



Clinical and biological markers in disease and biologics to treat chronic rhinosinusitis

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Purpose of review

Chronic rhinosinusitis (CRS) is a heterogeneous disorder with diverse responses to conventional anti-inflammatory medical and surgical treatments. Even for the newly developed mAbs targeting type 2 (T2) reaction, a considerable number of patients with CRS with nasal polyps (CRSwNP) exhibited unsatisfying response. Identifying patients with a tendency to poor prognosis is critical for selecting targeted therapies to improve the treatment outcome. This review focuses on clinical and biological markers associated with prognosis of CRS patients under conventional medical and surgical treatments and provides an update summary of potential markers for T2 biologics.

Recent findings

Allergic rhinitis, asthma, prior sinus surgery, nasal polyps, tissue eosinophilia and neutrophilia, blood eosinophilia and high levels of Charcot-Leyden crystal, cystatin SN, chemokine (C-C motif) ligand 17, macrophage inflammatory protein-1 β and interleukin (IL)-5 in nasal secretions have been associated with poor prognosis in CRS patients under conventional medical and surgical treatments. Blood eosinophil level might be a biomarker for anti-IL-5 (mepolizumab) and anti-IL-5R (benralizumab) biologic in patients with refractory CRSwNP.

Summary

Several clinical and biological markers have been associated with poor response to conventional treatments in CRS patients; however, majority of them should be verified by large-scale multicentre studies. More efforts are needed to identify biomarkers for biologics.

Keywords

biologic, biomarker, chronic rhinosinusitis, clinical factor, outcome

INTRODUCTION

Chronic rhinosinusitis (CRS) is a highly heterogeneous disease, which affects more than 8% of adults in Asian and western countries [1]. On the basis of clinically observable trait: presence or absence of nasal polyps, CRS can be classified into two phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [1]. Nasal glucocorticoids, in combination with systemic one for severe cases, are the first-line treatment for patients with CRS. Surgery is used to treat CRS patients who are unresponsive to medical treatments. However, around 20–40% of CRS patients cannot be appropriately controlled by adequate medical and subsequent surgical interventions [2,3,4]. Recently, phase 3 trials have shown promising efficacy of biologics targeting type 2 (T2) inflammation, including omalizumab [antiimmunoglobulin (Ig)E], dupilumab [antiinterleukin (IL)-4R α] and mepolizumab (anti-IL-5), on CRSwNP patients refractory to conventional glucocorticoid

and surgical treatments [5,6,7^{***}]. Nevertheless, 40–60% of them also poorly responded to these T2 biologics [5,6,7^{***}]. Multiple immune cells and inflammatory mediators participate in the pathological process of CRS, which may drive diverse responses to glucocorticoid, surgical and biological therapies. Therefore, identifying patients with a tendency to poor prognosis is critical for selecting targeted therapies and strengthening follow-up to

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Curr Opin Allergy Clin Immunol 2022, 22:16–23

DOI:10.1097/ACI.0000000000000799

KEY POINTS

- Allergic rhinitis, asthma, prior sinus surgery, nasal polyps and tissue eosinophilia and neutrophilia have been associated with poor prognosis in patients with CRS.
- Blood eosinophilia, and high levels of Charcot-Leyden crystal, cystatin SN, CCL17, MIP-1 β and IL-5 in nasal secretions might be good predictors of treatment outcomes due to their advantages of objectivity, noninvasiveness and easy accessibility.
- Blood eosinophil level is a potential biomarker for anti-IL-5 (mepolizumab) and anti-IL-5R (benralizumab) biologic in patients with refractory CRSwNP.

improve the treatment outcome and reduce recurrence. The aim of this review is to summarize the clinical and biological markers associated with poor prognosis of CRS patients under conventional medical and surgical treatments, and to provide an updated summary of potential markers for efficacy of T2 biologics. Given the space limitation, the biomarkers related to disease diagnosis and severity will not be included in this review.

