

Clinical & Experimental Allergy / Early View

REVIEW ARTICLE | [Full Access](#)

Revisiting Asian chronic rhinosinusitis in the era of type 2 biologics

Yin Yao, Ming Zeng , Zheng Liu 

First published: 01 December 2021

<https://doi-org.bibliosan.clas.cineca.it/10.1111/cea.14065>

Funding information:

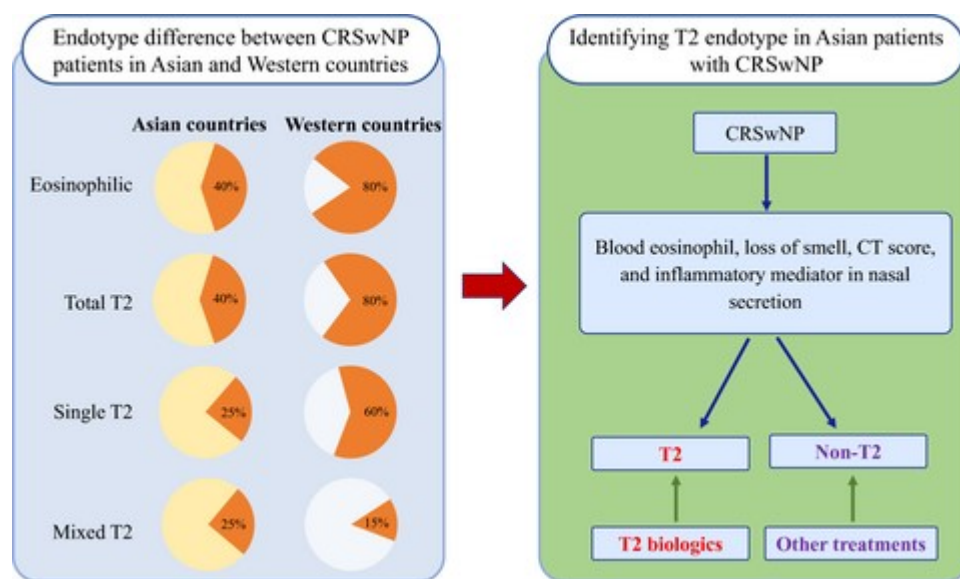
This study was supported by grants from the National Natural Science Foundation of China (NSFC) 81920108011 and 81630024 (Z.L.), 82071025 (M.Z.) and 82101198 (Y.Y.).

Abstract

Chronic rhinosinusitis (CRS) is a highly heterogeneous disorder exhibiting considerable epidemiological, clinical and immunopathological variations across patients with distinct ethnic backgrounds and in different geographic locations. Asian CRS patients present less eosinophilic and type 2 (T2) inflammation, but more prominent neutrophilic inflammation compared with patients in Western countries. Although several biologics targeting important elements of T2 inflammation, such as IL-4, IL-5, IL-13 and IgE, demonstrate promising benefit for Caucasian patients with recurrent nasal polyps, their efficacy in Asian patients remains poorly defined. The distinct endotypes in Asian patients warrant the identification and selection of patients who would benefit from T2 biologics in Asian countries. Additionally, developing novel treatments targeting neutrophilic, type 1, and type 3 inflammation may benefit approximately 50% of Asian CRS patients with non-T2 inflammation. In this review, we summarized and discussed recent progress in the study of Asian CRS endotypes in comparison with those in patients in Western countries, and the methods of identifying Asian patients with eosinophilic or T2 inflammation. T2 biologic treatment of Asian CRS patients, potential therapeutic candidates targeting non-T2 inflammation in Asian CRS patients and the progress on developing other T2 biologics were discussed.

Abstract

Patients with chronic rhinosinusitis (CRS) in Asian and Western countries demonstrate distinct endotypes. Asian patients with CRS with nasal polyps (CRSwNP) present less type 2 (T2) inflammation and more mixed inflammation compared with patients in Western countries. It is critical to identify and select patients who would benefit from T2 biologics in Asian countries.



Key Messages

Asian chronic rhinosinusitis (CRS) patients display less eosinophilic and type 2 (T2) inflammation, but more prominent neutrophilic inflammation compared with patients in Western countries.

Mixed feature of T2 inflammation in Asian CRS patients may influence the efficacy of T2 biologics in Asian population.

Given the lower prevalence of T2 inflammation in Asian CRS patients, it is critical to select patients by identifying T2 inflammation for T2 biologic treatment

1 INTRODUCTION

Chronic rhinosinusitis (CRS) is defined as the inflammation of the mucosa of the nose and paranasal sinuses over 12 weeks, occurring in 11%–12% of adults in Europe and the United States,¹ and approximately 8% of adults in China and Korea.^{2,3} CRS frequently presents with other inflammatory airway conditions such as asthma and allergic rhinitis (AR), and imposes huge global health and economic burdens.^{1,2} CRS is a highly heterogeneous disorder with diverse inflammatory profiles.^{4–6} Based on endoscopic examination finding, CRS is clinically subclassified into CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP).^{4,5} Studies in Caucasian patients have shown that CRSwNP is characterized by type 2 (T2) [high interleukin (IL)-4, IL-5, IL-13 and IgE expression] and eosinophilic inflammation,

whereas CRSsNP is primarily characterized by type 1 (T1) [high interferon (IFN)- γ expression] and type 3 (T3) (high IL-17A expression) inflammation.^{1, 4, 6} Conventional anti-inflammatory treatments of CRS include intranasal and systemic corticosteroids.^{1, 4} Endoscopic sinus surgery is considered when medical therapy fails.^{1, 4} However, it has been shown that approximately 20% of CRSsNP and 40% of CRSwNP patients relapse 1–2 years after surgery.^{7–9} Eosinophilic inflammation and T2 immune response have been identified as important risk factors for disease relapse in CRS patients,^{1, 4, 6, 10, 11} thus stimulating the study of T2 biologics in Caucasian patients with severe CRSwNP. Four multicentre and international phase 3 trials have demonstrated promising effect of omalizumab (anti-IgE), dupilumab (anti-IL-4R α), mepolizumab (anti-IL-5) and benralizumab (anti-IL-5R α) in reducing nasal polyp (NP) size and relieving symptoms in patients with refractory and severe CRSwNP.^{12–15}

However, the phase 3 trials were primarily conducted on CRS patients in Western countries. Moreover, CRS shows considerable epidemiological, clinical and immunopathological variations across patients with distinct ethnical backgrounds and geographic locations.^{8, 16, 17} Earlier studies showed that Asian CRS patients have less eosinophilic and T2 inflammation compared with Caucasian patients and that approximately half of Asian CRSwNP patients demonstrate noneosinophilic inflammation.^{8, 16–20} Recent studies indicate predominant neutrophilic and T1 and T3 inflammation in noneosinophilic CRSwNP Asian patients.^{8, 9, 21}

The efficacy of T2 biologics in treating Asian CRS patient may be limited by the different CRS endotypes among Asian patients. Therefore, this review aimed to examine the current research progress on CRS endotypes among Asian patients and the implications for the application of treatments with T2 biologics. Additionally, we provide a perspective on potential candidate treatments targeting non-T2 inflammation in Asian patients with CRS.

