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Review

Interpretation of Clinical Efficacy of Biologics in Chronic Rhinosinusitis With Nasal Polyps via Understanding the Local and Systemic Pathomechanisms

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ABSTRACT

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a heterogeneous disease treated with medication or surgery. For recalcitrant type 2 CRSwNP, biological agents have been effectively used to improve nasal polyp score, nasal congestion score, daily symptoms related to CRSwNP, and time to systemic corticosteroid use or revision surgery. Although general guidelines for using biologics to treat CRSwNP were proposed by the European Position Paper on Rhinosinusitis and Nasal Polyps in 2020 and various studies have tested their efficacy, there is much more to learn about biologics—specific indication and choice of biologics based on the endotypes, for instance. Understanding the vascular distribution of monoclonal antibodies and the differences in the vascularity of the non-polyp mucosa and nasal polyp tissue will not only aid understanding of each biologic's clinical effect but also provide insights to establishing a more personalized approach to treating recalcitrant CRSwNP with biologics.

Keywords: Chronic rhinosinusitis; nasal polyp; dupilumab; omalizumab; mepolizumab; benralizumab; reslizumab; nasal polyp score; nasal congestion score; olfaction

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a heterogeneous disease characterized by sino-nasal inflammation that persists for at least 12 weeks.[1] Therapeutic strategies for CRSwNP encompass surgical and medical treatments, including saline irrigation and medications, such as topical or oral corticosteroids, antibiotics, or leukotriene antagonists.[2] A recent multi-center, randomized controlled study demonstrated that endoscopic sinus surgery together with medical therapy was more efficacious than medical therapy alone—excluding biologics—in patients with CRSwNP in terms of the improvement of Sino-Nasal Outcome Test-22 (SNOT-22) scores.[3] However, surgical treatment has a recurrence rate of 40%–79%, and 36% of these cases require revision surgery.[4-7] A meta-analysis of 45 studies with 34,220 subjects showed that the long-term revision rates of endoscopic sinus surgery

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were approximately 14% to 24%.[8] Many of these recalcitrant CRSwNP cases are related to type 2 inflammation, and eosinophilia is a strong prognostic factor for recurrence.[9] As a result, type 2 CRSwNP often necessitates repetitive use of systemic corticosteroids or revision surgeries, underscoring the ultimate need for a new treatment option.[10] Type 2 asthma patients refractory to systemic corticosteroids have been successfully treated with biologics (anti-interleukin [IL]-5, anti-IL-5R, anti-IL-4 receptor alpha [4Rα], anti-immunoglobulin [Ig] E).[11] Since type 2 CRSwNP has a similar immunological mechanism, biologics were introduced to treat uncontrolled severe CRSwNP patients with a poor response to traditional medications and surgery.[4] Many studies have demonstrated the effectiveness of biologics at improving various endpoints, including nasal polyp score (NPS), nasal congestion score (NCS), quality of life as assessed by SNOT-22, olfaction, sinus opacification, and time to first systemic corticosteroid use or surgery.[12-15]

Biologics have different mechanisms for targeting different molecules, resulting in a spectrum of clinical effects in terms of the effect size and the treatment response pattern. Developing more personalized indications for each biological agent can be an effective approach in treating patients with recalcitrant CRSwNP. Therefore, a thorough understanding of each biologic's mechanism of action would be critical. In this review, we propose three ideas: 1) unique pathomechanisms of CRSwNP and mechanisms of action of biologics on two different levels—local and systemic; 2) histological variation between non-polyp nasal mucosa and nasal polyps in terms of vascularity as non-polyp mucosa is well-vascularized while polyps are not; 3) pharmacokinetics (PK) and pharmacodynamics (PD) of monoclonal antibodies, especially their natural distribution in vascular and interstitial spaces. Connecting the dots among these ideas strongly improves understanding of the clinical effects of biologics. We hope this review will provide helpful insights on the use of biologics in treating severe, refractory CRSwNP, contributing to the development of more personalized, specific indications of biologics.

PHARMACOKINETICS AND PHARMACODYNAMICS OF MONOCLONAL ANTIBODIES

Monoclonal antibodies consist of IgG isotypes: IgG1 (omalizumab, mepolizumab, benralizumab), IgG2, and IgG4 (dupilumab, reslizumab).[16-20] They are characterized by long half-lives and slow clearance,[21] requiring less frequent dosing than is needed for small molecules with shorter half-lives. Pharmacokinetically, monoclonal antibodies show a rapid distribution phase, followed by a slow elimination phase.[22] IgG can bind to the neonatal fragment crystallizable (Fc) receptor,[23] which is an important reason why the half-life of IgG is significantly longer (up to 23 days) than that of free IgE (2–3 days).[24] Parenteral administration of monoclonal antibodies is preferred since oral administration is limited due to their instability and poor absorption.[21] Their distribution is limited to the vascular and interstitial spaces due to their large size and hydrophilicity.[22] The size of monoclonal antibodies exceeds the glomerular filtration cut-off threshold; hence, they are usually eliminated by the breakdown of proteolytic enzymes.[22]

