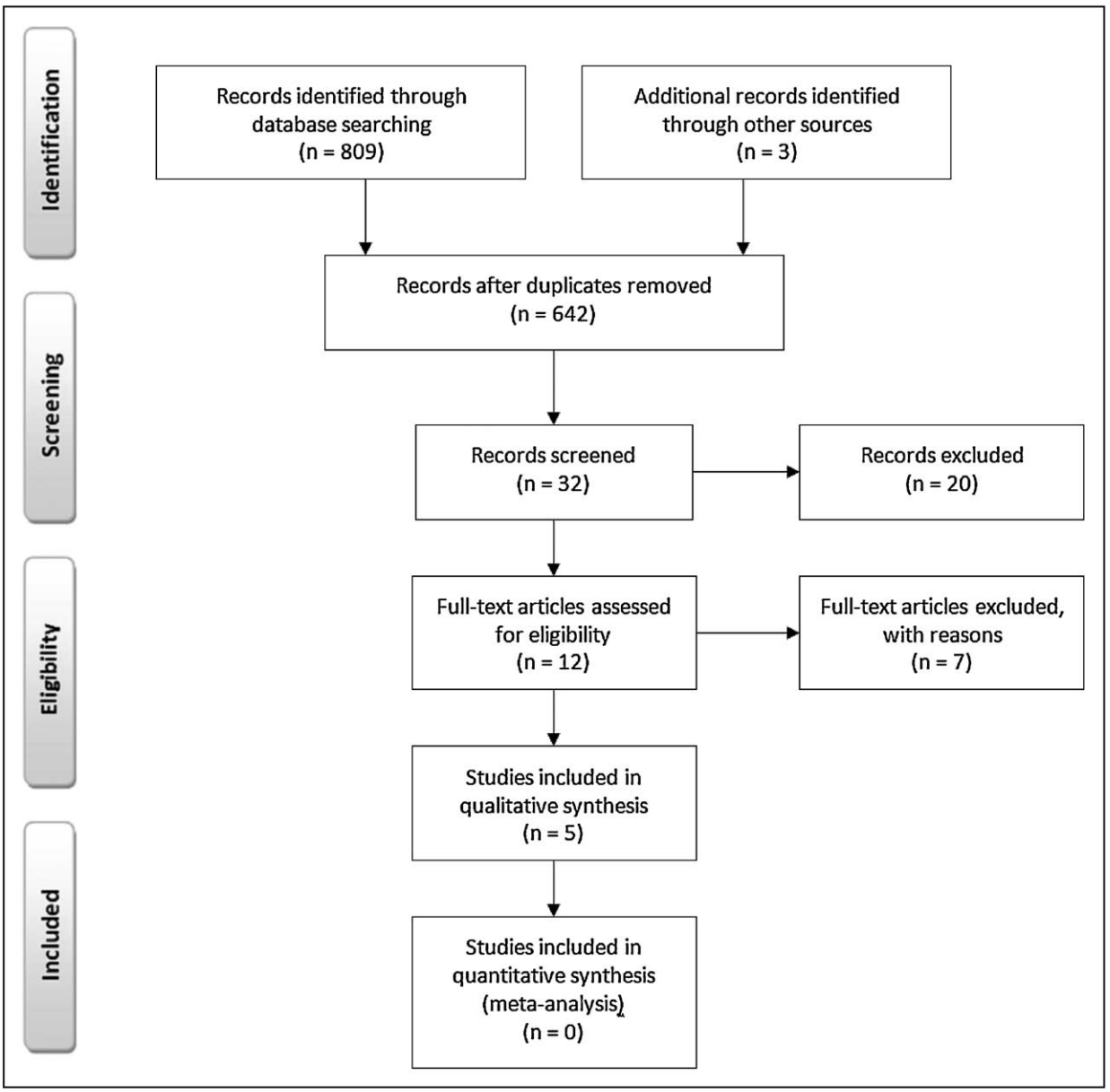

FIGURE 1. Literature search strategy. Detailed literature search and review – PRISMA flowchart. [Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ 2009;339:b2535, doi:10.1136/bmj.b2535].

principally eosinophils and signaling proteins such as IL-4, IL-13, IL-5, IL-10, IL-13, eosinophil cationic protein S and IgE [14–16]. Antibodies are considered central agents of the Type 2 inflammatory response. Th17-driven inflammation is associated with CRSwNP in Asian patients with high levels of IL-6, IL-17, IL-22 and TNF-a [12–16]. The separation and categorization of CRS in endotypes is important for personalized therapy in these patients.