2 DISTINCT CHARACTERISTICS OF CRS IN ASIAN PATIENTS

2.1 Epidemiology and comorbidity

The exact prevalence of CRS is difficult to determine because of the need for objective confirmation of diagnosis. According to epidemiological studies primarily based on symptom questionnaire, CRS has been found to affect approximately 12% of individuals in the United States, and 11% in Europe (Figure 1).^{4, 22} In China, a prevalence of 8% was reported (Figure 1).² In two Korean nationwide surveys, the prevalence of CRS was 6.95% and 8.4%, as defined by symptoms and endoscopic findings.^{3, 23} Based on endoscopic results, the prevalence of CRSwNP was 2.5%–2.6% in Korea, 2.7% in Sweden, and 1.1% in China (Figure 1).¹⁹ Although the overall CRS prevalence in Asia, Europe and North America is similar, the prevalence of T2-related comorbidities in CRS patients differs substantially between Asian and Western countries (Figure 1).¹⁶ AR is one of the most common comorbidities in CRS patients in Western countries and affects approximately 75% of

CRSwNP patients.^{1, 4} However, the frequency of AR comorbidity is much lower in China, and only 10% of CRS patients and 13% of CRSwNP patients experience AR (Figure 1).^{2, 24} Notably, the overlap of symptoms between CRS and AR may cause the overdiagnosis of AR in patients with CRS, although AR was diagnosed based on positive skin prick test and nasal symptoms.⁴ Regarding asthma, the frequency of asthma comorbidity is only 7% in CRS patients and 9% in CRSwNP patients in China, whereas the frequency of asthma comorbidity could be over 50% in CRSwNP patients in Western countries (Figure 1).^{1, 2, 24, 25} Similarly, the frequency of nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) comorbidity is approximately 21% in CRSwNP patients in Western countries, in contrast to a very low frequency of 0.6% in patients in China (Figure 1).^{1, 4, 26} Nevertheless, it should be noted that there is a lack of extensive epidemiological studies regarding N-ERD prevalence in Chinese CRS patients, and N-ERD was diagnosed based on the history instead of oral challenge in most studies, which may cause the underdiagnosis of N-ERD in China.²⁷ Low frequencies of AR and asthma comorbidities are also found in Korean CRS patients, ranging from 4.5% to 22.4% and 1.6% to 5.6%, respectively.^{3, 28-30} However, the prevalence of AR and asthma comorbidity seems to be higher in Japan than that in China and Korea, which is approximately 35% and 17.8%–65%, respectively.^{31, 32}

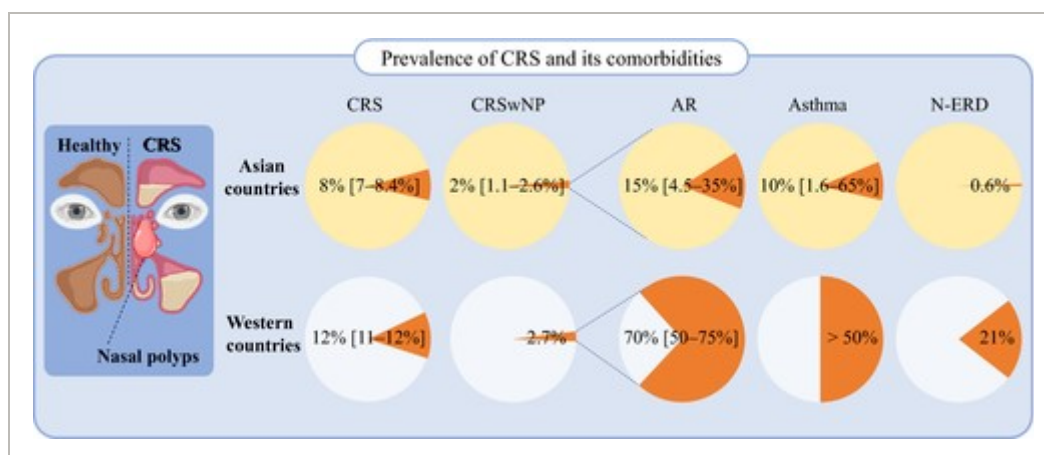


FIGURE 1

[Open in figure viewer](#) | [Download PowerPoint](#)

Schematic view of epidemiological difference between CRS patients in Asian and Western countries. Prevalence of CRS primarily based on symptom questionnaire. Prevalence of CRSwNP based on endoscopic results and its comorbidities including AR, asthma and N-ERD in Asian and Caucasian populations. The picture created with BioRender.com. Within the cakes, the prevalence reported by a single study, or a median value of the reported prevalence followed by the range of prevalence is shown. AR, allergic rhinitis; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; N-ERD, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease

2.2 Eosinophilic and neutrophilic inflammation

Eosinophilic inflammation has been considered as a major feature in Caucasian CRSwNP patients, with 80% of them having dominant eosinophilic inflammation (Figure 2). However,

eosinophilic inflammation can only be observed in 20%–60% of CRSwNP patients in Asian countries including China, Korea, Japan, Thailand and Malaysia (Figure 2), which is consistent with the low prevalence of AR, asthma and N-ERD comorbidity in Asian patients.^{19, 33, 34} In contrast, neutrophilic inflammation has been observed in a large percentage of Asian CRSwNP patients.^{19, 35, 36} Increased numbers of neutrophils have been found in Chinese patients with both eosinophilic and noneosinophilic CRSwNP in comparison with control subjects.^{37–39} Interestingly, noneosinophilic CRSwNP Chinese patients exhibited higher numbers of neutrophils than did eosinophilic CRSwNP patients, indicating a divergence between neutrophilic and eosinophilic inflammation in Chinese CRSwNP patients.^{37–39} Using cluster analysis, Liao et al.⁸ detected two distinct clusters characterized by T2 response and eosinophil-dominated endotype, and neutrophil-dominated endotype with high IL-8 levels. Consistently, studies in China and Korea have shown that only a small percentage of CRSwNP patients (4.4%–11.2%) exhibited both high eosinophilic and neutrophilic inflammation.^{39–41} In contrast, recent studies indicate a positive interaction between eosinophilic and neutrophilic inflammation in CRSwNP patients in Western countries.⁴² CRSwNP patients with markedly eosinophilic inflammation exhibit substantial levels of neutrophil infiltration.³⁶ High neutrophilic inflammation is associated with eosinophil extracellular trap cell death and Charcot-Leyden crystals (CLCs) in Caucasian CRSwNP patients.⁴² CLCs were found to facilitate neutrophil chemotaxis by promoting IL-8 production.⁴² The reasons for the distinct relationship between neutrophilic and eosinophilic inflammation in Caucasian and Asian patients are currently unclear. Whether the intensity of eosinophilic inflammation and CLC formation influences the relationship between neutrophilic and eosinophilic inflammation in CRSwNP in Western and Asian countries deserves further investigations.

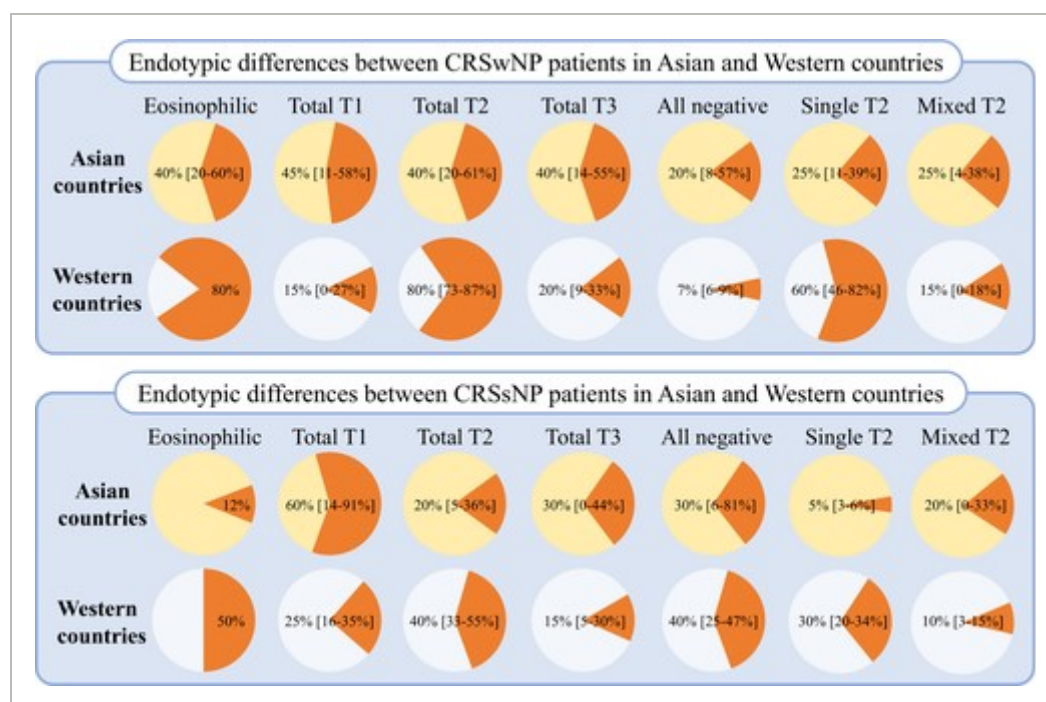


FIGURE 2[Open in figure viewer](#) | [PowerPoint](#)

