Uncontrolled Chronic Rhinosinusitis with Nasal Polyps

Subjects: Otorhinolaryngology

Contributor: Sung-Dong Kim, Kyu-Sup Cho

Chronic rhinosinusitis (CRS) is recognized as a heterogeneous disease with a wide range of clinical features, resulting in significant morbidity and cost to the healthcare system. The phenotypic classification is determined by the presence or absence of nasal polyps and comorbidities, the endotype classification has been established based on molecular biomarkers or specific mechanisms.

Keywords: chronic rhinosinusitis ; nasal polyps ; endotype

1. Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous disease with a wide range of clinical features and mechanisms that results in significant morbidity and cost to the healthcare system. CRS affects approximately 3–6% [1][2] of the general population and causes poor quality of life (QOL) and personal productivity in up to 10% of the adult population. CRS leads to more than one million surgical procedures worldwide each year. CRS is diagnosed when there is objective evidence of inflammation or polypoid tissue on endoscopy and CT scans of the sinuses, along with symptoms such as nasal congestion, stuffiness, runny nose, facial pain or tightness, difficulty or loss of smell (anosmia), cough, and fatigue persisting for at least 12 weeks [3].

Although the 2017 European Position Paper on Rhinosinusitis and Nasal Polyposis (EPOS) guidelines divided CRS into two main phenotypes, CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [3], the new 2020 EPOS guidelines categorize primary CRS into type 2 and non-type 2 [4]. Type 2 includes allergic fungal rhinosinusitis, eosinophilic CRS among CRSwNP, and central compartment allergic diseases [4]. Recently, as studies on biomarkers reflecting biological mechanisms have been conducted, more personalized medicine has become available.

The EPOS guidelines define CRS as controlled, partially controlled, or uncontrolled, on the basis of objectively determining the degree of subjective symptom reduction, mucosal condition, side effects, need for systemic medications, and need for functional endoscopic sinus surgery.

2. Phenotype and Endotype Based Treatment

2.1. Antibiotics

According to existing guidelines, antibiotics, such as macrolides and doxycycline, can be considered for the treatment of CRS [3][5]. However, as several studies have reported, there is no recommendation for antibiotic use for CRS, given the lack of placebo-controlled studies [4][6][7]. Bacterial infections based on the endotype are type 3, which is the rationale for antibiotic use in this setting [8]. More than 50% of CRSsNP patient tissues have a partial type 2 endotype, and CRS patients with type 3 endotypes, including those with cost, are likely to respond well to broad-spectrum antibiotics [9]. In a recent study using 625 mg amoxicillin–clavulanic acid, significant objective and subjective results were reported only in the non-type 2 endotype [10]. Although Staphylococcus aureus has been reported to play an important role in type 2 inflammation in CRS, objective studies on the efficacy of antibiotics based on this have been lacking [11][12].

Macrolides are characterized by antibiotic properties and immunomodulation by the inhibition of inflammatory cytokines [7][13][14] and are considered for long-term use as a CRS treatment based on randomized controlled trials [15][16]. Non-type 2 patients with low serum IgE responded well to treatment and showed significantly reduced IL-8 levels [15]. One study targeting eosinophilic CRSwNP patients also showed a significant therapeutic effect; however, additional research is needed to determine whether the effect is greater when used in combination with steroids and biological agents for significant effects in type 1, type 3, or mixed endotypes [17][18][19][20]. Doxycycline is characterized by its antibiotic properties through the inhibition of cytokines and chemokines. It has a significant effect on reducing the size of polyps and

improving symptoms by suppressing the type 2 response caused by Staphylococcus aureus in type 2 CRSwNP patients [21][22][23].

2.2. Corticosteroids

Corticosteroids are considered a mainstream treatment for CRS with anti-inflammatory properties, and are more useful for suppressing type 2 inflammation than type 1 or type 3 inflammation, suppressing ILC2s, Th2 cells, basophils, and eosinophils. This therapy has been used in the treatment of CRSwNP patients rather than CRSsNP [24][25][26][27][28]. Neutrophils are relatively resistant to the effects of corticosteroids, and the reduced effect compared to Western CRSwNP, especially in type 3 inflammation, is supported by studies of Asian CRSwNP and CRSsNP patients [29][30][31][32][33][34][35].

Topical corticosteroid sprays are used in conjunction with oral medications to treat CRS. Although access to sinus tissue is limited, drug delivery has been improved with high-volume steroid irrigation or steroid-impregnated implants [36][37][38][39][40]. A recent study reported that the higher the nasal IL-8 level in CRS patients after surgery, the more difficult it is to control inflammation with topical steroids [41].

In CRS, barrier defects can exacerbate inflammation by increasing the antigen access. Furthermore, epithelial barrier remodeling defects or basal cell hyperplasia induced by type 2 inflammation can be partially ameliorated by corticosteroids [42][43][44][45].