Although the PK of small molecules is usually independent of the PD, the PK of monoclonal antibodies usually depends on the PD and target antigens due to the target-mediated drug disposition phenomenon, in which a drug binds to the target site, such as a receptor, with high affinity to such an extent that PK characteristics are affected.[25] As monoclonal

antibodies bind to target antigens and their effector functions are carried out, numerous PD responses may occur, including downregulation of the target antigens, hindrance of cell signaling via receptor blockage, or restriction of ligand-receptor interactions.[21] A variety of characteristics, such as the expression level of the target antigen, tissue distribution, and binding affinity of monoclonal antibodies to the target antigen, impact the PK and PD of monoclonal antibodies.[22]

Since the distribution of biologics is usually confined to vascular and interstitial spaces, understanding the histological characteristics—more specifically, the vasculature—of the sinus mucosa and nasal polyps may provide insights into the interpretation of the clinical efficacy of biologics. In other words, understanding the pathophysiology of CRSwNP on two distinct levels—*local* and *systemic*—is important; *local* refers to nasal polyp tissue, while *systemic* involves the circulation of blood and lymphatics and perivascular tissue such as non-polyp mucosa. A previous study reported that the amount of vasculature, as demonstrated by CD34 immunostaining, is the lowest in allergic polyps,[26] which is consistent with our preliminary study showing hypervascularity in non-polyp mucosa and hypovascularity in type 2 nasal polyps (**Fig. 1**). Considering their natural distribution in the body once administered, biologics tend to affect the systemic pathophysiology more than the local one in CRSwNP.