DEMOGRAPHIC AND CLINICAL MARKERS FOR CONVENTIONAL MEDICAL AND SURGICAL TREATMENTS

Clinical and demographic features can be obtained from medical records and the baseline features having potential to predict CRS outcomes are summarized in Fig. 1.

Age

The influence of age on the surgical outcome of CRS patients remains controversial. Liao *et al.* [8] reported that younger age group (age: 18–50 years) was more likely to have difficult-to-treat disease 1 year after surgery than older patients (age > 50). The difficult-to-treat CRS was defined according to European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 [1]. However, Feng *et al.* [9] reported that older age (≥ 60 years) was a risk factor of ineffective treatment in CRS patients followed up for 10 months to 3 years after surgery with an odds ratio (OR) of 2.325 [95% confidence interval (95% CI), 1.745–3.525]. Elderly CRS patients have been reported to have a pro-inflammatory and neutrophilic immune signature which may impair the response to glucocorticoid treatment [10]. Obviously, the interaction between age, inflammation pattern and treatment outcome warrants further investigations.

Sex

The association between sex and CRS outcome has also been discordantly reported in the literature. No association between sex and CRS prognosis was observed by some studies [9,11,12]. However, in a large retrospective cohort study ($n = 61\,339$; follow-up time: at least 7 years), female sex was identified as a risk factor for revision surgery in CRS patients [OR (95%CI): 1.20 (1.11–1.29)] [13]. Women have been reported to have a higher prevalence of asthma and experience more severe CRS symptoms [13,14]. Oestrogen may promote T2 airway inflammation by activating eosinophils. Nevertheless, more efforts are needed in future to explore the mechanisms underlying sex differences in CRS control.

Concomitant allergic disease

Asthma and allergic rhinitis are the most common comorbidities of CRS and have been consistently identified as risk factors for poor prognosis of CRS in numbers of studies [2^a,8,13,15,16]. Allergic rhinitis and asthma are frequently associated with eosinophilic and T2 responses in CRS patients, which are critical contributing factors for disease relapse [9,17].

Previous sinus surgery history

The history of previous sinus surgery has been strongly associated with poor outcome in CRS patients [18]. A meta-analysis revealed that compared with those without previous surgery, the revision surgery rate was significantly higher in CRSwNP patients with prior surgery history [2^a].

Nasal polyps

Nasal polyps increase the rate of revision surgery in CRS patients [4,19,20]. In a large prospective study of 1459 CRS patients, Hopkins *et al.* [19] discovered that 20.6% of CRSwNP patients underwent revision surgery compared with 15.5% of CRSsNP patients in 5-year follow-up. Nasal polyps were also identified as an important risk factor for revision surgery in a large retrospective study of 61 339 CRS patients with follow-up of at least 7 years [OR (95% CI): 1.20 (1.11–1.29)] [13].

Smell impairment

Smell impairment has been reported as an important feature of T2 inflammation [21]. Guo *et al.* [22] discovered that the baseline smell impairment score at least 8 was a predictor of difficult-to-treat disease in CRS patients 1 year after surgery. Interestingly, Bakhshaei *et al.* [23] found that smell dysfunction