2.3. Leukotriene Antagonist

AERD is classified as a type 2 sub-endotype with increased production of prostaglandin D2 (PGD2) and cysteinyl leukotrienes [46]. A recent study reported that PGD2 activates the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2), which is important for the recruitment and activation of eosinophils, basophils, and lymphocytes [47].

2.4. Surgery

Surgical treatment can be considered selectively if it does not respond to appropriate pharmacological treatment, and the scope of surgery is controversial [7][48]. Standard endoscopic sinus surgery (ESS) aims to remove inflammatory tissue, ventilate and drain the sinuses, and improve the delivery of topical agents [49]. Although mucus retention due to sinus obstruction promotes microbial overgrowth and infectious inflammation in type 1 and type 3 inflammation, it is relatively less important in CRSwNP and CRSsNP related to type 2 inflammation [50][51].

The important point in standard ESS is to preserve the sinus mucosa as much as possible while extensively dilating the outflow tract of the sinuses and removing the ethmoid lamella, which can cause obstruction [52][53]. The index of successful surgical treatment is the recurrence rate, and the rate of reoperation for 5 years is reportedly 15–20%; the recurrence rate is higher in CRSwNP than in CRSsNP [54]. Although the recurrence rate can be reduced through the use of high-volume corticosteroid nasal irrigation or systemic steroids after surgery, some researchers have reported that more extensive removal of the sinus mucosa, including the floor of the frontal sinus, is required [55][56][57].

Extensive surgery is termed “re-boot” surgery and significant reductions in eosinophilic cationic protein and IL-5 in postoperative nasal secretions have been reported. However, in terms of the endotype, surgical failure is correlated with the presence and intensity of type 2 eosinophilic inflammation and blood eosinophilia [58][59][60][61]. For standard ESS failures, nasalization and Draf III (endoscopic lothrop) can be considered, including re-boot surgery [55][56][57]. The nasalization procedure aggressively removes the middle turbinate and paranasal mucosa to induce healing of normal mucosa. The Draf III procedure maximizes access to the frontal and ethmoid sinuses by removing all the bones and mucosa of the upper part of the middle turbinate and the floor of the frontal sinuses. Re-boot surgery includes both the previous surgeries to remove mucosa in the nasal and paranasal sinuses and the floor of the frontal sinuses [55][56][57]. Although the effectiveness of the aggressive surgical approach is controversial, there are reports of positive results in recurrent or high-risk type 2 type CRSwNP [58]. In addition, there is a potential benefit of improved drug delivery after surgical treatment, and some studies have reported that it is effective in type 1 or type 3 inflammatory endotypes [60].

Several studies have reported on the prediction of surgical outcomes according to endotype. In one study, cluster analysis was performed to determine the correlation between endotypes and treatment outcomes. The treatment outcome was worst when asthma was accompanied by type 2 inflammation, in which IL-5, Immunoglobulin E (IgE), and eosinophils were increased in the nasal mucosa [62]. In another study, the T2 cytokine IL-5 and the type 2 biomarkers periostin and C-C motif chemokine ligand 26 (CCL26) were higher in patients with difficult-to-treat CRSwNP but were not associated with treatment outcome. However, yet another study reported that type 2 inflammation correlated with the epithelial secreted

cysteine proteinase inhibitor cystatin SN and was associated with poor outcome [63]. Some studies have reported that higher intensities of type 1 and type 3 inflammations are associated with surgical failure [62][64].

2.5. Biological Treatment

Omalizumab is a humanized recombinant DNA-derived IgG1k monoclonal antibody that specifically binds to free IgE in interstitial and blood fluid and to membrane-bound forms of IgE (mIgE) on the surface of mIgE-expressing B lymphocytes [65]. The mechanism of reduced sensitivity to allergen stimulation is the gradual downregulation of FcεRI receptors on basophils, mast cells, and dendritic cells by free IgE binding to omalizumab. In particular, omalizumab does not bind to IgE, which is already bound to the high-affinity IgE receptor (FceRI) on the surface of antigen-presenting dendritic cells, basophils, and mast cells [66]. Nasal polyps, local eosinophilic inflammation, and asthma are associated with elevated local IgE levels. Several studies have reported that omalizumab reduces the size of polyps and significantly improves the quality of life of CRSwNP patients [67][68][69]. Although endoscopic finding and CT score showed improvement, there was no significant improvement in tissue and blood eosinophilia [70]. Based on this, Omalizumab was approved by the FDA for the treatment of nasal polyps in 2020.