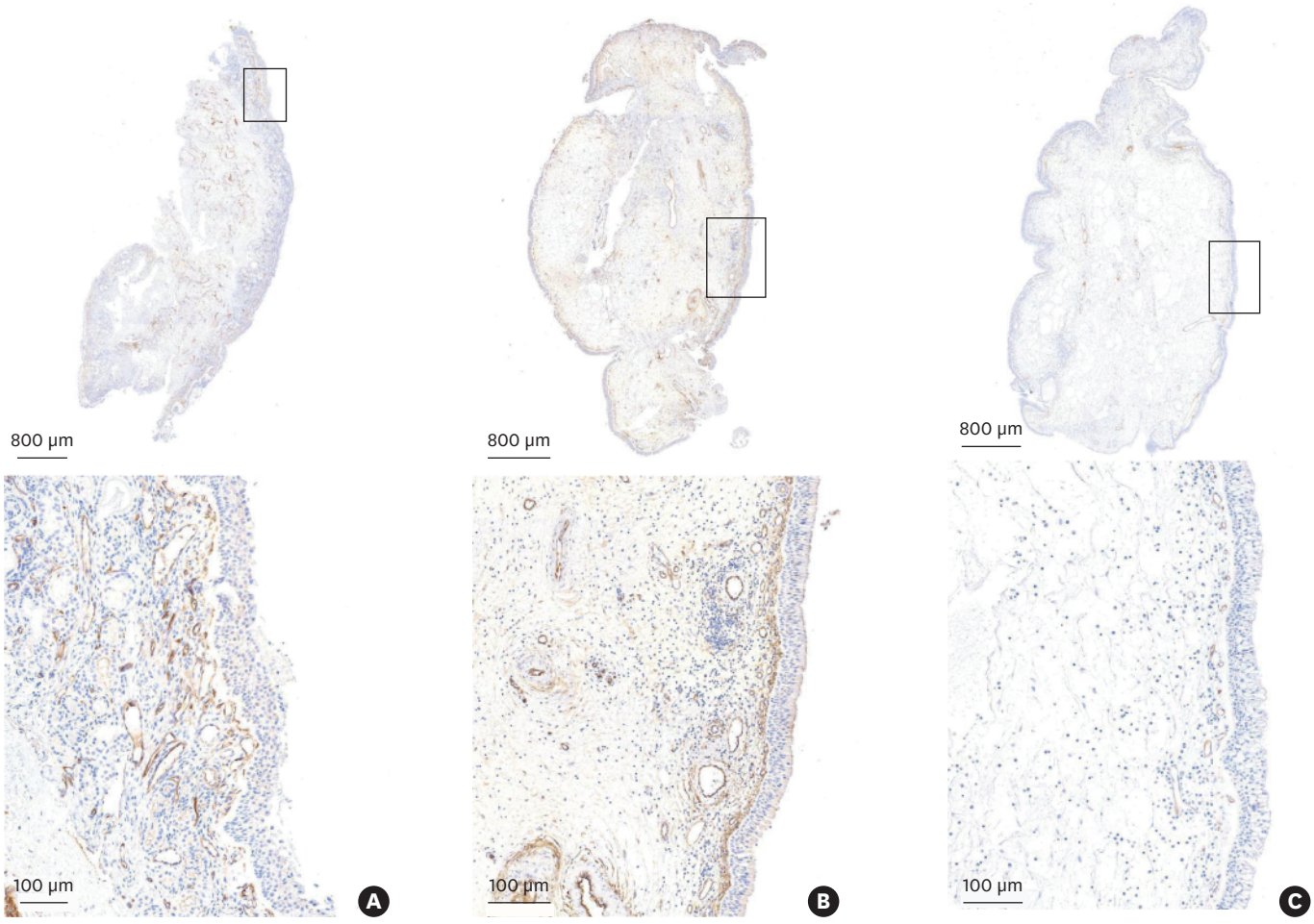

Fig. 1. Vascularity (CD34+ cells) in the non-polyp nasal mucosa and nasal polyps. CD34 immunostaining exhibits hypervascularity in the nasal mucosa (A), relative hypovascularity in non-type 2 nasal polyps (B), and definite hypovascularity in type 2 nasal polyps (C).

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CLINICAL EFFICACY OF BIOLOGICAL AGENTS

Dupilumab (Dupixent®) is approved for the treatment of CRSwNP in the United States, Europe, and South Korea. In a double-blind, randomized, phase 3, multi-center clinical trial, patients treated with dupilumab showed improvement in NPS, NCS, and Lund-Mackay (LM) scores at weeks 24 and 52 after the initial treatment of dupilumab.[12] The improvement of olfaction was one of the earliest changes, which was noted in less than a month—by day 3 according to daily patient-reported loss of smell data, and by week 2 on the University of Pennsylvania Smell Identification Test (UPSIT)—after the beginning of treatment for CRSwNP.[27] In addition, dupilumab alleviated the treatment burden by reducing systemic steroid use (74.6%) and the need for surgery (89.4%).[12]

Omalizumab (Xolair®) is approved for the treatment of CRSwNP in the United States, Europe, and South Korea. In a double-blind, randomized, phase 3 trial of 265 patients with severe CRSwNP refractory to intranasal corticosteroids, an analysis of mean changes from baseline at week 24 showed significant improvements in NPS, NCS, and SNOT-22 in the omalizumab group compared to the placebo group. In contrast, both the omalizumab and placebo groups had similar adverse events.[14] In a small single-center study, Gevaert *et al.*[28] also demonstrated the efficacy of omalizumab in the treatment of CRSwNP patients with asthma by analyzing NPS, computed tomography (CT), and SNOT-22. A study examining CT sinus opacities—nasal polyps, sinusitis *plus* nasal polyps, and sinusitis—of 24 patients with severe allergic asthma and CRSwNP before and after the treatment with omalizumab for six months showed the proportion of subjects with sinusitis decreased from 70% to 29%, while that with nasal polyps increased from 87.5% to 95.8%,[29] demonstrating sinusitis responds better to omalizumab than nasal polyps.

Few studies have reported the efficacy of mepolizumab (Nucala®), reslizumab (Cinqair®), and benralizumab (Farsenra®), which are biological agents targeting IL-5 or IL-5Rα. In a randomized, double-blind, phase 3 trial (SYNAPSE study), mepolizumab improved nasal polyp size and nasal obstruction in patients with severe CRSwNP compared to placebo[15] and alleviated the need for revision surgery in severe CRSwNP.[30] A double-blind, placebo-controlled, randomized, two-center study demonstrated that reslizumab decreased NPS in CRSwNP patients.[31] A phase 3 trial (OSTRO study) showed that benralizumab improved NPS and NCS in severe CRSwNP patients, suggesting that benralizumab is especially beneficial in treating CRSwNP patients with asthma and eosinophilia.[13] In addition, female patients and those with comorbid asthma or blood eosinophils exceeding 560/μL demonstrated more significant improvements in NPS and NCS after the administration of benralizumab, although these differences were statistically insignificant.[13]

Dupilumab showed superiority over omalizumab in improving NPS at week 24 or 52[32] and restoring olfaction, which was usually evident within 2 to 3 months after the initial dosage.[12] A systematic review and network meta-analysis on the comparative efficacy and safety of different kinds of biologics analyzed a variety of outcomes, such as quality of life as determined by SNOT-22, symptoms based on visual analogue scores, olfaction according to the UPSIT, the need for rescue oral corticosteroids or rescue polyp surgery, nasal polyp size, and CT score based on the LM score. This study demonstrated dupilumab, omalizumab, and mepolizumab as "among most beneficial" for seven, two, and one of the outcomes, respectively.[33] When compared to placebo, health-related quality of life, as assessed by SNOT-22, was improved with the use of all biologics: dupilumab (mean difference [MD],

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–19.91), omalizumab (MD, –16.09), mepolizumab (MD, –12.89), and benralizumab (MD, –7.68).[33] Existing studies on individual biologics are organized to show the effect size of each endpoint by the percentage of improvement in **Table**. Changes in NCS and SNOT-22 were comparable at week 52 in dupilumab (55% and 58%), omalizumab (48% and 48%), and mepolizumab (47% and 45%). The change in NPS was smaller than in NCS and SNOT-22, although the effect size of dupilumab (36% at week 52) outweighed that of other biologics. The improvement of olfaction was superior for dupilumab (UPSIT, 72%; loss of smell score [LSS], 40%) when compared to omalizumab (UPSIT, 34%; LSS, 22%) at week 24. In short, symptom-based endpoints—NCS, SNOT-22, UPSIT, and LSS—showed greater improvement rates than NPS for all biologics, which is consistent with a previous study reporting larger improvements in symptoms than in the polyp burden in CRS patients with asthma.[34]