CURRENT TREATMENT

Management of both CRS phenotypes, is currently based on the 2016 International Consensus Statement on Allergy and Rhinology: Rhinosinusitis [17], which is a more recent and complete update of the 2012 European Position Paper on Rhinosinusitis and Nasal Polyps [1]. Pharmaceutical treatment, consisting mainly of antiinflammatory medication, aims at the expression of IL-4, IL-5 and IL-13 and combines the administration of local, intranasal glucocorticoids along with high-volume (>200 ml) natural saline irrigations [18]. Multiple studies have shown this combination to be efficient both in controlling symptoms as well as improving endoscopic scores (LoE: grade A) [17]. When achieving optimal disease control is not possible, which is not unusual for CRSwNP patients, oral corticosteroids are recommended in brief courses with or without tapering. Antibiotics have no role in the management of CRS, neither intravenous nor per os, except for macrolide therapy that could benefit some patients (LoE: B) [17]. Endoscopic sinus surgery is the gold standard treatment reserved when appropriate medical treatment fails. Despite the fact that it is not curative, as it does not treat the underlying cause, it can be indispensable in relieving obstruction, restoring mucociliary clearance and facilitating delivery of local corticosteroids. Optimal time for surgical intervention remains controversial. Despite combined surgical and conservative treatment, ongoing symptoms or recurrence rates for nasal polyposis are as high as 20–50% [19] and even higher in the presence of certain comorbidities (e.g. Aspirin-Exacerbated Respiratory , Type II disease etc.) It is precisely for such patients that there may be a role for targeted biological therapies.

CURRENT BIOLOGICS

The high rate of uncontrolled disease, the recurrence of nasal polyps after systemic corticosteroids treatment and endoscopic sinus surgery highlight the need for alternative therapies. Monoclonal antibodies have been used as an innovative therapy for a variety of allergy-mediated conditions, such as asthma and atopic dermatitis with encouraging outcomes for almost 15 years [5]. The pathophysiology of CRSwNP overlaps with that of asthma [13]. Currently there is no biologic therapy under investigation for CRSsNP or noneosinophilic or Th1-driven and Th17-driven inflammation. Five monoclonal antibodies for eosinophilic CRS (CRSwNP) are under investigation and one of them was approved by FDA in June 2019: That is the mAb anti-IL-4 receptor α (Dupilumab) for chronic inflammation of the paranasal sinuses with nasal polyps for adults with inadequately controlled disease [20]. Three main monoclonal antibodies have been assessed regarding efficacy and safety in these patients [21,22] (Fig. 2).

ANTI-IL-4 RECEPTOR α THERAPY

Dupilumab is a fully human mAb targeting the α subunit of the IL-4 receptor that inhibits signaling of IL-4 and IL-13, aiming thus to reduce the Th-2-driven inflammation [23]. A randomized, double-blind, placebo-controlled group study, published in October 2018, involved 276 patients with CRSwNP refractory to corticosteroids with and without asthma, taking either Dupilumab ($n = 143$) or placebo ($n = 133$). After 4 weeks where all participants received mometasone furoate nasal spray (100 mg/nostril twice daily), 143 patients were randomly allocated to receive a 300 mg of dupilumab every 2 weeks for 24 weeks. In the Dupilumab group the total nasal polyp score was significantly improved (−2.06) as well as nasal congestion score (−0.89) from baseline to week 24 (difference versus placebo group; $P < 0.0001$ for both groups) [24▪▪]. A randomized, double-blind, placebo-controlled group study involved 60 patients with CRSwNP refractory to corticosteroids with and without asthma. After 4 weeks of treatment with mometasone furoate nasal spray (100 mg/nostril twice daily), 30 patients were randomly allocated to receive a 600 mg loading dose of dupilumab followed by 16 weeks of 300 mg dupilumab ($n = 30$) or matched placebo ($n = 30$). Corticosteroid spray was continued at a stable dose throughout the study, and inhaled asthma control therapies were allowed. The primary efficacy endpoint was a change in total endoscopic polyp score from baseline to week 16 ($P < .001$). Secondary endpoints included change in Lund–Mackay computed tomography score, Sino-Nasal Outcome Test (SNOT-22) score ($P < 0.001$), University of Pennsylvania Smell Identification Test score, and peak nasal inspiratory flow, as well as patient-rated nasal congestion or obstruction, anterior and posterior rhinorrhea and loss in sense of smell. The study analyzed the serum biomarkers and found a statistically