Reslizumab and Mepolizumab are monoclonal antibodies that block IL-5, which contributes to the activation, maturation, and survival of eosinophils [71]. IL-5 is an important mediator of tissue eosinophilia in CRSwNP patients and is derived from T cells and ILC2s [72]. Reslizumab reported improvement in nasal polyp scores in a small study, and mepolizumab reported significant improvements in nasal polyp severity and symptom scores, along with a reduction in the need for surgery in CRSwNP patients in a multicenter randomized controlled trial study [73][74]. In particular, Mepolizumab showed a significant improvement to visual analogue score (VAS), Sino-Nasal Outcome Test (SNOT-22) score, nasal polyposis severity, and endoscopic nasal polyp score compared with placebo groups [75]. Based on this, mepolizumab has recently been reported in phase 3 trials for subjective and objective efficacy for CRSwNP, and the FDA approved its use [75].

Benralizumab is a cytotoxic monoclonal antibody that blocks the IL-5 receptors to eliminate eosinophils. Several studies have reported that it reduces annual asthma exacerbation rates and increases the lung function in uncontrolled asthma. Moreover, a phase 3 trial of CRSwNP was conducted [76][77][78][79]. However, additional studies on CRS patients are needed in the future.

Dupilumab is a monoclonal antibody that blocks IL-4 and IL-13, which are important in type 2 inflammation by binding to the α component of the shared receptor and is approved for the treatment of unregulated CRSwNPs. In two multicenter phase 3 trial randomized controlled trials, dupilumab improved quality of life in patients with severe CRSwNP, as well as reported reductions in nasal polyp size, nasal congestion, and sense of smell [80]. In addition, Ryu et al. reported that dupilumab significantly reduced the use of systemic corticosteroids compared to placebo and reduced nasal surgery by 76%. When serum and nasal secretions of CRSwNP patients were analyzed, type 2 inflammatory markers were significantly reduced in nasal secretions [81].

In a study comparing dupilumab and functional endoscopic sinus surgery (FESS) in CRSwNP patients, both methods were effective in reducing symptoms following the Sino-Nasal Outcome Test (SNOT-22). Furthermore, patients treated with FESS reported greater reductions in polyp burden than patients treated with dupilumab, whereas patients treated with dupilumab reported an improved sense of smell and greater reductions in postnasal drip, cough, and thick nasal drainage [82]. When the combination use of FESS and biologics is required, a retrospective matched cohort study on the timing of biologic use was reported [83]. The treatment effect size of dupilumab versus placebo was generally significantly greater in patients who had recent surgery, especially within 3 years. On the other hand, the number of surgeries did not show significant results.

Different biologics and ASA-D reported significant clinical improvement in patient outcomes in a meta study including 29 randomized controlled trials evaluating eight treatments (n = 3461) comparing monoclonal antibodies and aspirin desensitization (ASA-D) in CRSwNP patients [84].

Although monoclonal antibodies are effective drugs for suppressing type 2 inflammation, there are no guidelines on which biological agents should be used first in patients with type 2 inflammation, because each target mechanism is different. There are reports of the various effects mentioned above, but a direct comparative evaluation for each has not been conducted. However, several recommendations for clinicians were presented at a recent expert board meeting, and dupilumab was reported to have the highest efficacy and objectivity among the currently available monoclonal antibodies [85]. However, a dosing interval has not yet been established. In a randomized, double-blind, phase 3 trial of dupilumab, there was no statistically significant difference in efficacy between a group of patients treated with dupilumab every 2 weeks for 52 weeks and another group treated with dupilumab every 2 weeks for 24 out of 52 weeks and then every 4

weeks for 28 weeks [80]. This may be positive in terms of patient burden if a certain level of therapeutic effect can be maintained by extending the dosage interval.