INTERPRETATION OF CLINICAL EFFICACY IN TERMS OF HISTOLOGICAL AND PATHOIMMUNOLOGICAL VARIATIONS

The interpretation of clinical efficacy of biologics in CRSwNP can be greatly assisted by understanding histological variations between the non-polyp mucosa and nasal polyp tissue as well as pathomechanisms that are confined to nasal polyp tissue (**Fig. 2**). Due to their natural distribution in vascular and interstitial spaces, biologics tend to affect the blood and the non-

Table. Immunological and clinical effects of each biological agent in the treatment of CRSwNP

Biological agent	Target molecule	Immunological effect	Dosage	Clinical effect				Time to the manifestation of clinical effect after medication§ (NPS/NCS)
				Endpoint	Baseline	Mean change	Time of assessment	
Dupilumab[12] (Dupixent®)	IL-4Rα	① IL-4↓: Th2 cell differentiation↓ ② IL-13↓: mucus secretion ↓ ③ IL-4↓, IL-13↓: IgE isotype switching ↓	SC 300 mg q2w for 52 weeks/SC 300 mg q2w for 24 weeks + q4w for 28 weeks	NPS	6.18	–1.71 (28%)	24 wk	4 weeks/4 weeks
						–2.24 (36%)	52 wk	
				NCS	2.46	–1.25 (51%)	24 wk	
						–1.35 (55%)	52 wk	
				SNOT-22	51.01	–27.77 (54%)	24 wk	
						–29.84 (58%)	52 wk	
				UPSIT	13.53	9.71 (72%)	24 wk	
				LSS	2.77	–1.21 (40%)	24 wk	
Omalizumab[14,51] (Xolair®)	Free IgE	① FcεRI downregulation ② Inactivation of mast cell, basophil ③ Inactivation of B cell (FcεRII)	SC 75–600 mg q2w or q4w*	NPS	6.29	–1.01 (16%)	24 wk	4 weeks/4 weeks
						–1.31 (21%)	52 wk	
				NCS	2.35	–0.85 (36%)	24 wk	
						–1.12 (48%)	52 wk	
				SNOT-22	59.52	–23.56 (40%)	24 wk	
						–28.47 (48%)	52 wk	
				UPSIT	12.8	4.38 (34%)	24 wk	
				LSS	2.55	–0.57 (22%)	24 wk	
Mepolizumab[15] (Nucala®)	IL-5	Inactivation of eosinophil	SC 100 mg q4w	NPS	5.4	–0.9 (17%)	52 wk	20 weeks/9–12 weeks‖
				NCS‡	8.9	–4.2 (47%)	49–52 wk	
				SNOT-22	63.7	–29 (45%)	52 wk	
				LSS‡	9.6	–2.8 (29%)	49–52 wk	
Benralizumab[13] (Farsenra®)	IL-5Rα	Inactivation of eosinophil	SC 30 mg q4w → q8w†	NPS	6.15	–0.42 (7%)	40 wk	24 weeks/34 weeks
				NCS	2.62	–0.71 (27%)	40 wk	
				SNOT-22	69.3	–16.25 (23%)	40 wk	

CRSwNP, chronic rhinosinusitis with nasal polyps; NPS, nasal polyp score (scale 0–8); NCS, nasal congestion score (scale 0–3); IL, interleukin; SC, subcutaneous; LSS, loss of smell score (scale 0–3); SNOT-22, Sino-Nasal Outcome Test-22 (scale 0–110); UPSIT, University of Pennsylvania Smell Identification Test (scale 0–40); q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; Ig, immunoglobulin.
*Dosage of omalizumab was determined by pretreatment serum total IgE level and body weight.
†Patients were given 30 mg of benralizumab (SC) every 4 weeks for the first 3 doses, followed by 30 mg of benralizumab (SC) every 8 weeks.
‡Marked scale range is 0–10.
§The earliest time when a statistically significant change was observed in NPS or NCS.
‖Due to the lack of exact data, time was estimated based on the graphs provided in the Supplementary of Han *et al*.[15]