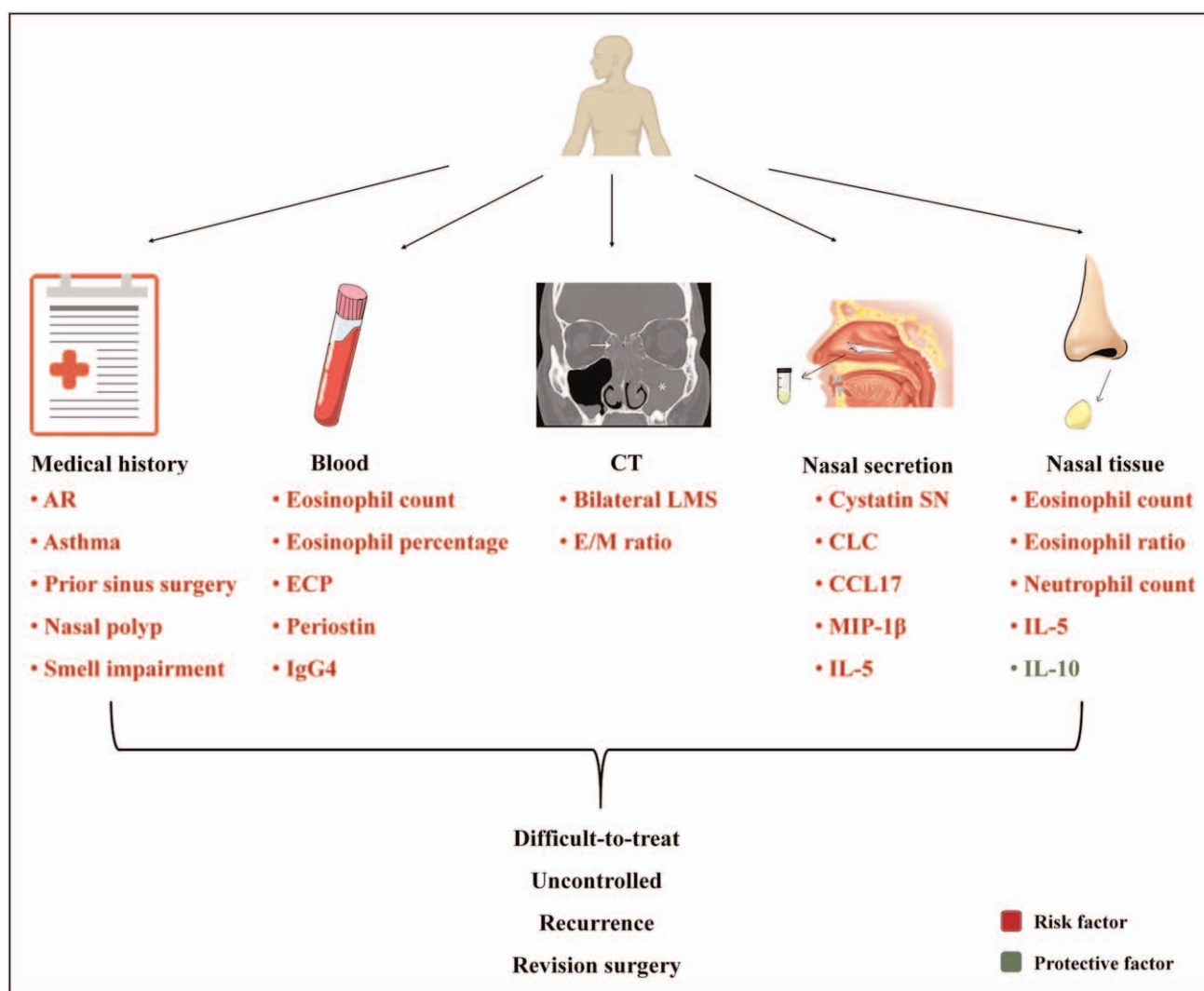


FIGURE 1. Clinical and biological markers associated with conventional medical and surgical treatments in patients with CRS. CCL, C-C motif ligand; CLC, Charcot-Leyden crystal; CT, computed tomography; E/M, ethmoid/maxillary sinus CT score; ECP, eosinophil cationic protein; Ig, immunoglobulin; IL, interleukin; LMS, Lund-Mackay CT score; MIP, macrophage inflammatory protein.

was the first symptom to deteriorate during follow-up in the patients with nasal polyp recurrence. Thus, smell function decline might serve as an 'early alarm symptom' reminding surgeons to carry out interventions in time to prevent disease deterioration [23].

Lund-Mackay computed tomography scores

The baseline total Lund-Mackay scores of sinus computed tomography (CT) have been reported associated with CRS recurrence and difficult-to-treat CRS [24]. In addition, the ratio of ethmoid and maxillary sinus score (E/M ratio) was found to have a high accuracy for predicting nasal polyp recurrence, achieving an area under the receiver operating

characteristic (ROC) curve (AUC) of 0.947 at a cut-off point of 2.55 [25]. Interestingly, 'ethmoid sinus-dominant opacification' on CT image has been linked with predominant eosinophilic inflammation in nasal polyps [24,26].