Schematic view of endotype difference between CRSwNP and CRSsNP patients in Asian and Western countries. Within the cakes, the prevalence reported by a single study, or a median value of the reported prevalence followed by the range of prevalence is shown. CRSsNP, chronic rhinosinusitis without nasal polyps, CRSwNP, chronic rhinosinusitis with nasal polyps

Recently, Wang et al.³⁹ discovered the importance of IL-36 γ , a member of IL-1 family, in the regulation of neutrophilic inflammation in Chinese CRSwNP patients. They found that IL-36 γ production was markedly elevated in both eosinophilic and noneosinophilic CRSwNP patients than in control subjects. Neutrophils were identified as the principal IL-36R-positive cell type in NPs. Full-length IL-36 γ produced by nasal epithelial cells was cleaved and activated by neutrophil-derived elastase, which in turn promoted the production of chemokine (C-X-C motif) ligands: CXCL1, CXCL2 and CXCL8, by neutrophils in NPs.³⁹ Thus, there is a positive feedback loop between IL-36 γ and neutrophilic inflammation in CRSwNP patients. Neutrophils may disrupt NP epithelial barrier by producing oncostatin M, contribute to tissue fibrosis by transforming growth factor- β 2 and secrete various mediators to regulate inflammatory response.^{36, 43} Neutrophilia impairs response to glucocorticoid and surgical treatment in Asian CRSwNP patients,^{44, 45} and is associated with poor quality of life in Caucasian CRS patients.^{36, 46} Further comparison of the difference in neutrophilic inflammation between CRSwNP patients in Asian and Western countries will enhance the understanding of the role of neutrophils in the pathophysiology of CRSwNP. Additionally, eosinophilic inflammation has been markedly augmented over the last decade, not only in China⁴⁷ but also in other Asian countries, such as Korea and Thailand.^{33, 48, 49} Future studies should investigate whether this shift would change the relationship between neutrophilic and eosinophilic inflammation in Asian CRSwNP patients.

CRSsNP is primarily characterized by either T1 or T3 and neutrophilic inflammation.^{20, 50, 51} However, recent studies in the United States and Europe demonstrated that a considerable percentage of CRSsNP patients displayed T2 immune response.⁵²⁻⁵⁵ Delemarre et al.⁵² found that approximately 50% of CRSsNP patients exhibit eosinophilic and T2 inflammation (Figure 2), although the T2 inflammation in CRSsNP patients is usually less pronounced than that in CRSwNP patients. In contrast, there was no increase in neutrophil numbers in CRSsNP patients compared with that in control subjects. Those findings point out an underappreciated role of eosinophils in Caucasian CRSsNP patients. In Chinese CRSsNP patients, less eosinophilic inflammation was observed, with only 12% of patients exhibiting eosinophilic inflammation (Figure 2), which was associated with the atopic status.⁵⁶ Additionally, the number of neutrophils was considerably higher in CRSsNP patients than in CRSwNP patients and control subjects in Chinese.³⁹

3 T1, T2 AND T3 INFLAMMATION IN CRS

Defining the CRS endotypes based on T1, T2 and T3 inflammation is critical in selecting suitable biologics for CRS treatment. Eosinophilic inflammation is commonly associated with T2 response. Consistent with eosinophilic inflammation, 73%–87% of CRSwNP patients in Western countries, including America, Europe and Australia, exhibit T2 signature, whereas the percentage ranges from 20% to 61% in Asian countries, including China, Korea and Japan (Figure 2 and Table 1).^{16, 39, 53, 54, 57} Another important difference between Asian and Caucasian patients is that most of T2 response in CRSwNP in Western countries is single T2 (46%–82%), while in Asian countries, most of T2 response is mixed with T1 and T3 response (Figure 2 and Table 1).^{16, 17, 39, 53, 54, 57} Regarding CRSsNP, 33%–55% and 5%–36% of patients exhibit T2 response in Western and Asian countries, respectively (Figure 2 and Table 1).^{16, 39, 53, 54, 57} Again, T2 inflammation in Asian CRSsNP patients is more likely mixed with T1 and T3 inflammation (Figure 2 and Table 1). The mixed feature of T2 inflammation in Asian CRS patients may influence the efficacy of T2 biologics in Asian population.

TABLE 1. Summary of endotypes of CRSwNP and CRSsNP patients in Asian and Western countries

	City (country)	Sample size	Markers for classification	Single T1 (%)	Single T2 (%)	Single T3 (%)	T1/T2 (%)	T1/T3 (%)	T2/T3 (%)	T1/T (%)
CRSwNP	Benelux (Europe)	45	T1 (IFN- γ protein); T2 (IL-5 protein); T3 (IL-17A protein)	4	62	2	16	2	5	2
	Berlin (Germany)	11	Same as above	0	82	9	0	0	0	0
	Adelaide (Australia)	33	Same as above	3	46	12	12	6	9	6
	Chicago (America)	134	T1 (IFN- γ mRNA and protein); T2 (CLC mRNA and ECP protein); T3 (IL-17A mRNA and protein)	1	62	2	10	1	10	5

Abbreviations: CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

In contrast to consistent findings in T2 inflammation, more diverse results have been reported for T1 and T3 inflammation. Studies in Europe indicate T1 inflammation in CRSsNP patients.^{35, 58} However, studies on Americans in Chicago failed to replicate the up-regulation of IFN- γ in CRSsNP patients.⁵⁵ Compared with Caucasian patients, Chinese CRSwNP and CRSsNP patients had higher IFN- γ and IL-17A levels.^{18, 39, 56} Approximately 0%–27% and 9%–33% CRSwNP patients in Western countries exhibit T1 and T3 inflammation, respectively, whereas 11%–58% and 14%–55% of patients in Asian countries exhibit T1 and T3 inflammation, respectively (Figure 2 and Table 1).^{16, 39, 53, 54, 57} Similarly, 16%–35% and 5%–30% of CRSsNP patients in Western countries, and 14%–91% and 0%–44% CRSsNP patients in China exhibit T1 and T3 inflammation, respectively (Figure 2 and Table 1).^{16, 39, 52–54, 56, 57} Thus, the frequencies of T1 and T3 inflammation are higher in Asian CRS patients than in Caucasian patients (Table 1). Both in Western and in Asian countries, most T1 inflammation and T3 inflammation are in combination with other T inflammation.^{16, 39, 53, 54, 57} Although T3 inflammation is traditionally considered a major driver of neutrophilia in several pathological conditions, this is not observed in CRS. Delemarre et al.⁴² found that neutrophil infiltration in CRSwNP patients was independent of IL-17. In the cluster analysis study of Liao, cluster 3 was characterized by predominant neutrophilic inflammation; however, there was only modest elevation of IL-17A in this cluster.⁸ Our unpublished data show a weak correlation between IL-17A and neutrophil levels in Chinese CRSwNP patients ($r = 0.149$, $n = 249$). Therefore, targeting T3 inflammation may have limited effect in regulating CRS-induced neutrophilia in both Asian and Caucasian patients. Moreover, T1, T2 and T3 inflammatory responses may not be present in some CRS patients in both Asian and Western countries (Figure 2 and Table 1).^{8, 16, 39, 53, 54, 57} Thus, such patients may not benefit from biologics targeting T1, T2 or T3 inflammation.

