

Mepolizumab for eosinophilic chronic rhinosinusitis, loss of smell and challenges with accessibility to allergen immunotherapy

In this month's editorial, we discuss three very interesting studies selected by the Editors of the journal. The first article describes how mepolizumab decreases tissue eosinophils while increasing type 2 cytokines in eosinophilic chronic rhinosinusitis.¹

Chronic rhinosinusitis (CRS) is a heterogeneous chronic inflammatory disease of the upper airways that often have a profound deleterious effect on the quality of life (QoL) of patients.² Moreover, it has a significant societal and economic burden. CRS comprises several disease variants that can be classified by endotype dominance into type 2 or non-type 2.³

The type 2 inflammation in CRS is driven by type 2 innate lymphoid (ILC2) cells, type 2 T helper (Th2) cells and cytokines, including interleukin (IL)-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4 and IL-13 working sequentially and synergistically to recruit eosinophils to sinonasal tissue.^{4,5} Walter et al. evaluated the local effect of mepolizumab,⁵ a humanized IgG1 monoclonal antibody (mAb) with neutralizing capacity for IL-5, to prevent recruitment of eosinophils and promote T2 responses in sinonasal tissue of eosinophilic CRS patients. They recruited well-characterized patients with chronic eosinophilic rhinosinusitis in a prospective phase 2 clinical trial. Study participants received 100mg mepolizumab subcutaneously at 4-week intervals for 24 weeks. Tissue eosinophil counts, eosinophil degranulation and cytokine levels were evaluated in ethmoid sinus tissue biopsies collected at baseline and Weeks 4, 8, 16 and 24. The study's findings revealed that sinonasal tissue eosinophil counts decreased after 24 weeks of treatment with mepolizumab. However, eosinophil degranulation remained unchanged, and type 2 cytokine levels increased in sinonasal tissue for IL-5, IL-13 and GM-CSF. The overall finding of this study underscores why the anti-IL-5 strategy in CRS has only a partial treatment response (Figure 1).

The second article in this month's Clinical & Experimental Allergy issue discusses how the loss of smell in patients with aspirin-exacerbated respiratory disease (AERD) impacts mental health and QoL.⁶ The impact of the loss of smell, also known as anosmia, on the QoL of patients with AERD⁷ is not well-characterized. Tchekmedyan and colleagues assessed how the severity of smell loss and olfactory dysfunction (OD) in patients with AERD affects

their QoL, mental health and physical well-being. The authors used five validated QoL questionnaires (Sinonasal Outcome Test-22, Asthma Control Test, Healthy Days Core Module-4, Short Form-36 and Patient Health Questionnaire-4) and two newly developed questionnaires assessing the severity and consequences of OD were electronically sent to all 2913 patients in the Brigham and Women's Hospital AERD registry. Eight hundred fifty-three participants responded and were included in the overall analysis. Eighty-five percent of participants reported a reduced sense of smell and taste, and 30% categorized their OD severity as "as bad as it can be." There were significant relationships between the severity of self-reported OD and both psychological distress and general health scores, even after adjusting for asthma control. The incidence rates for physically and mentally unhealthy days in the prior month were higher for patients with moderate or severe OD than for normosmic patients. Patients with diminished smell responded that they could not identify spoiled food, did not enjoy food, felt unsafe and had encountered dangerous situations as consequences of their OD (Figure 2).

Our final Editors in Chief article for this issue evaluated patient care with allergen immunotherapy for allergic respiratory diseases in Germany. Allergen immunotherapy (AIT) represents the only disease-modifying therapeutic option for allergic respiratory illnesses. Despite being the standard of care, the authors report that AIT is offered to a limited number of patients in Germany, who have specific characteristics.

Valbert et al.^{8,9} evaluated 2505 insured patients with documented allergic respiratory disease in one of the most extensive statutory health insurances in Germany, "DAK-Gesundheit." Patient characteristics, predictors of being offered AIT, predictors of receiving AIT and predictors of guideline-compliant care were evaluated. Predictors of being offered AIT included allergy to tree pollen and native speaking, whereas those with non-German citizenship or lower educational attainment were less likely to be offered AIT. Receiving AIT was associated with tree pollen allergy and male sex, whereas smokers, non-German citizens and those with only allergic asthma were less likely to receive AIT. This study highlights important issues of equity in access to AIT care in Germany.