BIOLOGICAL MARKERS FOR CONVENTIONAL MEDICAL AND SURGICAL TREATMENTS

Biological markers reflect disease inflammatory status and can be quantified by standard laboratory methods with reduced subjective bias. Various biomarkers in sinus tissues, peripheral bloods and nasal secretions have been reported associated with CRS outcome (Fig. 1).

Tissue eosinophils and neutrophils

Eosinophils are key effector cells affecting CRS prognosis. Tissue eosinophil count more than 48/high power field (HPF) or the ratio of tissue eosinophils/total inflammatory cells more than 20.6% was reported as an independent risk factor of uncontrolled CRS at least 1 year after surgery, with an OR (95%CI) of 5.56 (2.12–15.07) and 10.09 (3.42–29.82), respectively [12]. Lou *et al.* [27] reported that a cut-off value of tissue eosinophil count more than 55/HPF or eosinophil/total inflammatory cell ratio more than 27% was able to predict nasal polyp recurrence with an AUC of 0.969. Compared with those with no eosinophilia, CRS patients with tissue eosinophilic aggregates (>20 eosinophils/HPF) required higher cumulative dose of nasal steroids to control mucosal inflammation during 6-month postoperative treatment period [28]. However, currently, no consensus regarding the tissue eosinophil threshold for poor outcome has been achieved. A wide acceptable cut-off value of tissue eosinophil for predicting a defined treatment outcome should be established in large-scale and multicentre studies [29].

The importance of neutrophils in the pathogenesis of CRS is attracting more and more attention. By cluster analysis, Liao *et al.* [30] found that 44% of Chinese CRS patients with neutrophilic endotype experienced difficult-to-treat disease 1 year after surgery, comparable to 50% in CRS patients with eosinophilic and T2 endotype. Kim *et al.* [31] found that the number of subepithelial human neutrophil elastase positive neutrophils more than 45/HPF might serve as a cellular marker for refractory (partly controlled and uncontrolled) CRS 1 year after surgery in Korean patients with CRSwNP, achieving an overall predictive accuracy of 84.04%. In their study, the CRS control was defined according to EPOS 2020 [1]. Tissue neutrophilia also impairs the efficacy of oral corticosteroid treatment in CRSwNP patients [32].

Tissue molecular markers

The diverse endotypes of CRS are important factors driving heterogeneous response to treatments. Different endotypes of CRS have their distinct molecular marker spectrum. A 12-year follow-up study showed that the baseline tissue IL-5 level was a predictor for the need of revision surgery [OR (95% CI): 1.004 (1.001–1.008)] in patients with CRSwNP [33]. In contrast, baseline tissue IL-10 levels were found negatively associated with difficult-to-treat CRS 1 year after surgery [OR (95% CI): 0.995 (0.993–0.997)] [8]. Regarding the response to glucocorticoid treatment, Hong *et al.* [34] reported that tissue IL-25 levels more than 22.50 pg/ml predicted well response to oral corticosteroid treatment, achieving an AUC of

0.963. Zeng *et al.* [35] explored efficacy of fluticasone propionate nasal spray and oral clarithromycin in the postoperative treatment of CRS patients. Through developing classification trees, high tissue levels of IL-8 and IgG4 were found associated with poor response to fluticasone propionate and clarithromycin treatment, respectively [35].