4 CLUSTER ANALYSIS OF CHRONIC RHINOSINUSITIS

Cluster analysis is a hypothesis-free and unsupervised statistical method that allows the grouping of several related variables into clusters without compromising information. Tomassen et al.¹⁷ performed a cluster analysis of biomarkers in nasal tissues from CRS patients in Europe, and detected 10 clusters, among which patients in four clusters had low or undetectable IL-5, eosinophil cationic protein, IgE and albumin concentrations, whereas those in six clusters had high concentrations of these markers. The IL-5⁺ clusters were further divided into a group of three clusters with moderate IL-5 concentrations and another three clusters with high IL-5 levels that were composed almost exclusively of CRSwNP patients.¹⁷ The three cluster with high T2 inflammation showed a markedly increased presence of neutrophil marker proteins, suggesting both eosinophilic and neutrophilic inflammation in CRSwNP patients with high T2 inflammation.¹⁷ Lou et al.⁵⁹ performed cluster analysis of Chinese CRSwNP patients based on the type of inflammatory cells, and

identified five clusters, with cluster 4 having predominant infiltration of neutrophils and cluster 5 exhibiting markedly eosinophilia.⁵⁹ They did not observe coexistence of neutrophilic and eosinophilic inflammation in Chinese patients.^{59, 60} By including 28 clinical parameters and 39 cellular and molecular parameters in cluster analysis, Liao et al.⁸ subclassified Chinese CRS patients into seven clusters with distinct biologic and clinical characteristics and treatment outcomes. As discussed above, they found two separated clusters characterized by markedly eosinophilic and neutrophilic inflammation. Cluster 1 was comparable to the classic well-defined eosinophilic CRSwNP in Western countries with the highest T2 levels and the highest prevalence of comorbid asthma (50%).⁸ Cluster 1 had low levels of neutrophils and IL-8. In contrast, cluster 3 was characterized by the highest levels of neutrophils and IL-8 without elevation of T2 cytokine and eosinophil levels.⁸ These two cluster studies on Chinese patients further indicate a divergence between neutrophilic and eosinophilic inflammation in Chinese CRS patients. In the study by Liao, cluster 3 had a high proportion of difficult-to-treat cases (44.44%) comparable with that in cluster 1 (50%), suggesting that both severe eosinophilic and neutrophilic inflammation can lead to poorly controlled disease in CRS patients.⁸ The cluster studies in Western and Asian countries underscore the challenge of regulating neutrophilic inflammation in CRS.

5 CONVENTIONAL MEDICAL TREATMENT, SURGERY AND UNMET NEEDS IN ASIAN CRS PATIENTS

High T2 inflammation is generally responsive to glucocorticoids. Intranasal glucocorticoids, in combination with systemic glucocorticoids for severe cases, are recommended by European, American and Asian guidelines for the treatment of CRS.^{4, 22, 24, 61} However, previous randomized controlled trials (RCTs) of glucocorticoid treatment for CRS were mostly performed on Caucasians. In an uncontrolled study using a small sample size, Wen et al.⁴⁴ found that short-term oral prednisone treatment was able to suppress eosinophilic inflammation and T2 and T1 response, but not neutrophilic inflammation and T3 response. Chinese CRSwNP patients with neutrophilic inflammation were less responsive to oral glucocorticoid treatment. In another study, Wu et al.⁶² found that only half of Chinese CRSwNP patients responded positively to oral glucocorticoid treatment, coinciding with the prevalence of eosinophilic inflammation in Chinese CRSwNP patients. Additionally, it was observed that high mucosal eosinophil percentage and CLC levels in nasal secretions were associated with positive response to oral glucocorticoids.⁶² The efficacy of long-term low-dose macrolides for CRS treatment remains controversial. Two RCTs conducted in Europe reported no substantial benefit of macrolides for CRS patients^{63, 64}; however, these studies did not consider the different clinical and pathological types of CRS. Several studies indicate that macrolides might be effective for CRS patients without elevated serum IgE levels or with high local IL-8 levels.⁶⁵ Therefore, macrolides are likely suitable for CRS patients with high neutrophilic inflammation. However, currently, there is a lack of high-quality evidence to support the use of glucocorticoids and macrolides treating CRS with different endotypes. As glucocorticoids and macrolides are still the most accessible treatments in the clinical setting,

it is necessary to conduct high-quality RCTs to compare their efficacy in treating CRS with different endotypes, particularly for Asian patients with more heterogeneous features. Recently, Zeng et al. subclassified Chinese CRS patients into CRSsNP, eosinophilic CRSwNP and noneosinophilic CRSwNP group, and compared the efficacy of post-operative nasal glucocorticoid and oral macrolide treatment in every group.^{9, 66} The findings of the study showed that there was no considerable difference in the efficacy of nasal glucocorticoid and oral macrolide.⁹ However, in a post hoc study, Zeng et al.⁶⁶ found that CRS patients with high tissue IL-8 and IgG4 levels were less likely to respond to nasal glucocorticoid and oral macrolide therapy, respectively. These data suggest that tissue eosinophilia and the presence of NPs may not be enough to conclude on the efficacy of post-operative glucocorticoid and macrolide treatments. Overall, it is critical and challenging to obtain optimal markers for endotype-guided treatment for CRS patients.

Surgery is used to treat CRS patients who are unresponsive to medical treatments.^{4, 67, 68} Surgical procedures for CRS can range from limited (functional) to extensive (radical or reboot) types. Jonstam et al.⁶⁸ showed that inflammation was not limited to NPs themselves but was equally present in the nonpolypoid tissues in Caucasian patients with CRSwNP. More extensive surgery involving sinus mucosa removal reduced relapse rates in Caucasian CRSwNP patients compared with conventional mucosa-sparing surgery.⁶⁸ As approximately half of Asian CRSwNP patients also experience eosinophilic and T2 inflammation, extensive surgical procedures will have to be adapted to Asian patients with refractory eosinophilic CRSwNP. Chen et al.⁶⁹ found that extensive sinus surgery (middle turbinate and superior turbinate resection and total ethmoidectomy) was more effective in improving olfactory function and endoscopic appearance than functional surgery in Chinese patients with concomitant CRSwNP and asthma, a T2-related phenotype. In addition to T2 and eosinophilic inflammation, neutrophilic inflammation is also associated with poor disease control after surgery in Asian CRSwNP patients. Whether extensive surgery is also suitable for refractory Asian CRSwNP patients with high neutrophilic inflammation requires further investigations.

6 T2 BIOLOGICS FOR ASIAN CRSwNP PATIENTS AND PATIENT SELECTION

6.1 Current evidence regarding T2 biologics in Asian CRSwNP patients

Recently, phase 3 trials of biologics, including omalizumab (anti-IgE), dupilumab (anti-IL-4R α), mepolizumab (anti-IL-5), and benralizumab (anti-IL-5R α), were performed on CRSwNP patients in primarily Western countries, and a limited number of patients from Japan and Korea participated in SINUS-52 dupilumab study and SYNAPSE mepolizumab study, respectively.^{12-15, 70, 71} As eosinophilic and T2 inflammation are the predominant features in and are associated with relapse in majority of CRSwNP patients in Western countries, the

presence of eosinophilic or T2 inflammation was not considered in selecting patients for the studies. However, considering the lower prevalence of eosinophilic and T2 inflammation in Asian CRS patients, it is critical to consider the presence of eosinophilic and T2 inflammation in selecting patients for T2 biologics treatments. In a post hoc analysis of Japanese patients enrolled in the SINUS-52 study, Fujieda et al.⁷² reported substantial effects of dupilumab in reducing NP size and nasal congestion. However, the sample size of Japanese patients was limited and more than 80% of those Japanese CRSwNP patients exhibited eosinophilic inflammation according to the algorithm of the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis Study (JESREC).⁷² Therefore, the results cannot be extrapolated to the general Asian population. Recently, Takabayashi et al.⁷³ conducted a phase 2 study on the effects of benralizumab, a humanized anti-IL-5R α monoclonal antibody, on Japanese patients with eosinophilic chronic rhinosinusitis,⁷³ and found 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. This finding further reinforces the endotype dependence of T2 biologics in Asian patients. However, even with proper selection of Asian CRSwNP patients with eosinophilic and T2 inflammation, the Asian patients might exhibit different response to T2 biologics when compared to Caucasian patients because of the combined presence of T2 with T1 and T3 inflammatory responses in Asian patients. Therefore, it is important to conduct RCTs to clarify the exact effect of T2 biologics in Asian CRSwNP patients exhibiting eosinophilia and T2 inflammation.

Epithelial cell–derived alarmins such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) play a critical role in the pathogenesis of CRS by activating innate immune cells.⁷⁴ Biologics targeting IL-25, IL-33 and TSLP are potential options for the treatment of severe CRSwNP. Notably, tezepelumab, an anti-TSLP monoclonal antibody, is currently under phase 3 trial (WAYPOINT) for treating severe CRSwNP, and several Asian centres are engaged in this trial (ClinicalTrials: NCT04851964). Etokimab, an IL-33 inhibitor, is currently under phase 2 trial for patients with CRSwNP (ClinicalTrials: NCT03614923); however, a recent press release reported that etokimab failed to achieve statistically significant improvement in bilateral NP scores and sinonasal outcome test 22 scores versus placebo at the week 8 time point.⁷⁴

Although the percentage of recurrence in CRSsNP patients is remarkably lower than that described in CRSwNP patients, approximately 12.9% of CRSsNP patients may recur within 12 years, and CRSsNP patients with T2 inflammation have higher recurrence rates.⁵² Thus, T2 biologics may be considered for treating CRSsNP patients with severe T2 inflammation; however, this is subject to further research.

