

Mepolizumab for chronic rhinosinusitis with nasal polyps

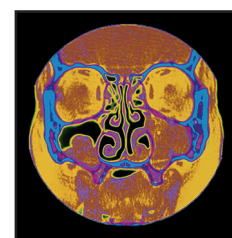


Chronic rhinosinusitis with nasal polyps affects 3% of the adult population and elicits symptoms of nasal obstruction, nasal secretions, facial pressure, and loss of smell, ultimately impairing health-related quality of life.¹ Chronic rhinosinusitis with nasal polyps is a heterogeneous disease associated with different inflammatory endotypes, most frequently causing eosinophilic inflammation, but also resulting in neutrophilic and mixed granulocytic inflammation of the upper airways.^{1,2} The standard of care for patients with chronic rhinosinusitis with nasal polyps includes intranasal corticosteroids, short courses of oral corticosteroids, and nasal surgery (eg, functional endoscopic sinus surgery and polypectomy). However, nasal surgery might induce mucosal damage and scarring, and is associated with high recurrence rates. Therefore, there is a high medical need for novel therapies that improve symptoms and quality of life of patients with chronic rhinosinusitis with nasal polyps and reduce the need for oral corticosteroids and surgery. In patients with a high degree of type 2 inflammation, chronic rhinosinusitis with nasal polyps tends to be more severe, recurrent, and frequently associated with late-onset eosinophilic severe asthma and respiratory disease exacerbated by nonsteroidal anti-inflammatory drugs, necessitating a holistic approach by ear, nose, and throat specialists and pulmonologists to treat this airway disease in the optimal way.³

Joseph Han and colleagues⁴ report the results of a phase 3 SYNAPSE study of mepolizumab in patients with chronic rhinosinusitis with nasal polyps. Mepolizumab is a monoclonal antibody blocking interleukin (IL)-5, a type 2 cytokine, which promotes the proliferation and differentiation of eosinophils in the bone marrow, prolongs eosinophil survival in mucosal tissues, and activates eosinophils to release toxic granules and cysteinyl leukotrienes.⁵ Because nasal polyps are often characterised by eosinophilic inflammation, Han and colleagues investigated the efficacy and safety of mepolizumab, an anti-IL-5 biological treatment, in patients with recurrent, severe, chronic rhinosinusitis with nasal polyps who were eligible for repeat nasal surgery. All patients had at least one nasal surgery in the past 10 years, before entry into the SYNAPSE study, implicating that the disease was refractory to medical and surgical treatment.

Mepolizumab 100mg (n=206) or placebo (n=201) were administered subcutaneously once every 4 weeks, in addition to standard of care, for 52 weeks. Mepolizumab significantly improved total endoscopic nasal polyp score at week 52 (adjusted difference in medians -0.73, 95% CI -1.11 to -0.34; $p<0.0001$) and nasal obstruction visual analogue scale (VAS) score during weeks 49–52 (-3.14, -4.09 to -2.18; $p<0.0001$), the two coprimary endpoints. Importantly, mepolizumab versus placebo significantly reduced oral corticosteroids use (52 [25%] vs 74 [37%] patients; odds ratio 0.58, 95% CI 0.36–0.92; $p=0.020$) and nasal surgery (18 [9%] vs 46 [23%] patients; hazard ratio 0.43, 0.25–0.76; $p=0.0032$) during the 52-week treatment. Additionally, quality of life (measured by the Sino-Nasal Outcome Test-22 [SNOT-22]), overall symptom VAS score, and loss of smell VAS score, also significantly improved in patients treated with mepolizumab. Serious adverse events occurred in 12 (6%) patients receiving mepolizumab and 13 (6%) receiving placebo; none were considered treatment-related, highlighting the safety of mepolizumab.

The SYNAPSE study⁴ has several strengths. First, the randomised, double-blind, placebo-controlled, multicentre study design is the gold standard to assess efficacy and safety of novel treatments. Second, images of endoscopies at each visit were sent to central laboratories and the endoscopic nasal polyp score was assessed by independent masked reviewers. However, several key research questions still need to be addressed. First, although the coprimary endpoints were statistically significant, these moderate changes might not be clinically relevant. Therefore, the nasal polyp scientific community needs to determine the minimal clinically important difference for these outcomes. Second, only 50% of patients who received mepolizumab had 1-point or higher improvement in nasal polyp score, implicating the need for predictors of response to mepolizumab in patients with chronic rhinosinusitis with nasal polyps. Subgroup analyses of the SYNAPSE study suggest that the efficacy of mepolizumab is higher with higher baseline blood eosinophil count. Similarly, in patients with severe eosinophilic asthma, blood eosinophil count is a well established biomarker for predicting the therapeutic response to mepolizumab.^{6,7} A thorough investigation



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of previously resected nasal polyp tissue to check for eosinophilic inflammation and IL-5 amounts might help to target mepolizumab treatment to those patients who will benefit the most.

Besides mepolizumab, the anti-IgE antibody omalizumab and the anti-IL-4 receptor α antibody dupilumab have been shown to be efficacious and safe in patients with chronic rhinosinusitis with nasal polyps by reducing nasal polyps size and improving symptoms.^{8,9} Although similar endpoints were used in the studies with dupilumab, omalizumab, and mepolizumab, the study designs differ substantially and any solid conclusions on indirect comparisons cannot be made. Nevertheless, mepolizumab and omalizumab seem to reduce nasal polyp size with the same efficacy, whereas dupilumab might be better. Although, all three biological treatments improve quality of life (SNOT-22) to a similar degree. Dupilumab also reduced oral corticosteroid use and the need for nasal surgery; thus, there is a need for pragmatic trials comparing the efficacy of mepolizumab, omalizumab, and dupilumab in patients with chronic rhinosinusitis with nasal polyps or severe eosinophilic asthma, or both; which will pave the way to precision medicine in type 2 airway diseases.

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