References

1. Dietz de Loos, D.; Lourijsen, E.S.; Wildeman, M.A.M.; Freling, N.J.M.; Wolvers, M.D.J.; Reitsma, S.; Fokkens, W.J. Prevalence of chronic rhinosinusitis in the general population based on sinus radiology and symptomatology. J. Allergy Clin. Immunol. 2019, 143, 1207–1214.
2. Tomassen, P.; Vandeplas, G.; Van Zele, T.; Cardell, L.O.; Arebro, J.; Olze, H.; Forster-Ruhrmann, U.; Kowalski, M.L.; Olszewska-ziaber, A.; Holtappels, G.; et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J. Allergy Clin. Immunol. 2016, 137, 1449–1456.
3. Fokkens, W.J.; Lund, V.J.; Hopkins, C.; Hellings, P.W.; Kern, R.; Reitsma, S.; Cohen, N.; Cervin, A.; Douglas, R.; Gevaert, P.; et al. EPOS 2012, European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology 2012, 50, 1–12.
4. Fokkens, W.J.; Lund, V.J.; Hopkins, C.; Hellings, P.W.; Kern, R.; Reitsma, S.; Cohen, N.; Cervin, A.; Douglas, R.; Gevaert, P.; et al. European position paper on rhinosinusitis and nasal polyps 2020. Rhinology 2020, 58 (Suppl. S29), 1–464.
5. Rosenfeld, R.M.; Piccirillo, J.F.; Chandrasekhar, S.S.; Brook, I.; Ashok Kumar, K.; Kramper, M.; Orlandi, R.R.; Palmer, J.N.; Patel, Z.M.; Peters, A.; et al. Clinical practice guideline (update), adult sinusitis. Otolaryngol. Head Neck Surg. 2015, 152 (Suppl. S2), S1–S39.
6. Smith, S.S.; Evans, C.T.; Tan, B.K.; Chandra, R.K.; Smith, S.B.; Kern, R.C. National burden of antibiotic use for adult rhinosinusitis. J. Allergy Clin. Immunol. 2013, 132, 1230–1232.
7. Orlandi, R.R.; Kingdom, T.T.; Smith, T.L.; Bleier, B.; DeConde, A.; Luong, A.U.; Poetker, D.M.; Soler, Z.; Welch, K.C.; Wise, S.K.; et al. International consensus statement on allergy and rhinology, rhinosinusitis 2021. Int. Forum Allergy Rhinol. 2021, 11, 213–739.
8. Van Zele, T.; Claeys, S.; Gevaert, P.; Van Maele, G.; Holtappels, G.; Van Cauwenberge, P.; Bachert, C. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy 2006, 61, 1280–1289.
9. Heffler, E.; Malvezzi, L.; Boita, M.; Brussino, L.; Virgilio, A.D.; Ferrando, M.; Puggioni, F.; Racca, F.; Stomeo, N.; Spriano, G.; et al. Immunological mechanisma underlying chronic rhinosinusitis with nasal polyps. Expert Rev Clin Immuno. 2018, 14, 731–737.
10. Gunel, C.; Bleier, B.S.; Meteoglu, I. Antibiotics in eosinophilic chronic rhinosinusitis, Rethinking maximal antimicrobial medical therapy. Laryngoscope 2017, 127, 794–796.
11. Lan, F.; Zhang, N.; Holtappels, G.; De Ruyck, N.; Krysko, O.; Van Crombruggen, K.; Braun, H.; Johnston, S.L.; Papadopoulos, N.G.; Zhang, L.; et al. Staphylococcus aureus Induces a mucosal Type 2 immune response via epithelial cell-derived cytokines. Am. J. Respir. Crit. Care Med. 2018, 198, 452–463.
12. Bachert, C.; Holtappels, G.; Merabishvili, M.; Meyer, T.; Murr, A.; Zhang, N.; Crombruggen, K.V.; Gevaert, E.; Volker, U.; Broker, B.M.; et al. Staphylococcus aureus controls interleukin-5 release in upper airway inflammation. J. Proteom. 2018, 180, 53–60.
13. Zhang, Y.; Gevaert, E.; Lou, H.; Wang, X.; Zhang, L.; Bacheert, C.; Zhang, N. Chronic rhinosinusitis in Asia. J. Allergy Clin. Immunol. 2017, 140, 1230–1239.
14. Healy, D.P. Macrolide immunomodulation of chronic respiratory diseases. Curr. Infect. Dis. Rep. 2007, 9, 7–13.
15. 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, 189–193.
16. Videler, W.J.; Badia, L.; Harvey, R.J.; Gane, S.; Georgalas, C.; Van Der Meulen, F.W.; Menger, D.J.; Lehtonen, M.T.; Toppila-Salmi, S.K.; Vento, S.I.; et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis, a randomized controlled trial. Allergy 2011, 66, 1457–1468.
17. Bezerra TF, P.; Pezato, R.; Barros PM, D.; Coutinho, L.L.; Costa, L.F.; Pinna, F.; Voegels, R. Prospective evaluation of clarithromycin in recurrent chronic rhinosinusitis with nasal polyps. Braz. J. Otorhinolaryngol. 2019, 87, 298–304.
18. Huang, Z.; Zhou, B. Clarithromycin for the treatment of adult chronic rhinosinusitis, a systematic review and meta-analysis. Int. Forum Allergy Rhinol. 2019, 9, 545–555.
19. Oakley, G.M.; Harvey, R.J.; Lund, V.J. The role of macrolides in chronic rhinosinusitis (CRSsNP and CRSwNP). Curr. Allergy Asthma Rep. 2017, 17, 30.