6.2 Identifying eosinophilic and T2 inflammation in Asian CRS patients

The direct way to define CRS endotypes is by analysing the inflammatory patterns of mucosal samples; however, this is not always feasible in clinical practice. Thus, clinical

symptoms and noninvasive biomarkers have been used to identify T2 and eosinophilic endotype in Asian CRS patients. Sakuma et al.⁷⁵ reported that a combination of increased blood eosinophil percentage and olfactory cleft and posterior ethmoid computerized tomography (CT) score achieved high diagnostic ability (sensitivity, 84.6%; specificity, 92.3%) for eosinophilic CRSwNP in Japanese patients (Table 2). Furthermore, Tokunaga et al.³¹ developed JESREC scoring system to diagnose eosinophilic CRS based on a study of 1716 Japanese patients. JESREC scoring system assesses unilateral or bilateral disease, the presence of NPs, blood eosinophilia and dominant shadow of ethmoid sinuses in CT scans, which are given weighted scores. The cut-off score ≥ 11 achieved a sensitivity of 83% and a specificity of 66% (Table 2). JESREC has been widely adopted in Japanese studies. In Chinese patients, Hu et al. found that the peripheral blood eosinophil abundance correlated with tissue eosinophilia, and blood eosinophil absolute count ($\geq 0.215 \times 10^9/L$) and percentage ($\geq 3.05\%$) could be used to diagnose eosinophilic CRSwNP in Chinese adults, both demonstrating an area under the curve (AUC) value of a receiver operating characteristic curve >0.8 (Table 2).⁷⁶ Similarly, Meng et al.⁷⁷ found that eosinophilic CRSwNP had a more severe ethmoid but less maxillary involvement in CT scanning, and an optimal cut-off value of ethmoid sinus/maxillary sinus CT score ratio >2.59 yielded a sensitivity of 94% and a specificity of 90% for the diagnosis of eosinophilic CRSwNP in Chinese patients (AUC = 0.94; Table 2). Xu et al.⁷⁸ discovered that the combination of olfaction symptom score and blood eosinophil percentage might be used to differentiate between eosinophilic and noneosinophilic CRSwNP in Chinese patients but with a low accuracy (AUC = 0.78; Table 2).

TABLE 2. Identifying eosinophilic inflammation in Asian CRS patients

Marker	Population and Sample size	Definition for tissue eosinophilia	Study strategy or method	Finding	Ref.
Blood eosinophil and CT score	124 Japanese CRSwNP patients (66 eosinophilic and 89 noneosinophilic)	Unknown	Single-centre prospective study; Analysed by logistic regression.	AUC = 0.88 for blood eosinophil percentage; The combination of blood eosinophil percentage $\geq 6\%$, olfactory cleft CT score ≥ 1 and posterior ethmoid CT score ≥ 1 had 84.6% of sensitivity and 92.3% of specificity to diagnose eosinophilic CRSwNP.	75
Blood eosinophil	1716 Japanese patients with CRS (672	≥ 70 eosinophils/HPF	Multicentre retrospective	AUC = 0.794 for JESREC score (weight of bilateral	31

Marker	Population and Sample size	Definition for tissue eosinophilia	Study strategy or method	Finding	Ref.
and CT score	eosinophilic and 1044 noneosinophilic)		study; Analysed by logistic	disease sites, nasal polyps, CT findings and blood eosinophil	

Abbreviations: AUC, area under the receiver operating characteristic curve; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computerized tomography; E/M: ethmoid sinus/maxillary sinus; HPF, high-power field; JESREC, Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis; NO, nitric oxide; VAS, visual analogue scale.

Nasal lavage fluids contain inflammatory mediators secreted by structural and inflammatory cells in diseased sinonasal mucosa, which may reflect inflammatory patterns in the mucosa of CRS patients.⁷⁹⁻⁸¹ Wu et al.⁶² found that CLC concentrations in nasal secretions correlated with eosinophil percentage in NPs, and were able to predict clinical response to glucocorticoid treatment in Chinese CRSwNP patients (AUC = 0.90). Nasal nitric oxide, a noninvasive biologic biomarker, is routinely used in the diagnosis and treatment of allergic airway diseases, including asthma.⁸² Zhu et al.⁸³ reported that nasal nitric oxide had high predictive value for the diagnosis of eosinophilic CRSwNP (AUC = 0.94; sensitivity: 76.74%; specificity: 96.67%; Table 2). However, it should be noted that most published studies on methods of identifying eosinophilic endotype in CRSwNP patients were poorly designed, lacking internal or external validation. Additionally, the definition for tissue eosinophilia was inconsistent in these studies (Table 2). In JESREC study, the cut-off value for eosinophilic inflammation was ≥70/high-power field,³¹ whereas, in Chinese studies, the cut-off was >10% eosinophils.¹⁸

Moreover, although T2 response is consistently associated with eosinophilic inflammation, eosinophilia and T2 response are not completely parallel in CRS patients.⁸⁴ For example, Caucasian patients with N-ERD have increased eosinophilia compared to patients with CRSwNP only, but no associated increase in T2 mediators.⁸⁴ The levels of IL-4, IL-5, IL-13 and IgE are not completely correlated with each other either. Thus, it is important to identify the unique biomarkers for each T2 biologic; however, research in this regard is still in its infancy. A post hoc analysis data obtained in SINUS-52 dupilumab study by Fujieda et al.⁷² showed that dupilumab significantly improved symptoms of severe CRSwNP patients irrespective of eosinophilic status based on JESREC classification. However, the results of SYNAPSE mepolizumab study showed that the efficacy of mepolizumab was higher in CRSwNP patients with higher baseline blood eosinophil count.¹⁴ In addition, an enhanced response to benralizumab was observed in CRSwNP patients with comorbid asthma or higher baseline levels of blood eosinophils,¹⁵ suggesting varied biomarkers for different biologics. Therefore, more clinical evidence is needed to cross-link the specific endotypes, clinically

applicable markers and biologic treatments, in order to provide precise therapeutic strategies for treating Asian CRS patients.

7 POTENTIAL TARGETS FOR NON-T2 RESPONSE OR DIFFERENT T RESPONSES SIMULTANEOUSLY

T1 and T3 responses are observed in half of Asian CRS patients. In Asian CRSwNP patients, elevated IL-17A expression has been reported to be associated with disease severity, steroid resistance and acute exacerbation.^{39, 85, 86} In contrast, IL-17A was only up-regulated in Caucasian patients with cystic fibrosis-related CRSwNP, but not in those without cystic fibrosis.^{1, 87} Several biologics targeting IL-17A, such as secukinumab and ixekizumab, have been approved for patients with plaque psoriasis, psoriatic arthritis or ankylosing spondylitis.⁸⁸⁻⁹⁰ Thus, the involvement of T3 response in some subtypes of Asian CRS suggests the potential applicability of anti-IL-17A biologics in the treatment of CRS in those patients. However, the weak link between IL-17A and neutrophilia limits their application in the treatment of neutrophilic CRSwNP patients. Elevated concentrations of IL-6 have been reported in the tissues of CRSwNP and CRSsNP patients.^{84, 91-93} A decrease in neutrophils is observed during treatment with anti-IL-6R (tocilizumab and sarilumab) in patients with rheumatoid arthritis.⁹⁴ It is interesting to evaluate the efficacy of anti-IL-6/IL-6R biologics in the treatment of noneosinophilic CRS in Asian patients, which are characterized by prominent neutrophilic inflammation.

Accumulating evidence indicates an important role of dysregulation of the coagulation and fibrinolytic cascade in oedema formation in Caucasian and Asian CRSwNP patients.⁹⁵ Down-regulation of tissue plasminogen activator (tPA), the central enzyme in the degradation of fibrin, and increased deposition of fibrin have been demonstrated in NPs irrespective of inflammatory endotypes.^{57, 96} Both T1 and T2 cytokines can suppress tPA expression in nasal epithelial cells.^{57, 96} These data suggest that dysregulation of the coagulation and fibrinolytic cascade might be a common downstream pathway involved in different inflammatory endotypes in NPs. Takabayashi et al.⁹⁷ reported that nattokinase, a serine protease possessing strong fibrinolytic activity, effectively shrunk NP tissue in vitro through fibrin degradation.

The Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway plays a key role in immune modulation.^{98, 99} T1, T2 and T3 cytokine receptors employ the JAK-STAT pathway to exert their effect, leading to the polarization and proliferation of T-helper cells.⁹⁸ The activated JAK-STAT cascade has been noted in CRSwNP patients.^{100, 101} A number of JAK inhibitors have been developed recently, among which tofacitinib (targeting JAK1 and JAK3) was the first to be approved by the U.S. Food and Drug Administration (FDA) for treating rheumatoid arthritis.^{102, 103} Recently, baricitinib, an orally administered JAK1 and JAK2 inhibitor, has proven to be efficacious in patients with moderate-to-severe atopic dermatitis.^{104, 105} Additionally, ruxolitinib, a topical JAK1 and JAK2 inhibitor, has been shown

effective in treating atopic dermatitis in a completed Phase 3 trial (ClinicalTrials: NCT03745638), and has been approved for the treatment of atopic dermatitis by FDA in 2021.¹⁰⁶ Small-molecule therapies offer an important alternative to biologics for the treatment of inflammatory diseases,¹⁰² which show advantage on oral or topical delivery. JAK inhibitors are good candidate therapies for treating immune imbalance associated with CRS.

8 CONCLUSIONS AND PERSPECTIVES

The advent of biologics for the treatment of severe T2 CRSwNP creates new options for the treatment of patients with severe inflammatory responses. However, CRS is a heterogeneous illness, and immune responses in CRS can vary across different geographic locations and ethnical backgrounds. Biologics are likely to have different efficacies in different patient populations depending on the inflammatory endotypes of CRS. Currently, only biologics targeting T2 pathway have been developed for the treatment of severe CRSwNP. A number of CRS patients, particularly those in Asian countries, display T1-, T3- or neutrophil-dominated endotype; however, researchers are yet to develop biologics targeting T1, T3 or neutrophilic inflammation.

Several key questions remain to be answered. A shift towards T2 inflammation has been observed in CRS patients in both Asian and Western countries.^{47, 107} Whether this shift affects the efficacy of biologics, and whether biologics can be used in treating CRSsNP patients remains unknown. Moreover, studies on the development of clinically applicable markers for distinct endotypes and biologics are still preliminary. Additionally, the efficacy of biologics in treating Asian CRS patients exhibiting combined T1, T2 and T3 inflammatory response requires further studies. Finally, the current recommendations for the use of T2 biologics in CRS treatment are based on RCTs and are yet to be confirmed in real-world studies.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors participated in drafting and writing the manuscript and approved the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

REFERENCES



1 Bachert C, Marple B, Schlosser RJ, et al. Adult chronic rhinosinusitis. *Nat Rev Dis Primers*. 2020; **6**(1): 1- 19.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

2 Shi JB, Fu QL, Zhang H, et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. *Allergy*. 2015; **70**(5): 533- 539.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

3 Ahn JC, Kim JW, Lee CH, Rhee CS. Prevalence and risk factors of chronic rhinosinusitis, allergic rhinitis, and nasal septal deviation: results of the Korean national health and nutrition survey 2008–2012. *JAMA Otolaryngol Head Neck Surg*. 2016; **142**(2): 162- 167.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

4 Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020; **58**(Suppl S29): 1- 464.

[Google Scholar](#)

5 Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. *Int Forum Allergy Rhinol*. 2016; **6**(Suppl 1): S22- S209.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

6 Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. *Annu Rev Pathol*. 2017; **12**: 331- 357.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

7 DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope*. 2017; **127**(3): 550- 555.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

8 Liao B, Liu JX, Li ZY, et al. Multidimensional endotypes of chronic rhinosinusitis and their association with treatment outcomes. *Allergy*. 2018; **73**(7): 1459- 1469.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

9 Zeng M, Wang H, Liao B, et al. Comparison of efficacy of fluticasone propionate versus clarithromycin for postoperative treatment of different phenotypic chronic rhinosinusitis: a randomized controlled trial. *Rhinology*. 2019; **57**(2): 101- 109.

[CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

10 Alsharif S, Jonstam K, van Zele T, Gevaert P, Holtappels G, Bachert C. Endoscopic sinus surgery for type-2 CRSwNP: an endotype-based retrospective study. *Laryngoscope*. 2019; **129**(6): 1286- 1292.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

11 Jonstam K, Swanson BN, Mannent LP, et al. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. *Allergy*. 2019; **74**(4): 743- 752.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

12 Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019; **394**(10209): 1638- 1650.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

13 Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. 2020; **146**(3): 595- 605.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

14 Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021; **9**(10): 1141- 1153.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Google Scholar](#)

15 Bachert C, Han JK, Desrosiers MY, et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2021;S0091-6749(21)01459-7. Online ahead of print.

[Crossref](#) | [Google Scholar](#)

16 Wang X, Zhang N, Bo M, et al. Diversity of TH cytokine profiles in patients with chronic rhinosinusitis: a multicenter study in Europe, Asia, and Oceania. *J Allergy Clin Immunol*. 2016; **138**(5): 1344- 1353.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

17 Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol*. 2016; **137**(5): 1449- 1456. e4.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

18 Cao PP, Li HB, Wang BF, et al. Distinct immunopathologic characteristics of various types of chronic rhinosinusitis in adult Chinese. *J Allergy Clin Immunol*. 2009; **124**(3): 478- 484.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

19 Zhang Y, Gevaert E, Lou H, et al. Chronic rhinosinusitis in Asia. *J Allergy Clin Immunol*. 2017; **140**(5): 1230- 1239.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

20 Van Zele T, Claeys S, Gevaert P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. *Allergy*. 2006; **61**(11): 1280- 1289.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

21 Cao PP, Wang ZC, Schleimer RP, Liu Z. Pathophysiologic mechanisms of chronic rhinosinusitis and their roles in emerging disease endotypes. *Ann Allergy Asthma Immunol*. 2019; **122**(1): 33- 40.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

22 Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol*. 2021; **11**(3): 213- 739.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

23 We J, Lee WH, Tan KL, et al. Prevalence of nasal polyps and its risk factors: Korean national health and nutrition examination survey 2009–2011. *Am J Rhinol Allergy*. 2015; **29**(1): e24- e28.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

24 Liu Z, Chen J, Cheng L, et al. Chinese Society of Allergy and Chinese Society of Otorhinolaryngology-Head and Neck Surgery guideline for chronic rhinosinusitis. *Allergy Asthma Immunol Res*. 2020; **12**(2): 176- 237.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

25 Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic rhinosinusitis with nasal polyps and asthma. *J Allergy Clin Immunol Pract*. 2021; **9**(3): 1133- 1141.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

26 Fan Y, Feng S, Xia W, et al. Aspirin-exacerbated respiratory disease in China: a cohort investigation and literature review. *Am J Rhinol Allergy*. 2012; **26**(1): e20- e22.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

27 Wang ZC, Yao Y, Chen CL, et al. Extrafollicular PD-1(high)CXCR5(-)CD4(+) T cells participate in local immunoglobulin production in nasal polyps. *J Allergy Clin Immunol*. 2021;S0091-6749(21)01050-2. Online ahead of print..

[Crossref](#) | [Google Scholar](#)

28 Kim JH, Cho C, Lee EJ, Suh YS, Choi BI, Kim KS. Prevalence and risk factors of chronic rhinosinusitis in South Korea according to diagnostic criteria. *Rhinology*. 2016; **54**(4): 329- 335.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

29 Kim JW, Jung HJ, Choi HG, Rhee C-S, Wee JH. Association between sleep duration and chronic

rhinosinusitis among the Korean general adult population: Korea national health and nutrition examination survey. *Sci Rep*. 2019; **9**(1): 1- 6.

[PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

30 Kim DH, Han K, Kim SW. Effect of chronic rhinosinusitis with or without nasal polyp on quality of life in South Korea: 5th Korea national health and nutrition examination survey Korean. *Clin Exp Otorhinolaryngol*. 2016; **9**(2): 150- 156.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

31 Tokunaga T, Sakashita M, Haruna T, et al. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study. *Allergy*. 2015; **70**(8): 995- 1003.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

32 Hakansson K, Thomsen SF, Konge L, Mortensen J, Backer V, von Buchwald C. A comparative and descriptive study of asthma in chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy*. 2014; **28**(5): 383- 387.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

33 Katotomichelakis M, Tantilipikorn P, Holtappels G, et al. Inflammatory patterns in upper airway disease in the same geographical area may change over time. *Am J Rhinol Allergy*. 2013; **27**(5): 354- 360.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

34 Fujieda S, Imoto Y, Kato Y, et al. Eosinophilic chronic rhinosinusitis. *Allergol Int*. 2019; **68**(4): 403- 412.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

35 Van Crombruggen K, Zhang N, Gevaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: inflammation. *J Allergy Clin Immunol*. 2011; **128**(4): 728- 732.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

36 Delemarre T, Bochner BS, Simon HU, Bachert C. Rethinking neutrophils and eosinophils in chronic rhinosinusitis. *J Allergy Clin Immunol*. 2021; **148**(2): 327- 335.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

37 Ma J, Shi LL, Deng YK, et al. CD8(+) T cells with distinct cytokine-producing features and low cytotoxic activity in eosinophilic and non-eosinophilic chronic rhinosinusitis with nasal polyps. *Clin Exp Allergy*. 2016; **46**(9): 1162- 1175.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

38 Shi LL, Xiong P, Zhang L, et al. Features of airway remodeling in different types of Chinese chronic rhinosinusitis are associated with inflammation patterns. *Allergy*. 2013; **68**(1): 101- 109.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

39 Wang H, Li ZY, Jiang WX, et al. The activation and function of IL-36γ in neutrophilic

inflammation in chronic rhinosinusitis. *J Allergy Clin Immunol*. 2018; **141**(5): 1646- 1658.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

40 Pan L, Liao B, Guo CL, et al. Inflammatory features and predictors for postsurgical outcomes in patients with nasal polyps stratified by local and systemic eosinophilia. *Int Forum Allergy Rhinol*. 2021; **11**(5): 846- 856.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

41 Kim DK, Kim JY, Han YE, et al. Elastase-positive neutrophils are associated with refractoriness of chronic rhinosinusitis with nasal polyps in an Asian population. *Allergy Asthma Immunol Res*. 2020; **12**(1): 42- 55.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

42 Delemarre T, Holtappels G, De Ruyck N, et al. A substantial neutrophilic inflammation as regular part of severe type 2 chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2021; **147**(1): 179- 188.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

43 Arebro J, Drakskog C, Winqvist O, et al. Subsetting reveals CD16(high) CD62L(dim) neutrophils in chronic rhinosinusitis with nasal polyps. *Allergy*. 2019; **74**(12): 2499- 2501.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

44 Wen W, Liu W, Zhang L, et al. Increased neutrophilia in nasal polyps reduces the response to oral corticosteroid therapy. *J Allergy Clin Immunol*. 2012; **129**(6): 1522- 1528.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

45 Kim DK, Lim HS, Eun KM, et al. Subepithelial neutrophil infiltration as a predictor of the surgical outcome of chronic rhinosinusitis with nasal polyps. *Rhinology*. 2021; **59**(2): 173- 180.

[PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

46 Wang H, Pan L, Liu Z. Neutrophils as a protagonist and target in chronic rhinosinusitis. *Clin Exp Otorhinolaryngol*. 2019; **12**(4): 337- 347.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

47 Jiang WX, Cao PP, Li ZY, et al. A retrospective study of changes of histopathology of nasal polyps in adult Chinese in central China. *Rhinology*. 2019; **57**(4): 261- 267.

[PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

48 Shin SH, Ye MK, Kim JK, Cho CH. Histological characteristics of chronic rhinosinusitis with nasal polyps: recent 10-year experience of a single center in Daegu. *Korea. Am J Rhinol Allergy*. 2014; **28**(2): 95- 98.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

49 Kim SJ, Lee KH, Kim SW, Cho JS, Park YK, Shin SY. Changes in histological features of nasal polyps in a Korean population over a 17-year period. *Otolaryngol Head Neck Surg*. 2013; **149**(3):

431- 437.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

50 De Greve G, Hellings PW, Fokkens WJ, Pugin B, Steelant B, Seys SF. Endotype-driven treatment in chronic upper airway diseases. *Clin Transl Allergy*. 2017; **7**(1): 1- 14.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

51 Stevens WW, Schleimer RP, Kern RC. Chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract*. 2016; **4**(4): 565- 572.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

52 Delemarre T, Holtappels G, De Ruyck N, et al. Type 2 inflammation in chronic rhinosinusitis without nasal polyps: another relevant endotype. *J Allergy Clin Immunol*. 2020; **146**(2): 337- 343.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

53 Stevens WW, Peters AT, Tan BK, et al. Associations between inflammatory endotypes and clinical presentations in chronic rhinosinusitis. *J Allergy Clin Immunol Pract*. 2019; **7**(8): 2812- 2820. e3.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

54 Staudacher AG, Peters AT, Kato A, Stevens WW. Use of endotypes, phenotypes, and inflammatory markers to guide treatment decisions in chronic rhinosinusitis. *Ann Allergy Asthma Immunol*. 2020; **124**(4): 318- 325.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

55 Tan BK, Klingler AI, Poposki JA, et al. Heterogeneous inflammatory patterns in chronic rhinosinusitis without nasal polyps in Chicago, Illinois. *J Allergy Clin Immunol*. 2017; **139**(2): 699- 703.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

56 Wang BF, Cao PP, Long XB, et al. Distinct mucosal immunopathologic profiles in atopic and nonatopic chronic rhinosinusitis without nasal polyps in Central China. *Int Forum Allergy Rhinol*. 2016; **6**(10): 1013- 1019.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

57 Chen CL, Yao Y, Pan L, et al. Common fibrin deposition and tissue plasminogen activator downregulation in nasal polyps with distinct inflammatory endotypes. *J Allergy Clin Immunol*. 2020; **146**(3): 677- 681.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

58 Van Bruaene N, Perez-Novo CA, Basinski TM, et al. T-cell regulation in chronic paranasal sinus disease. *J Allergy Clin Immunol*. 2008; **121**(6): 1435- 1441.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

59 Lou H, Meng Y, Piao Y, et al. Cellular phenotyping of chronic rhinosinusitis with nasal polyps.

Rhinology. 2016; **54**(2): 150- 159.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

60 Meng Y, Lou H, Wang Y, et al. Endotypes of chronic rhinitis: a cluster analysis study. *Allergy*. 2019; **74**(4): 720- 730.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

61 Bachert C, Zhang N. Medical algorithm: diagnosis and treatment of chronic rhinosinusitis. *Allergy*. 2020; **75**(1): 240- 242.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

62 Wu D, Yan B, Wang Y, Zhang L, Wang C. Charcot-Leyden crystal concentration in nasal secretions predicts clinical response to glucocorticoids in patients with chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2019; **144**(1): 345- 348.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

63 Videler WJ, Badia L, Harvey RJ, et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. *Allergy*. 2011; **66**(11): 1457- 1468.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

64 Haxel BR, Clemens M, Karaiskaki N, Dippold U, Kettern L, Mann WJ. Controlled trial for long-term low-dose erythromycin after sinus surgery for chronic rhinosinusitis. *Laryngoscope*. 2015; **125**(5): 1048- 1055.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

65 Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope*. 2006; **116**(2): 189- 193.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

66 Zeng M, Wang H, Liao B, et al. Clinical and biological markers predict the efficacy of glucocorticoid- and macrolide-based postoperative therapy in patients with chronic rhinosinusitis. *Am J Rhinol Allergy*. 2020; **35**(5): 596- 606.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

67 Xu X, Ong YK, Wang Y. Novel findings in immunopathophysiology of chronic rhinosinusitis and their role in a model of precision medicine. *Allergy*. 2020; **75**(4): 769- 780.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

68 Jonstam K, Alsharif S, Bogaert S, et al. Extent of inflammation in severe nasal polyposis and effect of sinus surgery on inflammation. *Allergy*. 2021; **76**(3): 933- 936.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

69 Chen FH, Deng J, Hong HY, et al. Extensive versus functional endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps and asthma: a 1-year study. *Am J Rhinol Allergy*. 2016;