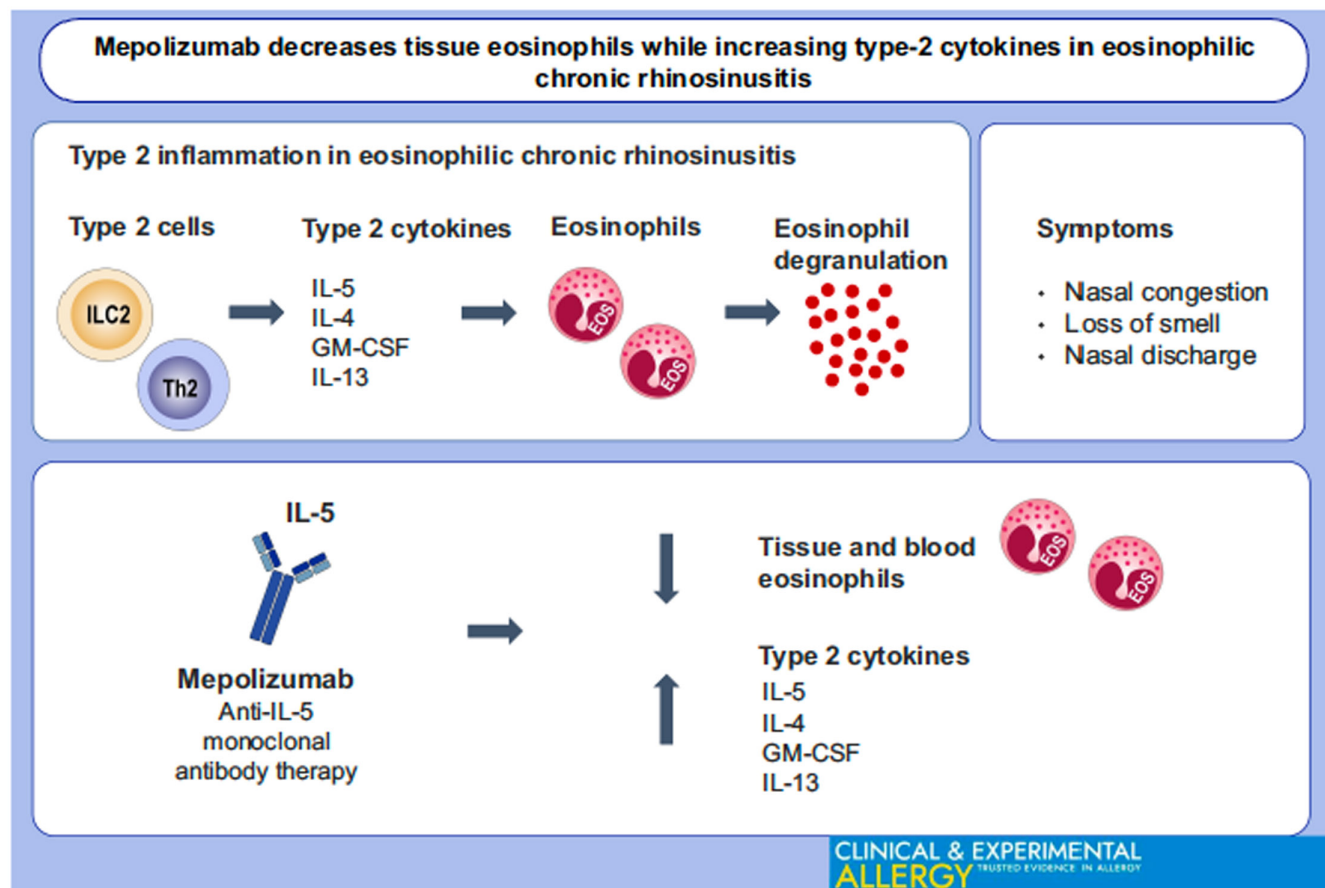


FIGURE 1 Eosinophilic chronic rhinosinusitis represents a type 2 inflammatory condition, which is often treatment resistant. Following treatment with mepolizumab in patients with eosinophilic chronic rhinosinusitis, sinonasal eosinophil counts decreased. Concentrations of type 2 cytokines were increased after treatment with mepolizumab. The findings suggest that mepolizumab's effectiveness in eosinophilic chronic rhinosinusitis appears to reflect its ability to decrease tissue eosinophil numbers, while the increase in type 2 cytokines may explain incomplete drug response. Adapted from reference¹

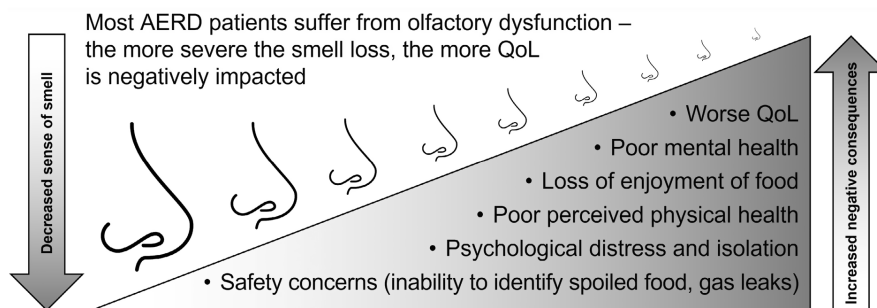


FIGURE 2 Survey responses from 853 patients with AERD demonstrate that most report diminished sense of smell/taste and 30% categorize it as a severe problem. The severity of olfactory dysfunction correlates with more psychological distress, worse general health scores and increased negative consequences on quality of life. The relevance of smell loss to patients' quality of life, and the safety concerns that may result from it, should be acknowledged and evaluated by clinicians caring for these patients. Adapted from reference⁷

Mohamed H. Shamji^{1,2}

Robert J. Boyle¹

Correspondence

Mohamed H. Shamji, Immunomodulation and Tolerance Group, Allergy & Clinical Immunology, Inflammation, Repair and Development, National Heart and Lung Institute, Faculty of Medicine, Imperial College London, London SW7 2AZ, UK.