Blood eosinophilia

Although tissue biomarkers reflect the local inflammatory characteristic of CRS straightforwardly, the invasive nature of sample acquisition limits its clinical application. Increasing studies have explored noninvasive biological markers in peripheral bloods and nasal secretions. Peripheral blood eosinophil levels positively correlated with tissue eosinophil counts in patients with CRSwNP [36]. Blood eosinophil count at least $0.215 \times 10^9/l$ and percentage at least 3.05% were able to diagnosis eosinophilic CRSwNP, with both AUC more than 0.8 [37]. Pan *et al.* [38] followed up a total of 535 Chinese CRSwNP patients for at least 1 year, and found that baseline blood eosinophilia ($> 0.5 \times 10^9/l$) was an independent risk factor for uncontrolled disease after surgery [OR (95% CI): 2.07 (1.14–3.52)]. In addition, baseline blood eosinophilia was significantly associated with post-surgical local corticosteroid failure [OR (95% CI): 9.28 (1.90–45.60)], and blood eosinophil count more than $0.455 \times 10^9/l$ indicated a need of repetitive oral corticosteroid therapy [39]. Collectively, these results suggest that blood eosinophilia is a surrogate noninvasive marker for unfavourable surgical and glucocorticoid treatment outcome in patients with CRS. Noninvasive nature of sampling and well established standard operating procedure make blood eosinophil a good biomarker for CRS patients in clinical practice.

Blood molecular markers

Other than blood eosinophil, few blood biomarkers have been proved associated with CRS outcome. Lu *et al.* [40] found that baseline serum eosinophil cationic protein (ECP) levels were able to predict nasal polyp recurrence 1 year after surgery, with a cut-off value of 21.8 $\mu g/l$ achieving an AUC of 0.729. In studies of Japanese CRSwNP patients with 5 to 8-year follow-up, baseline serum periostin and IgG4 levels were found to predict postoperative recurrence, but had poor performance with an AUC of 0.595 and 0.610, respectively [41,42]. Guo *et al.* [22] conducted a comprehensive study of 35 mediators in plasma including pro-inflammatory cytokines, T cell related cytokines, chemokines and immunoglobulins in CRS patients. They failed to find any difference between

patients with and without difficult-to-treat CRS [22]. Taken together, these results suggest that peripheral blood molecular markers may not have sufficient resolution to capture the difference at mucosal site in CRS patients with different outcomes. Nevertheless, to date, only limited blood biomarkers have been investigated, and it cannot be excluded that there might be some valuable biomarkers not covered in previous studies.

Nasal secretion biomarkers

Significant correlations between the levels of several cytokines including IL-5 and IL-13 in nasal secretions and sinus tissues have been reported [43,44]. Cystatin SN is a cysteine protease inhibitor, which enhances IL-5 mediated eosinophil activation. Wu *et al.* [45[■]] demonstrated that cystatin SN levels higher than 2.63 µg/ml in nasal secretions efficiently predicted uncontrolled status of CRSwNP over a 2-year period after surgery, achieving an AUC of 0.966. They also reported that Charcot-Leyden crystal (CLC) levels at least 34.243 ng/ml in nasal secretions predicted nasal polyp recurrence 12–33 months after surgery, with an AUC of 0.933 [46]. Guo *et al.* [22] applied classification and regression tree analysis to establish prediction model for difficult-to-treat CRS 1 year after surgery; they found that high levels of chemokine C-C motif ligand 17 (CCL17) and macrophage inflammatory protein (MIP)-1β in nasal secretions were important predictors with an overall predictive accuracy of 94% [22]. Cluster analysis of nasal mucus cytokines identified two CRS clusters with predominant T2 signature, which had poor SNOT-22 improvement 1 year after surgery [47].

Although several biomarkers in nasal secretions may serve as predictors of poor treatment outcome in CRS patients, the detection of biological mediators in nasal secretions, including sample collection and measurement methods, currently faces the difficulty in standardization of operating procedure. In future, more efforts are needed to tackle this issue before the wide application of those markers in clinic.