30(2): 143- 148.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

70 Bachert C, Zhang N, Cavaliere C, Weiping W, Gevaert E, Krysko O. Biologics for chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2020; **145**(3): 725- 739.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

71 Fokkens WJ, Lund V, Bachert C, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy*. 2019; **74**(12): 2312- 2319.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

72 Fujieda S, Matsune S, Takeno S, et al. The effect of dupilumab on intractable chronic rhinosinusitis with nasal polyps in Japan. *Laryngoscope*. 2021; **131**(6): e1770- e1777.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

73 Takabayashi T, Asaka D, Okamoto Y, et al. A phase II, multicenter, randomized, placebo-controlled study of benralizumab, a humanized anti-IL-5R alpha monoclonal antibody, in patients with eosinophilic chronic rhinosinusitis. *Am J Rhinol Allergy*. 2021; **35**(6): 861- 870.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

74 Schneider AL, Schleimer RP, Tan BK. Targetable pathogenic mechanisms in nasal polyposis. *Int Forum Allergy Rhinol*. 2021; **11**(8): 1220- 1234.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

75 Sakuma Y, Ishitoya J, Komatsu M, et al. New clinical diagnostic criteria for eosinophilic chronic rhinosinusitis. *Auris Nasus Larynx*. 2011; **38**(5): 583- 588.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

76 Hu Y, Cao PP, Liang GT, Cui Y-H, Liu Z. Diagnostic significance of blood eosinophil count in eosinophilic chronic rhinosinusitis with nasal polyps in Chinese adults. *Laryngoscope*. 2012; **122**(3): 498- 503.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

77 Meng Y, Lou H, Wang C, Zhang L. Predictive significance of computed tomography in eosinophilic chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol*. 2016; **6**(8): 812- 819.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

78 Xu Q, Du K, Zheng M, et al. Application of clinical scores in the differential diagnosis of chronic rhinosinusitis with nasal polyps in a Chinese population. *Am J Rhinol Allergy*. 2020; **34**(3): 401- 408.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

79 Klingler AI, Stevens WW, Tan BK, et al. Mechanisms and biomarkers of inflammatory endotypes in chronic rhinosinusitis without nasal polyps. *J Allergy Clin Immunol*. 2021; **147**(4): 1306- 1317.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

- 80 Takahashi T, Kato A, Suh LA, et al. Integrin $\beta 6$ microparticles in nasal lavage fluids; potential new biomarkers for basal cell activation in chronic rhinosinusitis. *Allergy*. 2020; **75**(12): 3261- 3264.
[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 81 Baumann R, Untersmayr E, Zissler UM, et al. Noninvasive and minimally invasive techniques for the diagnosis and management of allergic diseases. *Allergy*. 2021; **76**(4): 1010- 1023.
[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 82 Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011; **184**(5): 602- 615.
[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 83 Zhu M, Gao X, Zhu Z, Hu X, Zhou H, Liu J. The roles of nasal nitric oxide in diagnosis and endotypes of chronic rhinosinusitis with nasal polyps. *J Otolaryngol Head Neck Surg*. 2020; **49**(1): 68.
[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 84 Stevens WW, Ocampo CJ, Berdnikovs S, et al. Cytokines in chronic rhinosinusitis. Role in eosinophilia and aspirin-exacerbated respiratory disease. *Am J Respir Crit Care Med*. 2015; **192**(6): 682- 694.
[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 85 Makihara S, Okano M, Fujiwara T, et al. Regulation and characterization of IL-17A expression in patients with chronic rhinosinusitis and its relationship with eosinophilic inflammation. *J Allergy Clin Immunol*. 2010; **126**(2): 397- 400.
[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 86 Wang ZZ, Song J, Wang H, et al. Stromal cells and B cells orchestrate ectopic lymphoid tissue formation in nasal polyps. *Allergy*. 2021; **76**(5): 1416- 1431.
[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 87 Derycke L, Zhang N, Holtappels G, Dutre T, Bachert C. IL-17A as a regulator of neutrophil survival in nasal polyp disease of patients with and without cystic fibrosis. *J Cyst Fibros*. 2012; **11**(3): 193- 200.
[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 88 Baeten D, Sieper J, Braun J, et al. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. *N Engl J Med*. 2015; **373**(26): 2534- 2548.
[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 89 Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. *N Engl J Med*. 2014; **371**(4): 326- 338.
[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)
- 90 Riggioni C, Alvaro-Lozano M, Alsina L. Biologics as a therapeutic approach for a Th17-mediated

severe dermatitis in skin barrier disorders. *Allergy*. 2020; **75**(11): 3007- 3008.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

91 Peters AT, Kato A, Zhang N, et al. Evidence for altered activity of the IL-6 pathway in chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2010; **125**(2): 397- 403.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

92 Kubota K, Takeno S, Taruya T, Sasaki A, Ishino T, Hirakawa K. IL-5 and IL-6 are increased in the frontal recess of eosinophilic chronic rhinosinusitis patients. *J Otolaryngol*. 2017; **46**(1): 1- 7.

[Google Scholar](#)

93 Zhang Y, Wang X, Jiao J, Li Y, Song X, Zhang L. Expression of T helper cytokines associated with MUC5AC secretion in eosinophil-based endotypes of nasal polyps. *Allergy*. 2021; **76**(2): 604- 609.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

94 Kang S, Tanaka T, Narazaki M, Kishimoto T. Targeting interleukin-6 signaling in clinic. *Immunity*. 2019; **50**(4): 1007- 1023.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

95 Takabayashi T, Schleimer RP. Formation of nasal polyps: The roles of innate type 2 inflammation and deposition of fibrin. *J Allergy Clin Immunol*. 2020; **145**(3): 740- 750.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

96 Takabayashi T, Kato A, Peters AT, et al. Increased expression of factor XIII-A in patients with chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2013; **132**(3): 584- 592.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

97 Takabayashi T, Imoto Y, Sakashita M, et al. Nattokinase, profibrinolytic enzyme, effectively shrinks the nasal polyp tissue and decreases viscosity of mucus. *Allergol Int*. 2017; **66**(4): 594- 602.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

98 Schwartz DM, Bonelli M, Gadina M, O'Shea JJ. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat Rev Rheumatol*. 2016; **12**(1): 25- 36.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

99 Schaper-Gerhardt K, Köther B, Wolff L, et al. The H(4) R is highly expressed on eosinophils from AD patients and IL-4 upregulates expression and function via the JAK/STAT pathway. *Allergy*. 2021; **76**(4): 1261- 1264.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

100 Joo YH, Cho HJ, Jeon YJ, et al. Therapeutic effects of intranasal tofacitinib on chronic rhinosinusitis with nasal polyps in mice. *Laryngoscope*. 2021; **131**(5): e1400- e1407.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

101 Yao Y, Yang C, Yi X, Xie S, Sun H. Comparative analysis of inflammatory signature profiles in

eosinophilic and noneosinophilic chronic rhinosinusitis with nasal polyposis. *Biosci Rep*. 2020; **40**(2): BSR20193101.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

102 Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. *Nat Rev Rheumatol*. 2017; **13**(4): 234- 243.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

103 Lee EB, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med*. 2014; **370**(25): 2377- 2386.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

104 Guttman-Yassky E, Silverberg JI, Nemoto O, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *J Am Acad Dermatol*. 2019; **80**(4): 913- 921.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

105 Simpson EL, Lacour JP, Spelman L, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *Br J Dermatol*. 2020; **183**(2): 242- 255.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

106 Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. *J Allergy Clin Immunol*. 2020; **145**(2): 572- 582.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

107 Karin J, Tim D, Gabriele H, Cardell L-O, Marit W, Claus B. Type 2 inflammatory shift in chronic rhinosinusitis during 2007–2018 in Belgium. *Laryngoscope*. 2021; **131**(5): e1408- e1414.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

[Download PDF](#)

About Wiley Online Library

Privacy Policy

Terms of Use

Cookies

Accessibility

Publishing Policies

Help & Support

Contact Us
Training and Support
DMCA & Reporting Piracy

Opportunities

Subscription Agents
Advertisers & Corporate Partners

Connect with Wiley

The Wiley Network
Wiley Press Room

Copyright © 1999-2021 John Wiley & Sons, Inc. All rights reserved