20. Seresirikachorn, K.; Suwanparin, N.; Srisunthornphanich, C.; Chitsuthipakorn, W.; Kanjanawasee, D.; Snidvongs, K. Factors of success of low-dose macrolides in chronic sinusitis, systematic review and meta-analysis. Laryngoscope 2019, 129, 1510–1519.
21. De Schryver, E.; Derycke, L.; Calus, L.; Holtappels, G.; Hellings, P.W.; Zele, T.V.; Bachert, C.; Gevaert, P. The effect of systemic treatments on periostin expression reflects their interference with the eosinophilic inflammation in chronic rhinosinusitis with nasal polyps. Rhinology 2017, 55, 152–160.
22. Lees, K.A.; Orlandi, R.R.; Oakley, G.; Alt, J.A. The role of macrolides and doxycycline in chronic rhinosinusitis. Immunol. Allergy Clin. North Am. 2020, 40, 303–315.
23. Henehan, M.; Montuno, M.; De Benedetto, A. Doxycycline as an anti-inflammatory agent, updates in dermatology. J. Eur. Acad. Derm. Venereol. 2017, 31, 1800–1808.
24. Banuelos, J.; Lu, N.Z. A gradient of glucocorticoid sensitivity among helper T cell cytokines. Cytokine Growth Factor Rev. 2016, 31, 27–35.
25. Strehl, C.; Ehlers, L.; Gaber, T.; Buttgereit, F. Glucocorticoids-all- rounders tackling the versatile players of the immune system. Front. Immunol. 2019, 10, 1744.
26. Walford, H.H.; Lund, S.J.; Baum, R.E.; White, A.A.; Bergeron, C.M.; Husseman, J.; Bethel, K.J.; Scott, D.R.; Khorrma, N.; Miller, M.; et al. Increased ILC2s in the eosinophilic nasal polyp endotype are associated with corticosteroid responsiveness. Clin. Immunol. 2014, 155, 126–135.
27. Doherty, T.A.; Broide, D.H. Pathways to limit group 2 innate lymphoid cell activation. J. Allergy Clin. Immunol. 2017, 139, 1465–1467.
28. Ogasawara, N.; Poposki, J.A.; Klingler, A.I.; Tan, B.K.; Weibman, A.R.; Hulse, K.E.; Stevens, W.W.; Peters, A.T.; Grammer, L.C.; Scheimer, R.P.; et al. IL-10, TGF-beta, and glucocorticoid prevent the production of type 2 cytokines in human group 2 innate lymphoid cells. J. Allergy Clin. Immunol. 2018, 141, 1147–1151.
29. Schleimer, R.P.; Freeland, H.S.; Peters, S.P.; Brown, K.E.; Derse, C.P. An assessment of the effects of glucocorticoids on degranulation, chemotaxis, binding to vascular endothelium and formation of leukotriene B4 by purified human neutrophils. J. Pharm. Exp. Ther. 1989, 250, 598–605.
30. Ray, A.; Kolls, J.K. Neutrophilic inflammation in asthma and association with disease severity. Trends Immunol. 2017, 38, 942–954.
31. Chong, L.Y.; Head, K.; Hopkins, C.; Philpott, C.; Burton, M.J.; Schilder, A.G. Different types of intranasal steroids for chronic rhinosinusitis. Cochrane Database Syst. Rev. 2016, 4, CD011993.
32. Head, K.; Chong, L.Y.; Piromchai, P.; Hopkins, C.; Philpott, C.; Schilder, A.G.; Burton, M.J. Systemic and topical antibiotics for chronic rhinosinusitis. Cochrane Database Syst. Rev. 2016, 4, CD011994.
33. Zhou, B.; He, G.; Liang, J.; Cheng, L.; Mehta, A.; Liu, S.; Yu, W.; Wang, Z.; Han, D. Mometasone furoate nasal spray in the treatment of nasal polyposis in Chinese patients, a double-blind, randomized, placebo-controlled trial. Int. Forum Allergy Rhinol. 2016, 6, 88–94.
34. Britt, R.D., Jr.; Thompson, M.A.; Sasse, S.; Pabelick, C.M.; Gerber, A.N.; Prakash, Y.S. Th1 cytokines TNF-alpha and IFN-gamma promote corticosteroid resistance in developing human airway smooth muscle. Am. J. Physiol. Lung Cell. Mol. Physiol. 2019, 316, L71–L81.
35. Nabe, T. Steroid-resistant asthma and neutrophils. Biol. Pharm. Bull. 2020, 43, 31–35.
36. Harvey, R.J.; Snidvongs, K.; Kalish, L.H.; Oakley, G.M.; Sacks, R. Corticosteroid nasal irrigations are more effective than simple sprays in a randomized double-blinded placebo-controlled trial for chronic rhinosinusitis after sinus surgery. Int. Forum Allergy Rhinol. 2018, 8, 461–470.
37. Kern, R.C.; Stolovitzky, J.P.; Silvers, S.L.; Singh, A.; Lee, J.T.; Yen, D.M.; Iloreta, A.M.; Langford, F.P.; Karanfilov, B.; Matheny, K.E.; et al. A phase 3 trial of mometasone furoate sinus implants for chronic sinusitis with recurrent nasal polyps. Int. Forum Allergy Rhinol. 2018, 8, 471–481.
38. Fokkens, W.; Reitsma, S. New delivery forms of nasal corticosteroids. J. Allergy Clin. Immunol. 2019, 143, 87–88.
39. Tait, S.; Kallogjeri, D.; Suko, J.; Kukuljan, S.; Schneider, J.; Piccirillo, J.F. Effect of budesonide added to large-volume, low-pressure saline sinus irrigation for chronic rhinosinusitis, a randomized clinical trial. JAMA Otolaryngol. Head Neck Surg. 2018, 144, 605–612.
40. Leopold, D.A.; Elkayam, D.; Messina, J.C.; Kosik-Gonzalez, C.; Djupesland, P.G.; Mahmoud, R.A. Navigate II, randomized, double-blind trial of the exhalation delivery system with fluticasone for nasal polyposis. J. Allergy Clin. Immunol. 2019, 143, 126–134.