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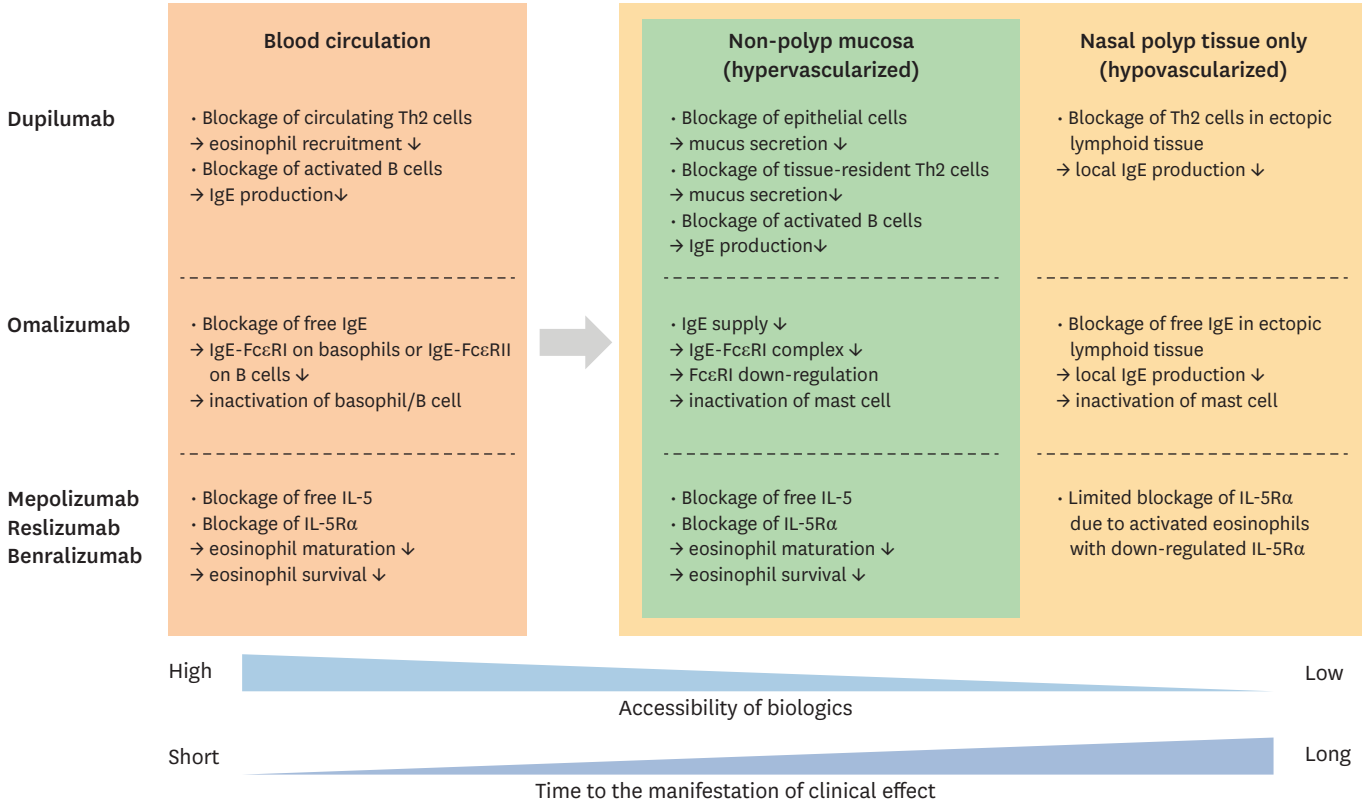

Fig. 2. Action of individual biologics in the blood circulation, non-polyp mucosa, and nasal polyp tissue. The higher accessibility of biologics translates into a shorter time until the manifestation of clinical effects and vice versa.
Th2, T helper 2; Ig, immunoglobulin; IL, interleukin.

polyp mucosa, which is hypervascular in nature, more strongly than nasal polyps, which are hypovascular in nature.[26] In addition to physical distance, the ability of biologics to access nasal polyps may be limited by 1) local IgE production[35] and 2) downregulation of IL-5Rα in activated eosinophils of nasal polyp tissue.[36] Local IgE production was once reported to be active within ectopic lymphoid tissue with germinal center-like structures in 20.69% and 17.31% of eosinophilic and non-eosinophilic CRSwNP cases, respectively.[37] Staphylococcal superantigens in nasal polyps contribute to local IgE production, as *Staphylococcus aureus* enterotoxin-specific IgE is detected in more than half of nasal polyp tissue.[38] The downregulation of IL-5Rα in activated eosinophils was demonstrated by an inverse correlation between the expression level of membrane-anchored IL-5Rα and disease severity.[36] This downregulation was reported to be due to cleavage by matrix metalloproteinase in peripheral blood eosinophils and inflammatory tissue of nasal polyps in patients with comorbid asthma.[36]

Biologics target cytokines and cells related to type 2 inflammation in CRSwNP.[39] Dupilumab, a monoclonal antibody IgG4, targets IL-4Rα, regulating type 2 inflammation by blocking effector functions of IL-4 and IL-13, two major cytokines in the initial steps of inflammation (**Fig. 3A**). IL-4 is a key cytokine required for T helper 2 (Th2) cell differentiation, while IL-13 acts on the epithelium to induce mucus secretion. Both IL-4 and IL-13 play crucial roles in IgE isotype switching,[39] which are upstream events of type 2 inflammation. Since IL-4Rα—expressed in Th2 cells, B cells, eosinophils, and the epithelium—is the primary target of dupilumab,[40] and Th2 cells and B cells exist in the systemic circulation, a quick, strong response is manifested after dupilumab administration.

