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Reconsidering biologic treatment recommendations for CRSwNP without asthma in EUFOREA guidelines

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Dear Editor:

The recently published EUFOREA pocket guide "Biologics in Upper and Lower Airway Diseases" summarises recommendations on the use of biologics in chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma [(1)] and offers advice on biologic choice for practicing clinicians. The creation of this pocket guide, in the absence of any head-to-head studies at that time, drew on expert opinions and published indirect treatment comparison (ITC) approaches [(2,3)]. It makes a single recommendation for a preferred biologic, in patients affected by CRSwNP, without concomitant asthma (apart from specific cases such as pregnancy), whilst offering different options in asthma endotypes and phenotypes. We wish to draw the attention of the readership to some additional considerations relating to biologic choice for these diseases and how they are classified.

It is well recognised that network analysis, such as ITCs, inherently warrant some caution in interpretation [(4)], due to study differences in heterogeneity of patient populations and approaches to data handling. This has relevance to conclusions drawn regarding biologic use in CRSwNP. Mepolizumab in its registration randomised controlled trial (RCT) in CRSwNP (SYNAPSE study, NCT03085797), met all its primary and secondary endpoints, significantly reducing nasal polyp size and nasal blockage score, whilst improving quality of life (Sino-Nasal Outcome Test-22 score) and other patient-reported outcomes, such as sense of smell [(5)]. The SYNAPSE study is, however, recognised to focus on a patient population that has more severe, refractory disease than that in the dupilumab registration trials (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52) [(6)]. As such, the dupilumab versus mepolizumab ITC [(2)] or the extended network meta-analysis comparison [(3)] are not comparing like-for-like and these statistical approaches should not be considered reliable grounds for recommending one treatment over another. All current licensed biologic therapies demonstrate efficacy in clinical practice [(7)]; there remains a need to better understand outcome heterogeneity and predictive response determinants which will not be forthcoming if use is restricted. Additional comparator studies, such as the EVEREST trial of dupilumab versus omalizumab [(8)], are required.

Mepolizumab targets interleukin (IL)-5, a pivotal type 2 (T2) cytokine influencing not only eosinophils but also epithelial cells, plasma cells, fibroblasts and mast cells [(9)]. Classifying dupilumab and tezepelumab as 'anti-T2' while labelling mepolizumab as merely 'anti-eosinophil' oversimplifies established disease biology and misrepresents the interconnected role and co-existent presence of T2 cytokines. These are often co-elevated in disease, with serum IL-5 levels correlating with elevated levels of IL-4, IL-13 and thymic stromal lymphopoietin [(10)]. The central role of IL-5 in the exaggerated tissue damage/repair response in chronic T2

disease is also evidenced by the reversal of airway remodelling in asthma with mepolizumab [11]. There is also evidence from the reverse perspective, with mepolizumab having a persistent benefit in improving patient outcomes despite therapy discontinuation in the RCT follow-up analysis [12], consistent with it having modified a key underlying pathological process in CRSwNP. As such studies are needed to understand if treatment is optimally used to improve severe disease once established or potentially applicable as adjunctive therapy to prevent disease recurrence after surgery or to stop progression in those with early post-surgical recurrence.

In summary, restricting the advice to a single biologic, in the absence of appropriately conducted head-to-head studies or long-term real-world outcomes, may limit patient options, undermine the ability to personalise care and constrain advances in treatment understanding. Although the EUFOREA pocket guide provides a valuable resource for practicing clinicians and we understand that regular updates are expected to reflect the fast-evolving therapeutic landscape, we feel that it is premature at present to restrict the recommendations on biologic choice in CRSwNP.

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Abbreviations

CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin; ITC, indirect treatment comparison; RCT, randomised controlled trial; T2, type 2; TSLP, thymic stromal lymphopoietin.

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All authors contributed to data interpretation, reviewed and revised the manuscript critically for important intellectual content, agreed to submit to Rhinology, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Conflict of interest

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