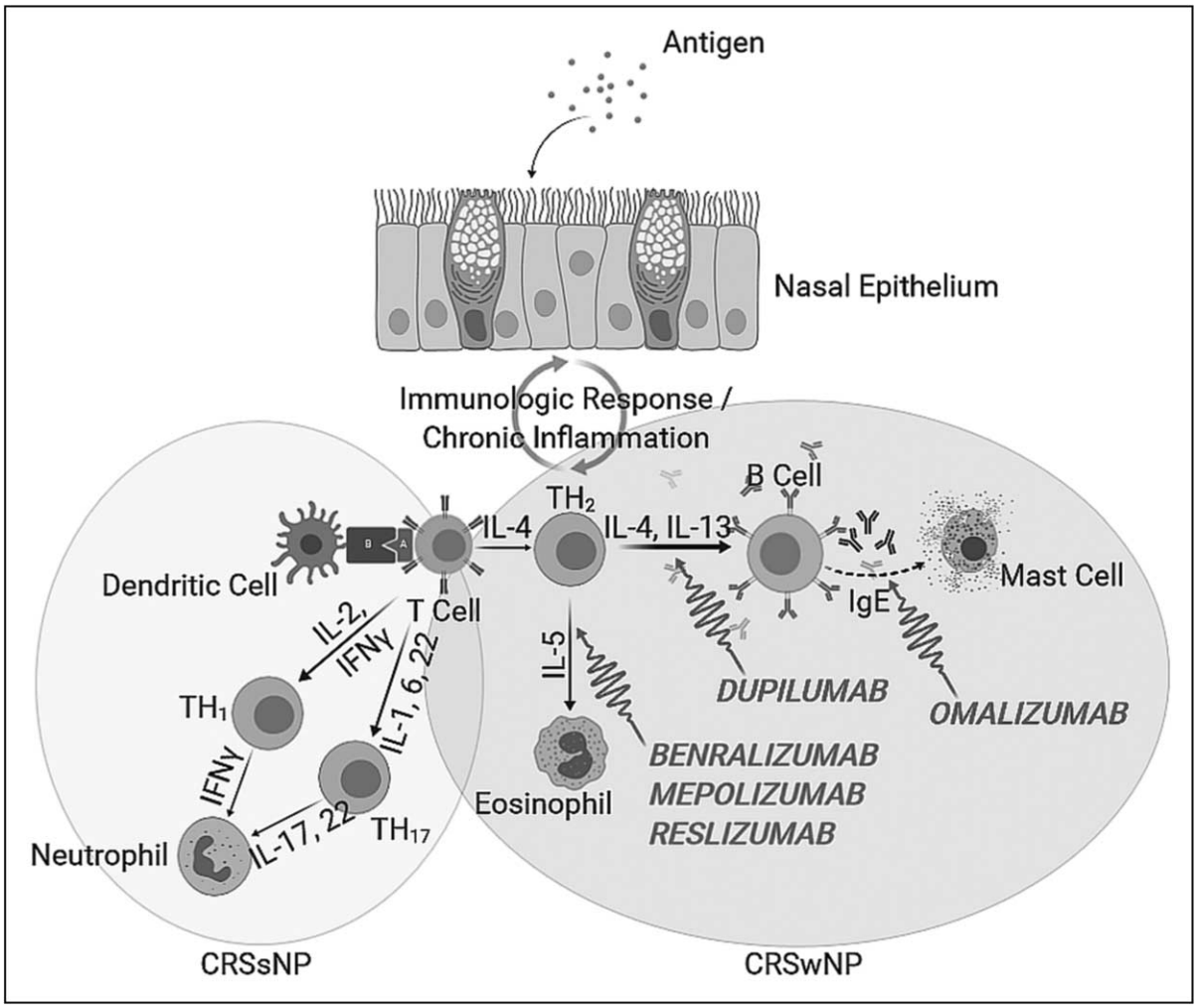

FIGURE 2. Simplified illustration of the pathophysiology of chronic rhinosinusitis and the target-points at which referred biologics act as inhibitors, with respect to phenotype. CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; IFN, interferon; IL, interleukin; TH_1, T helper cell type 1; TH_{17}, T helper cell type 17; TH_2, T helper cell type 2.

significant decrease in the levels of total serum IgE in the treatment group when compared with the placebo group ($P < 0.001$) [25]. Dupilumab is the first biologic antibody approved by FDA to treat nasal polyps [24▪▪,25–28,29▪].