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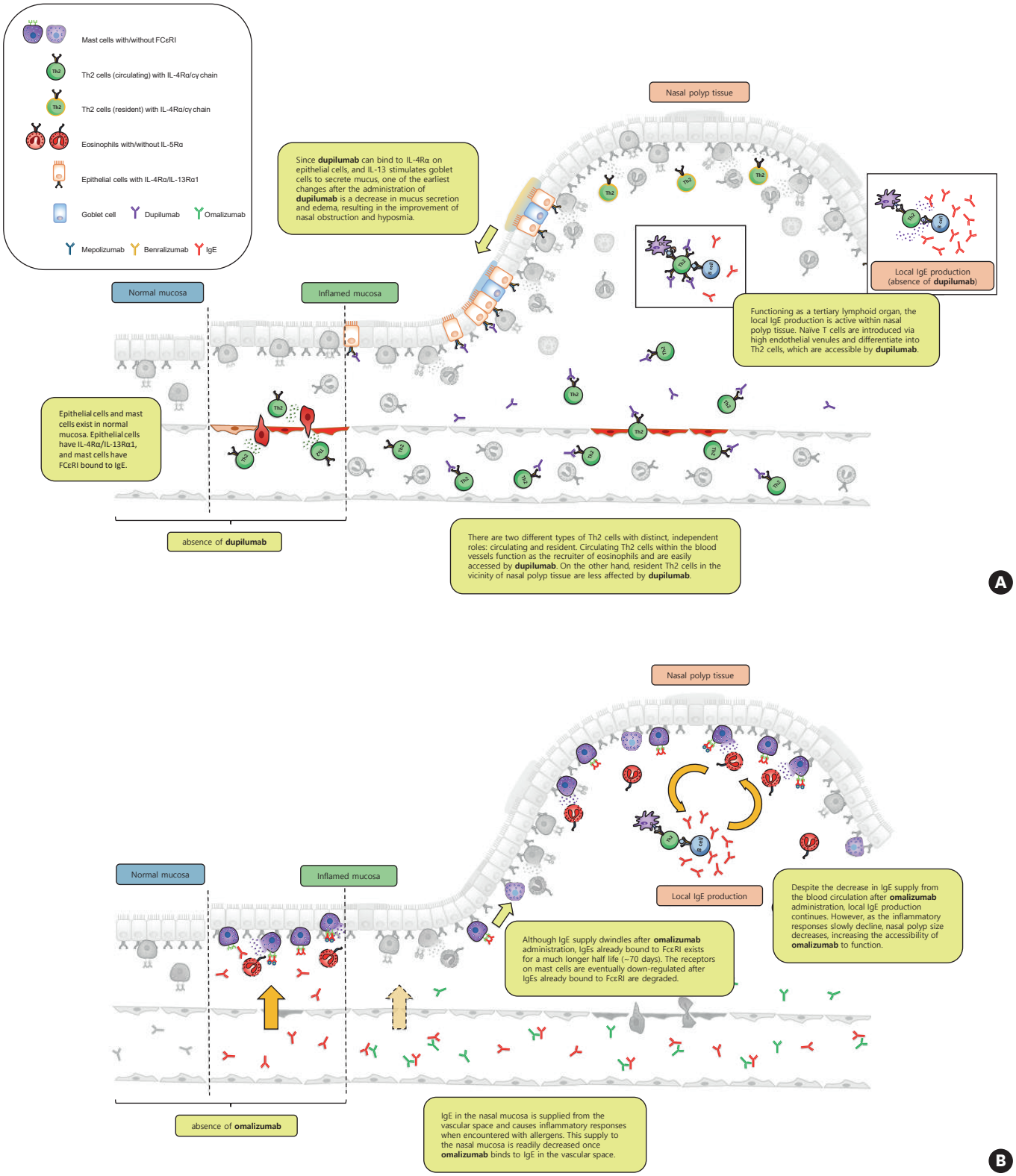

Fig. 3. Pharmacologic mechanisms of dupilumab (A), omalizumab (B), and mepolizumab/benralizumab (C) in normal tissue, inflamed non-polyp mucosa, and nasal polyp tissue in severe CRSwNP.
Th2, T helper 2; CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin.