BIOLOGICS AND POTENTIAL BIOMARKERS

Eosinophilic and T2 response are critical factors leading to disease relapse after conventional medical and surgical treatments in patients with CRS. An array of biologics targeting eosinophilic and T2 response have been developed or are under developing for treating refractory or recurrent CRS, particularly CRSwNP. Recently, three phase 3 trials of T2 biologics, including omalizumab (anti-IgE), dupilumab (anti-IL-4Rα)

and mepolizumab (anti-IL-5), have shown promising effects of these biologics on shrinking nasal polyps, relieving symptoms, improving quality of life and reducing revised surgery in CRSwNP patients refractory to conventional glucocorticoid and surgical treatments [5,6,7[■]]. However, these trials also revealed that about 40–60% of CRSwNP patients had poor response to T2 biologics as defined by the change of nasal polyp scores and nasal congestion scores less than 1 point [5,6,7[■]]. Thus, it is important to find the clinical and biological markers associated with efficacy of T2 biologics for the purpose of selecting right patients for the biologic treatments.

Mepolizumab is a humanized mAb that targets soluble IL-5, thereby inhibiting eosinophilic inflammation. The first randomized, double-blinded, placebo-controlled proof-of-concept study of mepolizumab demonstrated that blood eosinophil counts, and serum ECP, periostin and IL-5Rα levels, and IL-5Rα, IL-6, IL-1β, periostin and myeloperoxidase (MPO) levels in nasal secretions were significantly decreased after treatment [48]. Recent phase 3 SYNAPSE study discovered that mepolizumab significantly reduced blood eosinophil by week 4 and last until week 52 [7[■]]. Similar findings were observed in the studies of patients with aspirin-exacerbated respiratory disease and severe asthma under mepolizumab treatment [49,50]. Importantly, higher baseline blood eosinophil count was associated with higher median change in nasal congestion scores from baseline overtime, but such association was not observed for nasal polyp scores [7[■]]. A phase 2 study of benralizumab, a humanized anti-IL-5Rα mAb, on Japanese patients with eosinophilic CRS demonstrated that although benralizumab did not meet the primary efficacy endpoint, patients with high blood eosinophil levels had a greater tendency to respond to benralizumab treatment [51]. Thus, baseline blood eosinophil level might be a biomarker for anti-IL-5 and anti-IL-5R biologic in patients with refractory CRSwNP. However, more researches are needed to confirm this notion.

Dupilumab is a human mAb against IL-4Rα. It effectively downregulates T2 inflammation by inhibiting both IL-4 and IL-13 signalling [52]. In 2019, Bachert *et al.* [6] published the results of two pivotal phase 3 studies termed LIBERTY NP SINUS-24 (of 24 weeks duration) and LIBERTY NP SINUS-52 (of 52 weeks duration). In the SINUS-52 study, T2 biomarkers were analysed simultaneously. Compared with placebo, dupilumab significantly decreased the blood levels of thymus and activation-regulated chemokine (TARC), periostin, total IgE and eotaxin-3 at week 24 and 52, and the levels of ECP, total IgE, eotaxin-3 and IL-5 in nasal secretions at week 24 [6]. It is consistent with the finding of

Table 1. Potential predictive biomarkers for efficacy of biologics targeting type 2 inflammation

	Mepolizumab (anti-IL-5)	Benralizumab (anti-IL-5Rα)	Dupilumab (anti-IL-4Rα)	Omalizumab (anti-IgE)
Decreased biomarker after treatment	Blood Eosinophil, ECP, IL-5R α , periostin Nasal secretion IL-5R α , IL-6, IL-1 β , MPO, periostin	Blood Eosinophil	Blood TARC, periostin, total IgE, eotaxin-3 Nasal secretion ECP, total IgE, eotaxin-3, IL-5 NP tissue ECP, eotaxin-2, eotaxin-3, PARC, total IgE, IL-13	Blood Periostin
Potential predictive biomarker of efficacy	Blood eosinophil	Blood eosinophil	Not yet defined	Not yet defined

ECP, eosinophil cationic protein; Ig, immunoglobulin; IL, interleukin; MPO, myeloperoxidase; PARC, pulmonary and activation-regulated chemokine; TARC, thymus and activation-regulated chemokine.