ANTI-IL-5 THERAPY

Reslizumab is a humanized IL-5 antagonist mAb. IL-5 is a proinflammoty cytokine that is binding to the α-subunit IL-5 receptor and stimulates B-celll growth and increases Ig secretion. IL-5 is also a key mediator to eosinophilic activation [22]. FDA approved the use of reslizumab in March 2016 for the treatment of severe asthma in adults despite receiving their current asthma medicines [30,31]. A randomized, double-blind placebo-control group study took place in 24 subjects with CRSwNP. In the control group a single intravenous dosage 1 mg/kg of reslizumab was given and the patients were followed up for 36 weeks. Half of the subjects received a single dose of reslizumab (3 mg/kg) and were followed up for 36 weeks. The study showed a reduction of nasal polyp score for 4–12 weeks. The end of this trial showed no difference in total nasal polyp score compared with baseline. Also, the study showed that the patients with CRSwNP who responded to reslizumab had higher level of eosinophils at baseline ($P < 0.5$) [22]. A randomized, double-blind placebo-control group study to evaluate the efficacy of reslizumab in CRSwNP is under completion (estimated study completion date: July 2019) [32].

Mepolizumab is an anti-IL-5 mAb that bind free IL-5 inhibits the IL-5 receptor. FDA-approved mepolizumab in November 2015 to treat eosinophilic asthma in patients aged 12 years and older [31,34]. A randomized, double-blind, placebo-controlled trial published in July 2017 assessed the effect of mepolizumab in reducing the need

for surgery in patients with severe CRSwNP. 54 treatment adults received 750 mg of intravenous mepolizumab every 4 weeks for a total dose of six doses combined with daily topical corticosteroid use. The primary endpoint was need for surgery based on total nasal polyp score and nasal polyposis severity assessed by a Visual Analog Score at 25 weeks. Secondary endpoints included symptomatic improvements. The trial showed that treatment with mepolizumab reduced the number of patients needing surgery as week 25 compared with placebo ($P = 0.006$). There was also a significant improvement in nasal blockage ($P < 0.1$) [33].

Benralizumab is a humanized mAb which targets the IL-5Rα receptor leading to degradation of signaling and apoptosis. This direct effect on eosinophils leads to reduce of proinflammatory processes [31,36,37].

The biologic agent was approved for patients aged 12 and older with eosinophilic asthma [34]. In a post-hoc pooled analysis of the Phase III in severe eosinophilic asthma patients with CRSwNP and CRSsNP were examined [35]. The outcome measures regarding nasal polyposis were not published.

ANTI IGE THERAPY

IgE is an antibody synthesized by B cells, especially by plasma cells, in response on allergens. IgE is binding to FcεRI, CD23 and other receptors expressed on mast cells. Omalizumab is the biologic agent that has been investigated more than any other and studies showed an effective in the treatment of allergic disorders, such as comorbid asthma [36,40]. A randomized, double-blind, placebo-controlled group study examined 24 patients having nasal polyps and severe asthma. Omalizumab injected subcutaneously in a maximum dose of 375 mg every 2 weeks for 4 months. The study resulted in significant reduction in total nasal score