Email: m.shamji@imperial.ac.uk

¹National Heart and Lung Institute, Imperial College London, London, UK

²NIHR Imperial Biomedical Research Centre, London, UK

REFERENCES

1. Walter S, Ho J, Alvarado R, et al. Mepolizumab decreases tissue eosinophils while increasing type-2 cytokines in eosinophilic chronic rhinosinusitis. *Clin Exp Allergy*. 2022. doi:10.1111/cea.14152
2. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020;58(Suppl S29):1-464. doi:10.4193/Rhin20.600
3. 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. doi:10.1111/all.13411
4. Shah SA, Ishinaga H, Takeuchi K. Pathogenesis of eosinophilic chronic rhinosinusitis. *J Inflamm (Lond)*. 2016;13:11. doi:10.1186/s12950-016-0121-8
5. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189-1197. doi:10.1056/NEJMoa1403291
6. Lee RU, Stevenson DD. Aspirin-exacerbated respiratory disease: evaluation and management. *Allergy Asthma Immunol Res*. 2011;3(1):3-10. doi:10.4168/aa.2011.3.1.3
7. Tchekmedyian R, Lundberg M, Buchheit KM, et al. Loss of smell in patients with aspirin-exacerbated respiratory disease impacts mental health and quality of life. *Clin Exp Allergy*. 2022. doi:10.1111/cea.14157
8. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. 2015;136(3):556-568. doi:10.1016/j.jaci.2015.04.047
9. Valbert F, Neusser S, Pfaar O, et al. Care with allergen immunotherapy for allergic respiratory diseases in Germany-predictors and deficits. *Clin Exp Allergy*. 2022. doi:10.1111/cea.14172