41. Zeng, M.; Wang, H.; Liao, B.; Wang, H.; Long, X.B.; Ma, J.; Liu, J.X.; Liu, Z. Clinical and biological markers predict the efficacy of glucocorticoid-and macrolide-based postoperative therapy in patients with chronic rhinosinusitis. Am. J. Rhinol. Allergy 2021, 35, 596–606.
42. Schleimer, R.P. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. Annu. Rev. Pathol. 2017, 12, 331–357.
43. Ordovas-Montanes, J.; Dwyer, D.F.; Nyquist, S.K.; Buchheit, K.M.; Vukovic, M.; Deb, C.; Wadsworth, M.H.; Hughes, T.K.; Kazer, S.W.; Yoshimoto, E.; et al. Allergic inflammatory memory in human respiratory epithelial progenitor cells. Nature 2018, 560, 649–654.
44. Sekiyama, A.; Gon, Y.; Terakado, M.; Takeshita, I.; Kozu, Y.; Maruoka, S.; Matsumoto, K.; Hashimoto, S. Glucocorticoids enhance airway epithelial barrier integrity. Int. Immunopharmacol. 2012, 12, 350–357.
45. Steelant, B.; Farre, R.; Wawrzyniak, P.; Belmans, J.; Dekimpe, E.; Vanheel, H.; Gerven, L.V.; Krohn, I.K.; Bullens, D.M.; Ceuppens, J.L.; et al. Impaired barrier function in patients with house dust mite-induced allergic rhinitis is accompanied by decreased occludin and zonula occludens-1 expression. J. Allergy Clin. Immunol. 2016, 137, 1043–1053.
46. Cahill, K.N.; Bensko, J.C.; Boyce, J.A.; Laidlaw, T.M. Prostaglandin D(2), a dominant mediator of aspirin-exacerbated respiratory disease. J. Allergy Clin. Immunol. 2015, 135, 245–252.
47. Corren, J. New targeted therapies for uncontrolled asthma. J. Allergy Clin. Immunol. Pract. 2019, 7, 1394–1403.
48. Ghogomu, N.; Kern, R. Chronic rhinosinusitis, the rationale for current treatments. Expert Rev. Clin. Immunol. 2017, 13, 259–270.
49. Chandra, R.K.; Kern, R.C.; Cutler, J.L.; Welch, K.C.; Russell, P.T. REMODEL larger cohort with long-term outcomes and meta-analysis of standalone balloon dilation studies. Laryngoscope 2016, 126, 44–50.
50. Leung, R.M.; Kern, R.C.; Conley, D.B.; Tan, B.K.; Chandra, R.K. Osteomeatal complex obstruction is not associated with adjacent sinus disease in chronic rhinosinusitis with polyps. Am. J. Rhinol. Allergy 2011, 25, 401–403.
51. Snidvongs, K.; Kalish, L.; Sacks, R.; Sivasubramaniam, R.; Cope, D.; Harvey, R.J. Sinus surgery and delivery method influence the effectiveness of topical corticosteroids for chronic rhinosinusitis, systematic review and meta-analysis. Am. J. Rhinol. Allergy 2013, 27, 221–233.
52. DeConde, A.S.; Smith, T.L. Outcomes after frontal sinus surgery, an evidence-based review. Otolaryngol. Clin. N. Am. 2016, 49, 1019–1033.
53. Bassiouni, A.; Ou, J.; Rajiv, S.; Cantero, D.; Vreugde, S.; Wormald, P.J. Subepithelial inflammatory load and basement membrane thickening in refractory chronic rhinosinusitis with nasal polyposis, a histopathological study. Int. Forum Allergy Rhinol. 2016, 6, 248–255.
54. Alanin, M.C.; Hopkins, C. Effect of functional endoscopic sinus surgery on outcomes in chronic rhinosinusitis. Curr. Allergy Asthma Rep. 2020, 20, 27.
55. Barham, H.P.; Ramakrishnan, V.R.; Knisely, A.; Do, T.Q.; Chan, L.S.; Gunaratne, D.A.; Weston, J.D.; Seneviratne, S.; Marcells, G.N.; Sacks, R.; et al. Frontal sinus surgery and sinus distribution of nasal irrigation. Int. Forum Allergy Rhinol. 2016, 6, 238–242.
56. Alsharif, S.; Jonstam, K.; van Zele, T.; Gevaert, P.; Holtappels, G.; Bachert, C. Endoscopic sinus surgery for Type-2 CRS wNP, an endotype-based retrospective study. Laryngoscope 2019, 129, 1286–1292.
57. Morrissey, D.K.; Bassiouni, A.; Psaltis, A.J.; Naidoo, Y.; Wormald, P.J. Outcomes of modified endoscopic Lothrop in aspirin-exacerbated respiratory disease with nasal polyposis. Int. Forum Allergy Rhinol. 2016, 6, 820–825.
58. Jonstam, K.; Alsharif, S.; Bogaert, S.; Suchonos, N.; Holtappels, G.; Park, J.J.; Bachert, C. Extent of inflammation in severe nasal polyposis and effect of sinus surgery on inflammation. Allergy 2021, 76, 933–936.
59. Khairuddin, N.K.; Salina, H.; Gendeh, B.S.; Wan Hamizan, A.K.; Lund, V.J. Quality of life and recurrence of disease in patients with eosinophilic and non-eosinophilic 1 chronic rhinosinusitis with nasal polyposis. Med. J. Malays. 2018, 73, 1–6.
60. Rosati, D.; Rosato, C.; Pagliuca, G.; Cerbelli, B.; Rocca, C.D.; Cristofano, C.D.; Martellucci, S.; Gallo, A. Predictive markers of long-term recurrence in chronic rhinosinusitis with nasal polyps. Am. J. Otolaryngol. 2020, 41, 102286.
61. Pan, L.; Liao, B.; Guo, C.L.; Liu, J.X.; Wanh, H.; Long, X.B.; Liu, Z. Inflammatory features and predictors for postsurgical outcomes in patients with nasal polyps stratified by local and systemic eosinophilia. Int. Forum Allergy Rhinol. 2021, 11, 846–856.
62. Liao, B.; Liu, J.X.; Li, Z.Y.; Zhen, Z.; Cao, P.P.; Long, X.B.; Long, X.B.; Wang, H.; Wang, Y.; Schleimer, R.; et al. Multidimensional endotypes of chronic rhinosinusitis and their association with treatment outcomes. Allergy 2018, 73, 1459–1469.