MONOCLONAL ANTIBODY	TARGET	STUDY	OUTCOMES	ADVERSE EFFECTS
Dupilumab	IL-4Rα	Han et al.[24]	NPS: P<0,001 Nasal congestion: -0,89 LMK: P<0,001 UPSIT: 10,56 SNOT-22: P<0,001 Corticoid use/NP surgery reduction: P<0,001	Epistaxis: 7,7% Nasopharyngitis:13,3%
		Bachert et al.[25]	NPS:P<0,001 LMK: P<0,001 UPSIT:14,8 SNOT-22: P<0,001	Nasopharyngitis 47% Headache: 20% Conjuctuvitis: 10% HSV: 2-4%
Reslizumab	IL-5	Gevaert et al.[22]	The study was not designed for evaluation of efficacy NPS: no difference Eosinophilia: rebound at the end	Common cold: 58,3% Nasopharyngitis: 21% Increase CPK: 20%
Mepolizumab	IL-5	Bachert et al.[33]	NPS: -1,8 Reduce number of patients needing surgery P=0.006 Improved VAS score in NP: P= 0.001 SNOT-22, PNIF: P=0,026	Headache: 25% Nasopharyngitis: 19% Back pain: 9% Influenza:8%
Benralizumab	IL-5Rα	Tian et al. [30]	No trials for nasal polyposis	
Omalizumab	IgE	Gevaert et al.[39]	NPS: P=0,2 LMK: P=0,04 Nasal congestion: P:0,002 Loss of sense of smell: P:0,004	Nasopharyngitis: 9% Headache: 6-12% Cardiovascular: <3%

FIGURE 3. Monoclonal antibodies investigated as biological therapies for chronic rhinosinusitis with nasal polyps. HSV, herpes simplex virus; IL, interleukin; LMK, Lund-Mackay computed tomography score; NPS, nasal polyp score; PNIF, peak nasal inspiratory flow; Rα, α subunit of the receptor; SNOT, Sino-nasal outcome test; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog score.

compared with placebo ($P = 0.01$ and 0.99). This study included only patients with severe nasal polyposis and comorbid asthma, so the results cannot be generalized. Omalizumab could be an effective and encouraging treatment for CRS [37–39]. Currently more studies are needed for further assessment (Fig. 3).

CONCERNS

The main concerns regarding biologics usage, are two; long-term side effects – for the given administration profiles-effectiveness and cost-effectiveness. Since most up-to-date cost-effectiveness studies concern administration for treating severe asthma, only indirect speculations can be made for the corresponding costs of treating CRS. Direct annual costs vary from \$10 000 to 40 000 for biologic antibodies [40,41]. Concerning severe eosinophilic asthma, Whittington *et al.* [42] estimated that to achieve cost effectiveness of approximately \$150 000 per QALY, mepolizumab would require more than a 60% price discount. Moreover, since biologics have been on the market only for the last 4 years or less, a series of risks need to be thoroughly examined. In addition to common side-effects (i.e. headaches or subcutaneous injection site reactions), several cardiovascular complications have been associated with long-term use of omalizumab, such as Deep Vein Thrombosis, pulmonary embolism, infractions and angina [43]. Dupilumab common (≥1/100–<1/10) side-effects, include conjunctivitis and herpes simplex virus reactivation. Serum sickness and anaphylaxis have been categorized as very rare (<1/10 000) [44]. Given these facts, several questions need to be answered before biologics find an established position in the CRS management algorithm: How can they be combined with surgery? What is the proper – from the cost-effectiveness point of view –timing? Should they be prescribed preoperatively, saving Endoscopic Sinus Surgery (ESS) for those who do not respond or vice-versa? Larger studies with long-term follow-up periods are needed for the foresaid to be given conclusive answers.

CONCLUSION

For the time being, downregulation of multiple Th2 inflammatory mediators through using nonspecific corticosteroids remains the standard of care for CRS, along with ESS for those who suffer from recurrent or persistent symptoms. After the recent approval of dupilumab for CRSwNP by FDA, a much faster pace is awaited, concerning future research on biologics. Specific indications and contraindications for the initiation of type 2 biological for CRSwNP with prior sinus surgery have already been proposed. Future large-scale clinical trials should emphasize patient selection criteria, duration of treatment, dosage, long-term side effects and discontinuation protocols. Moreover, the vast heterogeneity of genetic alterations, resulting in different phenotypes and endotypes urge the need of a more personalized approach. Such an approach would hierarchize the expression of certain mediators as more important than symptom-grouping or objective polyp scoring, when biologic treatment is the choice. The identification of a biomarker predicting response to treatment with each mAb could prove to be a great leap forward. Until now, only IL-5 levels in nasal secretions have been adequately studied as a predictive marker [22]. It is probable that forthcoming therapies will target Th1, Th17 and noneosinophilic endotypes, since most of research until now targets allergic CRS and eosinophilic ones.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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