

# Potential of biologics to alter the need for repeated surgery in patients with chronic rhinosinusitis with nasal polyps

Chronic rhinosinusitis with nasal polyps (CRSwN P) is a common disease associated with high clinical and socioeconomic burden. At present, clinicians are still short of curative treatment for CRSwNP, and more than 15–20% of patients are poorly controlled and undergo multiple revision surgeries.<sup>1</sup> It is generally accepted that endoscopic sinus surgery (ESS) cannot control the underlying inflammation. Furthermore, repeated surgeries often result in higher risk of surgical complications, diminishing success rates, and permanent scarring.<sup>2</sup> Reported complication rates of surgical intervention for CRS varied significantly, from 1.8 to 14.3%,<sup>3,4</sup> with epistaxis being most common. Although constituting <1%,<sup>4</sup> severe complications can lead to devastating results including vision impairment or even death.

Recently, therapeutic biologics that directly target fundamental type 2 inflammation have shown potential to minimize the need for repeated surgeries with an acceptable safety profile. A phase III study of mepolizumab, an anti-interleukin-5 (IL-5) antibody (SYNAPSE<sup>5</sup>), exclusively enrolled patients with CRSwNP who had undergone at least one prior sinus surgery and were in need of revision surgery. Compared with placebo, mepolizumab not only improved the total endoscopic nasal polyp score (NPS) and nasal obstruction Visual Analogue Scale (VAS) score from baseline but also significantly reduced the risk of and requirement for surgery. In an in-depth analysis of both actual and scheduled sinus surgeries, Fokkens et al.<sup>6</sup> reported that 9% ( $n = 18/206$ ) of mepolizumab-treated and 23% ( $n = 46/201$ ) of placebo-treated patients underwent  $\geq 1$  ESS during the 52-week study period. Moreover, the proportions of patients on the waiting list for ESS were 16% ( $n = 33/206$ ) and 30% ( $n = 60/210$ ) in each arm.

The original SYNAPSE<sup>5</sup> investigation demonstrated that 72% of patients in the mepolizumab group no longer needed surgery at the end of the study, versus 51% in the control group. However, the need for surgery was based on the achievement of an NPS  $\leq 4$  ( $\leq 2$  for each nostril) and an overall symptom VAS score  $\leq 7$  or an improvement of at least the minimal clinically important difference ( $>8.9$  points) in the Sino-Nasal Outcome Test (SNOT-22) score. These definitions have not been fully validated in the real-world treatment of CRSwNP. Moreover, clinicians have raised several questions regarding the relationship between surgery and biologics.

First, the criteria used to define non-response and the need for systemic corticosteroids/surgery have not been clearly delineated.

Decisions to treat with additional systemic corticosteroids or switch to surgery are influenced by many subjective factors other than treatment failure, including surgeon preference, patient desire, treatment availability, and comorbidities. Although oral corticosteroids (OCS) are effective in the treatment of nasal polyps, there is no consensus regarding the indications, timing, dosage, time course, and safety of their administration. Therefore, evidence-based guidelines for the use of OCS in patients with CRSwNP considering relapse frequency, side effects, and contraindications remain necessary.

As proposed by the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA<sup>7</sup>) and the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020<sup>8</sup>), biologics are indicated for patients with previous sinus surgery. However, phase III studies of the anti-IL-4R $\alpha$  antibody dupilumab (SINUS<sup>9</sup>) and the anti-IgE antibody omalizumab (POLYP<sup>10</sup>) have demonstrated that patients without previous surgery (37% in SINUS and 40% in POLYP) may also benefit from biologics. Although ESS aids in sinus drainage and releases trapped mucin, repeated surgeries are associated with diminished success. Future studies should aim to determine whether sequential ESS and biological treatment can improve the treatment response. In their post hoc analysis according to time since the last surgery, Fokkens et al.<sup>6</sup> observed that patients who underwent sinus surgery during SYNAPSE had a history of more frequent surgeries. In a phase III study of benralizumab, an anti-IL-5 receptor antibody (OSTRO<sup>11</sup>), although the treatment effect was greater in patients with a history of two prior surgeries than in those with one or no prior surgeries, the trend did not continue in patients with more than two prior surgeries. However, the context of the previous surgery (e.g., polypectomy/ESS/extended surgery) was not considered.

Analyzing the baseline characteristics of patients undergoing surgery during biological treatment may also shed light on markers of reduced responsiveness. In contrast to its verified role in predicting the clinical response in patients with asthma, the relevance of baseline blood eosinophil count (BEC) to CRSwNP remains controversial. Subgroup analyses in SYNAPSE suggested that the efficacy of mepolizumab was higher in those with a higher baseline BEC.<sup>5</sup> However, there were no significant differences in baseline BEC between patients with and without ESS during the study.<sup>6</sup> Dupilumab significantly improves NPS, nasal congestion scores, and CT scores in patients with severe CRSwNP, irrespective of blood eosinophil

status, indicating that blood eosinophil levels may not be a suitable biomarker for dupilumab efficacy.<sup>12</sup> Tissue eosinophil aggregates are strongly associated with the type 2 inflammation underlying CRSwNP, are correlated with increased postoperative prednisone requirements, and can serve as a predictor of polyp recurrence.<sup>13</sup> Several type 2 biomarkers including IgE, cystatin SN, and bone morphogenetic protein have been associated with tissue eosinophil aggregates and postoperative recurrence. Thus, the roles of these markers as predictors of the biological treatment response require further investigation.