63. Wu, D.; Yan, B.; Wang, Y.; Wang, C.; Zhang, L. Prognostic and pharmacologic value of cystatin SN for chronic rhinosinusitis with nasal polyps. J. Allergy Clin. Immunol. 2021, 148, 450–460.

64. Ryu, G.; Kim, D.K.; Dhong, H.J.; Eun, K.M.; Lee, K.E.; Kong, I.G.; Kim, H.Y.; Chung, S.K.; Kim, D.Y.; Rhee, C.S.; et al. Immunological characteristics in refractory chronic rhinosinusitis with nasal polyps undergoing revision surgeries. Allergy Asthma Immunol. Res. 2019, 11, 664–676.

65. Chang, T.W.; Davis, F.M.; Sun, N.C.; Sun, C.R.; MacGlashan, D.W., Jr.; Hamilton, R.G. Monoclonal antibodies specific for human IgE-producing B cells, a potential therapeutic for IgE-mediated Allergic diseases. Biotechnology 1990, 8, 122–126.

66. Chang, T.W.; Wu, P.C.; Hsu, C.L.; Hung, A.F. Anti-IgE antibodies for the treatment of IgE-mediated allergic diseases. Adv. Immunol. 2007, 93, 63–119.

67. Buchheit, K.M.; Dwyer, D.F.; Ordovas-Montanes, J.; Katz, H.R.; Lewis, E.; Vukovic, M.; Kau, J.; Bankova, L.G.; Bhattacharyya, N.; Schalek, A.; et al. IL-5Ralpha marks nasal polyp IgG4-and IgE-expressing cells in aspirin-exacerbated respiratory disease. J. Allergy Clin. Immunol. 2020, 145, 1574–1584.

68. Feldman, S.; Kasjanski, R.; Poposki, J.; Hernandez, D.; Chen, J.N.; Norton, J.E.; Suh, L.; Carter, R.G.; Stevens, W.W.; Peters, A.T.; et al. Chronic airway inflammation provides a unique environment for B cell activation and antibody production. Clin. Exp. Allergy 2017, 47, 457–466.

69. Gevaert, P.; Omachi, T.A.; Corren, J.; Mullol, J.; Han, J.; Lee, S.E.; Kaufman, D.; Ligueros-Saylan, M.; Howard, M.; Zhu, R.; et al. Efficacy and safety of omalizumab in nasal polyposis, 2 randomized phase 3 trials. J. Allergy Clin. Immunol. 2020, 146, 595–605.