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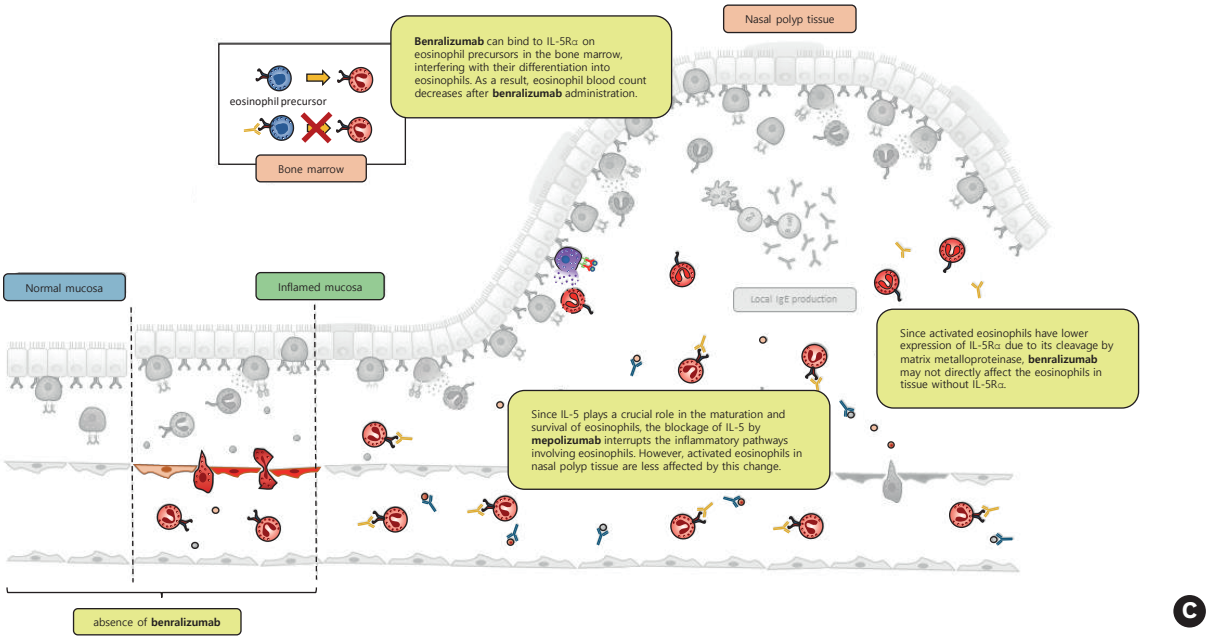

Fig. 3. (Continued) Pharmacologic mechanisms of dupilumab (A), omalizumab (B), and mepolizumab/benralizumab (C) in normal tissue, inflamed non-polyp mucosa, and nasal polyp tissue in severe CRSwNP.
Th2, T helper 2; CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin.

Epithelial cells and mast cells exist in the nasal mucosa. Epithelial cells have IL-4Rα/IL-13Rα1, while mast cells have Fc epsilon receptor I (FcεRI) bound to IgE. Since dupilumab can bind to IL-4Rα on epithelial cells and IL-13 stimulates goblet cells to secrete mucus, one of the earliest changes after the administration of dupilumab is a decrease in mucus secretion and edema, which may be related to improvements in nasal obstruction and the sense of smell. Concerning the mechanisms behind the improvement of olfaction, understanding which cytokines play important roles in olfaction is crucial. Wu *et al.*[41] reported that an increase in IL-2, IL-5, IL-6, IL-10, and IL-13 in the mucus of the olfactory cleft was related to a decrease in olfactory identification scores in patients with chronic rhinosinusitis (CRS). Kim *et al.*[42] proposed that tumor necrosis factor-alpha and IL-5 promote apoptosis in olfactory sphere cells in a murine model of allergic rhinitis.[42] In addition, the number of immature olfactory neurons was decreased in the type 2/Th2-mediated allergic CRS mouse model, suggesting the effect of inflammation on olfactory neurogenesis.[43] In a transgenic mouse model in which IL-13 is inducibly expressed in the olfactory epithelium, a time-dependent neuronal loss was observed.[44] Since Th2 cells are the primary suppliers of IL-5 and IL-13, may play a role in olfactory neurogenesis, and are readily accessed by dupilumab in the blood vessels, the blockage of Th2 cells may be the primary mechanism of improvement in the sense of smell.

Furthermore, there are two different types of Th2 cells with distinct, independent roles: circulating Th2 cells cause perivascular inflammation and recruit eosinophils, while resident Th2 cells are known to activate airway eosinophils in asthma.[45] Since circulating Th2 cells are readily accessible by dupilumab, the recruitment of eosinophils is easily hindered by the administration of dupilumab. Naïve T cells are introduced via high endothelial venules and differentiate into Th2 cells in ectopic lymphoid tissue,[46] which may be accessible by dupilumab. This access may explain the superiority of dupilumab over other biologics in improving NPS.

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Omalizumab, a monoclonal antibody IgG1, inhibits free IgE and downregulates FcεRI, ultimately suppressing the inflammatory factors activated by basophils or mast cells.[47,48] Omalizumab directly affects basophils and B cells in the blood by blocking the binding of IgE to FcεRI and FcεRII, respectively, and inhibits further production of IgE,[49] resulting in a rapid response. Since IgE in the mucosa is supplied from the circulating blood, the formation of the omalizumab-IgE complex in the vascular space readily decreases this supply, but IgE already bound to FcεRI has a much longer half-life of about 70 days.[50] This may explain the response pattern of omalizumab, characterized by an early improvement of many endpoints after its administration, followed by a plateau from weeks 8–16 to weeks 28–36.[51] IgE in nasal polyps is locally produced through a cycle involving eosinophils and Th2 cells which may be difficult to control by systemic IgE blockage. As the local IgE supply declines over time along with a decrease in local inflammation, nasal polyps slowly decrease in size, and the reduction in polyp size may make it easier for omalizumab to function in nasal polyp tissue (**Fig. 3B**).