decreased levels of ECP, eotaxin-2, eotaxin-3, pulmonary and activation-regulated chemokine, total IgE and IL-13 in nasal polyp tissues after 16-week treatment with dupilumab in a previous phase 2 trial [53²²]. However, blood eosinophil counts increased transiently followed by decreasing to below-baseline levels in patients with dupilumab treatment [6]. In addition, a post hoc analysis of SINUS-52 study by Fujieda *et al.* [54] showed that dupilumab efficacy was unaffected by baseline eosinophilic status in CRSwNP patients. Nevertheless, higher baseline levels of blood eosinophil ($\geq 0.15 \times 10^9/l$) and fractional exhaled nitric oxide (≥ 25 parts per billion) were found associated with greater benefits of dupilumab in asthmatic patients [55]. It will be very interesting to explore whether TARC, periostin, IgE and eotaxin-3 levels in serum and nasal secretions can serve as biomarkers for dupilumab efficacy in patients with CRS.

Omalizumab, a monoclonal anti-IgE antibody, prevents IgE from interacting with the receptor on the cell surface and inhibiting subsequent mast cell and basophil activation and degranulation by steric hindrance [56]. In 2020, two replicate phase 3 trials (POLYP 1 and POLYP 2) reported that omalizumab significantly improved nasal polyp scores and nasal congestion scores [5]. However, no analysis of biomarkers was reported in this study. A small sample size and multicentre retrospective study ($n=23$) demonstrated that baseline serum IgE levels and tissue eosinophils were not associated with treatment effects of omalizumab in patients with CRSwNP [57]. Similarly, a randomized, double-blind, placebo-controlled, small sample size study ($n=16$) of patients with nasal polyps and comorbid asthma showed that ECP, tryptase and total IgE levels in serum and nasal secretions were not influenced by omalizumab [58]. However, De Schryver *et al.* [59] reported that omalizumab reduced serum periostin

in patients with CRSwNP. In patients with asthma, Hanania *et al.* [60] found that patients with higher baseline fractional exhaled nitric oxide levels, blood eosinophil counts or serum periostin levels achieved greater benefits from omalizumab therapy. It is worth studying the potential role of baseline blood eosinophils and periostin in predicting omalizumab efficacy in patients with CRSwNP in future.

To date, limited studies have explored the biomarkers associating the efficiency of T2 biologics in patients with CRSwNP (Table 1). More clinical evidence is needed to crosslink the specific endotypes, clinically applicable markers and biologic treatments, in order to provide precise therapeutic strategies for patients with refractory CRSwNP.

CONCLUSION

Concomitant allergic rhinitis and asthma, prior sinus surgery, nasal polyps, severe smell decline and high Lund-Mackay scores of sinus CT indicate poor prognosis of CRS patients under conventional medical and surgical treatments. However, the subjective property of clinical feature evaluation impairs repeatability of clinical and demographic markers. Tissue biomarkers may directly reflect the inflammatory characteristics of CRS and high levels of eosinophils, neutrophils and IL-5 in sinonasal tissue have been associated with CRS poor outcome. Nevertheless, the invasive sampling process restricts its wide clinical application. Peripheral blood biomarkers can be easily acquired and standardized, but most of them lack good predictive performance. Fortunately, peripheral blood eosinophil level has been confirmed by several studies to have a strong correlation with CRS prognosis. Nasal secretions can be obtained noninvasively and high levels of CLC, cystatin SN, CCL17, MIP-1 β and IL-5 in nasal secretions are potential predictors of poor outcome.

However, sample collection process and cytokine detection in nasal secretions are not yet to be standardized. Although T2 biologics have shown significant benefits for refractory CRSwNP, the studies of biomarkers associated with treatment efficiency are still in infant stage. It should be noted that there are several limitations for those published biomarker studies, such as retrospective study design, small sample size, single-centre study and lacking internal or external validation. In addition, the follow-up time and definition of outcome are inconsistent, making it difficult to compare the results between different studies. Thus, further rigorous researches are required to establish prediction models with clinical accessible and reliable biomarkers for CRS.

Acknowledgements

None.

Financial support and sponsorship

This study was supported by grants from the National Natural Science Foundation of China (NSFC) 81920108011, 82130030 and 81630024 (Z.L.).

Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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