70. Gevaert, P.; Calus, L.; Van Zele, T.; Blomme, K.; De Ruyck, N.; Bauters, W.; Hellings, P.; Brusselle, G.; Bacquer, D.D.; Cauwenberge, P.V.; et al. Omalizumab is effective in allergic and non-allergic patients with nasal polyposis and co-morbid asthma. J. Allergy Clin. Immunol. 2013, 131, 110–116.

71. Nussbaum, J.C.; Van Dyken, S.J.; von Moltke, J.; Cheng, L.E.; Mohapatra, A.; Molofsky, A.B.; Thornton, E.E.; Krummel, M.F.; Chawla, A.; Liang, H.E.; et al. Type 2 innate lymphoid cells control eosinophil homeostasis. Nature 2013, 502, 245–248.

72. Kato, A. Immunopathology of chronic rhinosinusitis. Allergol. Int. 2015, 64, 121–130.

73. Gevaert, P.; Lang-Loidolt, D.; Lackner, A.; Stammberger, H.; Staudinger, H.; Van Zele, T.; Holtappels, G.; Tavernier, J.; Cauwenberge, P.V.; Bachert, C. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. J. Allergy Clin. Immunol. 2006, 118, 1133–1141.

74. Bachert, C.; Sousa, A.R.; Lund, V.J.; Scadding, G.K.; Gevaert, P.; Nasser, S.; Durham, S.R.; Cornet, M.E.; Kariyawasam, H.H.; Gilbert, J.; et al. Reduced need for surgery in severe nasal polyposis with mepolizumab, randomized trial. J. Allergy Clin. Immunol. 2017, 140, 1024–1031.

75. Han, J.K.; Bachert, C.; Fokkens, W.; Desrosiers, M.; Wagenmann, M.; Lee, S.E.; Smith, S.G.; Martin, N.; Mayer, B.; Yancey, S.W.; et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE), a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Resp. Med. 2021, 9, 1141–1153.

76. Bleecker, E.R.; FitzGerald, J.M.; Chanez, P.; Papi, A.; Weinstein, S.F.; Barker, P.; Sproule, S.; Gilmartin, G.; Aurivillius, M.; Werkstrom, V.; et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO), a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016, 388, 2115–2127.

77. Goldman, M.; Hirsch, I.; Zangrilli, J.G.; Newbold, P.; Xu, X. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma, subanalyses of the Phase III SIROCCO and CALIMA studies. Curr. Med. Res. Opin. 2017, 33, 1605–1613.

78. Park, H.S.; Lee, S.H.; Lee, S.Y.; Kim, M.K.; Lee, B.J.; Werkström, V.; Baker, P.; Zangrilli, J.G. Efficacy and Safety of Benralizumab for Korean Patients with Severe, Uncontrolled Eosinophilic Asthma. Allergy Asthma Immunol. Res. 2019, 11, 508–518.

79. Korn, S.; Bourdin, A.; Chupp, G.; Cosio, B.G.; Arbetter, D.; Shah, M.; Gil, E.G. Integrated Safety and Efficacy Among Patients Receiving Benralizumab for Up to 5 Years. J. Allergy Clin. Immunol. Pract. 2021, 9, 4381–4392.

80. Bachert, C.; Han, J.K.; Desrosiers, M.; Hellings, P.W.; Amin, N.; Lee, S.E.; Mullol, J.; Greos, L.S.; Bosso, J.V.; Laidlaw, T.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, 1638–1650.

81. Bachert, C.; Mannent, L.; Naclerio, R.M.; Mullol, J.; Ferguson, B.J.; Gevaert, P.; Hellings, P.; Jiao, L.; Wang, L.; Evans, R.R.; et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal

polyposis, a randomized clinical trial. JAMA 2016, 315, 469–479.

82. Dharmarajan, H.; Falade, O.; Lee, S.E.; Wang, E.W. Outcomes of dupilumab treatment versus endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps. Int. Forum Allergy Rhinol. 2022, 12, 986–995.
83. Hopkins, C.; Wagenmann, M.; Bachert, C.; Desrosiers, M.; Han, J.K.; Hellings, P.W.; Lee, S.E.; Msihid, J.; Radwan, A.; Rowe, P.; et al. Efficacy of duplimab in patients with a history of prior sinus surgery for chronic rhinosinusitis with nasal polyps. Int. Forum Allergy Rhinol. 2021, 11, 1087–1101.
84. Oykhman, P.; Paramo, F.A.; Bousquet, J.; Kennedy, D.W.; Brignardello-Petersen, R.; Chu, D.K. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis, A systematic review and network meta-analysis. J. Allergy Clin. Immunol. 2022, 149, 1286–1295.
85. Bachert, C.; Han, J.K.; Wagenmann, M.; Hosemann, W.; Lee, S.E.; Backer, V.; Mullol, J.; Gevaert, P.; Klimek, L.; Prokopakis, E.; et al. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics, definitions and management. J. Allergy Clin. Immunol. 2021, 147, 29–36.