Mepolizumab and reslizumab target IL-5, and benralizumab targets IL-5Rα, regulating eosinophils, which play an important role in type 2 inflammation.[52] Since IL-5 plays a crucial role in the maturation and survival of eosinophils,[53] blockages of IL-5 by mepolizumab and reslizumab interrupt the inflammatory pathway involving eosinophils, whereas eosinophils already activated in nasal polyp tissues may be less affected by this change (**Fig. 3C**). Benralizumab reduces the blood eosinophil count via antibody-dependent cell-mediated cytotoxicity[54] and binding to IL-5Rα on eosinophil precursors.[55] Benralizumab may not directly affect activated eosinophils in nasal polyp tissue due to the downregulation of IL-5Rα and low accessibility, which may explain its poor improvement of NPS (7% at week 40) in CRSwNP. However, benralizumab effectively improves all clinical outcome measures in severe eosinophilic asthma,[56] which may be explained by the fact that airway tissue is well-vascularized and highly accessible by benralizumab.[57] In summary, the mechanistic effects of biologics targeting IL-5 and IL-5Rα on a systemic level result in an instant decrease in the eosinophil count after their administration, but clinical changes in nasal polyps take time to manifest. Although IL-5Rα on eosinophils and basophils is the primary target, the lack of access to activated eosinophils with the downregulated expression of IL-5Rα may be the reason why the dramatic decrease in the blood eosinophil count by more than 75% during the first 4 weeks[15] does not necessarily correlate with the clinical effects of biologics in CRSwNP.

FUTURE ROLE OF BIOLOGICS IN CRSwNP

Although biologicals have been recently introduced to treat CRSwNP, they have been used to treat other diseases for longer periods. Reviewing their disease-modifying effect on other diseases may provide helpful insights into their use for CRSwNP. A 3-year withdrawal follow-up study of omalizumab in adults with severe allergic asthma showed that 67% of patients reported improved or unchanged asthma three years after discontinuation of omalizumab.[58] An observational retrospective study in children and adults with severe allergic asthma demonstrated that 44% of patients reported no loss of asthma control after discontinuation of omalizumab.[59] In a recent open-label extension study of omalizumab in CRSwNP, all efficacy endpoints gradually worsened following the discontinuation of omalizumab after it had been administered for 52 weeks. Yet, these endpoints at 76 weeks after the first dosage were still better than the pretreatment levels.[51] As mentioned earlier, omalizumab binds to the FcεRI-binding site of free IgE, preventing its attachment to mast cells and basophils. This ultimately decreases the free IgE level and downregulates FcεRI expression.[50] One

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of the primary mechanisms of omalizumab is the downregulation of FcεRI in mast cells and basophils due to the reduced supply of free IgE. In addition, downregulated FcεRI in mast cells may require a substantial amount of time for restoration once IgE is resupplied. The mechanism of potential disease modification and long-term effects of omalizumab in CRSwNP need to be studied.

A treatment algorithm for CRSwNP places biologics as a last resort for uncontrolled, severe CRSwNP patients who do not respond to traditional medications or surgery. However, understanding the mechanism of each biologic on the local and systemic levels can assist in the development of a more personalized approach in choosing the type of biologics and timing of other interventions. For example, dupilumab may show early responses to hyposmia related to CRSwNP,[27] since dupilumab can work at the vascularized mucosa, such as olfactory epithelium, and inhibit the production of type 2 cytokines which impairs neural regeneration. In cases with large nasal polyps which are less responsive to biologics, surgical procedures or local drug injections into nasal polyps can be combined with the biologics to improve symptoms more effectively,[52,60] because they may complement biologics' disadvantage in having limited access to nasal polyps. The role of combined therapy of biologics and surgical procedures in CRSwNP needs to be investigated in the future.

CONCLUSION

The role of biologics in treating severe CRSwNP has been demonstrated in numerous studies, as biologics can decrease nasal polyp size, improve the overall quality of life by enhancing olfaction and resolving nasal obstruction, and reduce the use of systemic corticosteroids. Understanding the pathomechanisms of CRSwNP on the local and systemic levels and the role of biologics at each level can facilitate the interpretation of clinical outcomes, *i.e.*, the more significant improvement rate in NCS than NPS, and the rapid improvement of olfaction after the administration of dupilumab. These findings will hopefully provide insights for the development of personalized treatments, allowing the selection of specific types of biologics based on an individual's symptoms and endoscopic or radiologic findings. In addition, biological agents may have the potential for disease modification or long-term effects in CRSwNP. As more studies are conducted in the near future, we hope for an international consensus guideline on the use of individual biological agents in CRSwNP.

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