There is also a need to define the symptom domains beyond nasal congestion that can be effectively relieved using biologics. In a retrospective matched cohort study comparing dupilumab with ESS in patients with CRSwNP, ESS reduced NPS more efficiently, while dupilumab more effectively improved olfaction and multiple extra-nasal symptoms.<sup>14</sup> These results suggest that the patient's major symptoms may influence the preference for surgery or biologics.

Finally, the future application and positioning of biologics in CRS treatment relies heavily on cost-effectiveness. In a study comparing the incremental cost per quality-adjusted life-year calculated from SNOT-22 scores, ESS was more cost-effective than dupilumab.<sup>15</sup> Notably, both the direct and indirect costs of care in the surgical treatment arm, as well as the benefits of improved comorbidities in the dupilumab arm, were underestimated. As continued treatment is necessary to maintain benefits, the cost of biologics will accumulate, even when the interval between treatments can be prolonged following disease control. According to the in-depth analysis by Fokkens et al.,<sup>6</sup> the 52-week treatment of mepolizumab resulted in 55 reduced surgeries (including cases on the waiting list), which would save approximately 550,000 US dollar.<sup>16</sup> However, in real-world, the overall cost of mepolizumab would be more than 3 million US dollar for this group of patients. Considering current price and dosage, it is less likely that biologics will become cost-effective soon. Instead, we might try different approaches to optimize the use of biologic therapy, such as looking for biomarkers that can predict treatment responsiveness, increasing dosing intervals gradually, or using biologics temporarily as rescue medication.

The study by Fokkens et al.<sup>6</sup> enriches our awareness that biologics can exempt certain subpopulations of patients with CRSwNP from repeated surgeries. Nonetheless, the relationship between biologics and surgery requires further investigation in long-term and real-world studies with clearly defined criteria for surgical eligibility. Prospective analyses of possible biomarkers will contribute to improved patient selection, clinical decision-making, and outcome prediction. Studies exploring administration of biologics in combination with surgery will undoubtedly improve cost-effectiveness and decrease surgical weight in the treatment of uncontrolled CRSwNP.

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## CONFLICT OF INTEREST

All authors declare no financial or commercial conflicts of interest.

Mu Xian<sup>1</sup> 

Luo Zhang<sup>1,2</sup> 

<sup>1</sup>Department of Otolaryngology, Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing, China

<sup>2</sup>Beijing Key Laboratory of Nasal Diseases, Beijing Institute of Otolaryngology, Beijing, China

## Correspondence

Luo Zhang, Department of Otolaryngology, Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, No. 1, DongJiaoMinXiang, DongCheng District, Beijing 100730, China.

Email: [dr.luozhang@139.com](mailto:dr.luozhang@139.com)

## ORCID

Mu Xian  <https://orcid.org/0000-0003-4153-6314>

Luo Zhang  <https://orcid.org/0000-0002-0910-9884>

## REFERENCES

- Smith KA, Orlandi RR, Oakley G, Meeks H, Curtin K, Alt JA. Long-term revision rates for endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2019;9(4):402-408.
- 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.
- Rimmer J, Fokkens W, Chong LY, Hopkins C. Surgical versus medical interventions for chronic rhinosinusitis with nasal polyps. *Cochrane Database Syst Rev*. 2014;12:CD006991.
- Lund VJ, Wright A, Yiotakis J. Complications and medicolegal aspects of endoscopic sinus surgery. *JR Soc Med*. 1997;90(8):422-428.
- 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.
- Fokkens WJ, Mullol J, Kennedy D, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): in-depth sinus surgery analysis. *Allergy*. 2023;78:812-821. doi:10.1111/all.15434
- Bachert C, Han JK, Wagenmann M, 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(1):29-36.
- Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020;58(Suppl S29):1-464.
- 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.
10. 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.
  11. 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*. 2022;149(4):1309-1317 e1312.
  12. Fujieda S, Matsune S, Takeno S, et al. Dupilumab efficacy in chronic rhinosinusitis with nasal polyps from SINUS-52 is unaffected by eosinophilic status. *Allergy*. 2022;77(1):186-196.
  13. Lou H, Meng Y, Piao Y, Wang C, Zhang L, Bachert C. Predictive significance of tissue eosinophilia for nasal polyp recurrence in the Chinese population. *Am J Rhinol Allergy*. 2015;29(5):350-356.
  14. Dharmarajan H, Falade O, Lee SE, Wang EW. Outcomes of dupilumab treatment versus endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol*. 2021;12:986-995.
  15. Parasher AK, Gliksman M, Segarra D, Lin T, Rudmik L, Quast T. Economic evaluation of dupilumab versus endoscopic sinus surgery for the treatment of chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol*. 2022;12(6):813-820.
  16. Smith KA, Orlandi RR, Rudmik L. Cost of adult chronic rhinosinusitis: a systematic review. *Laryngoscope*. 2015;125(7):1547-1556.