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RESEARCH LETTER

Dupilumab in Chronic Rhinosinusitis With Nasal Polyps Patients: Impact on Tissue Eosinophilic Inflammation and Eosinophil Subphenotypes

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To the Editor,
Dupilumab is an IgG4 mAb, targeting the IL-4Rα chain and inhibiting the biological effects of both cytokines IL-4 and IL-13. In clinical trials, it has been demonstrated to be effective in reducing nasal polyp size and CRSwNP symptoms, with a good safety profile [1].

Here, we investigated dupilumab's effects on blood and tissue inflammatory cells, including eosinophil subpopulations and the relationship between such modifications and the clinical outcomes in 30 dupilumab-treated CRSwNP patients. For detailed methods, all demographic and clinical data, as well as additional experimental data not shown in Figure 1, see online repository (https://doi.org/10.5281/zenodo.19236051).

In our cohort, at the follow-up ENT visit (range 3–41 months), a statistically significant improvement of median SNOT-22, NPS, modified Lund-Kennedy (mL-K) score and Sniffin' sticks test was observed. More importantly, 10 patients (33.3%) showed a complete disappearance of polyps (NPS = 0). A positive correlation between the number of dupilumab administrations and the modification of NPS, mL-K, SST-16 scores, but not SNOT-22, was found. Patients with NPS = 0 had significantly longer treatment duration [23 (IQR 23) months] compared to those with residual nasal polyps [8.5 (IQR 8); $p < 0.01$]. The importance of dupilumab treatment duration and polyp disappearance was confirmed by the ROC analysis, showing an 80% probability of achieving NPS = 0 after 11.5 months of treatment (Figure 1A).

Histological analysis in 20 patients with residual NP, demonstrated a marked reduction of median tissue eosinophil number [17.8 (IQR 26.1) vs. 4.3 (IQR 5.6) cells/hpf, $p < 0.0005$] (Figure 1B). the total number of NP tissue eosinophils correlated with NPS and mL-K, but not with SNOT-22 and SST-16. A no significant increase in tissue neutrophils was noted, with a certain heterogeneity within the cohort. No differences in both goblet cells hyperplasia and sub-epithelial oedema score were observed, probably due to low values of these parameters at baseline.

Recent research described different eosinophil subtypes, called resident (rEos) and inflammatory eosinophils (iEos), according to the surface expression of CD62L [2, 3]. In our analysis at baseline, the percentage and absolute value of tissue iEos positively correlated with SNOT-22 ($p < 0.05$), NPS ($p < 0.05$), mL-K score ($p < 0.01$), but not SST-16. A significant reduction of tissue iEos after dupilumab treatment was observed (Figure 1B). Notably, the more the reduction of NP tissue iEos after dupilumab treatment (delta Δ iEos cells), the better the improvement of clinical outcomes expressed by Δ NPS, Δ mL-K score and Δ SST-16 score. Notably, no significant correlation between total tissue eosinophils' reduction and the degree of the improvement of clinical outcomes was found (Figure 1D).

Alessandra Vultaggio and Matteo Accinno contributed equally to this work as co-first authors.
Giandomenico Maggiore and Andrea Matucci contributed equally to this work as co-last authors.

Summary

- Dupilumab reduces tissue eosinophils in nasal polyps beyond improving clinical and endoscopic outcomes.
- Dupilumab treatment is associated with a reduction of tissue inflammatory eosinophils that correlates with higher clinical and endoscopic improvement.

Our data appear of great interest in demonstrating the effects of dupilumab on upper airway eosinophilic inflammation. This effect can be attributed to the reduced expression of adhesion molecules on endothelial cells after blocking IL-4/IL-13 signalling. Anyway, considering the crucial role for IL-4 in Th2 cells differentiation [4], the reduction of tissue eos can be attributed also to the capacity of dupilumab to modulate the full type 2 immunity with reduction of type 2 cytokines release, such as IL-3, IL-5 and GM-CSF, involved in eosinophil biology during their lifespan. The progressive reduction of serum total IgE described in dupilumab-treated patients additionally supports the immunomodulation of type 2 immune response operated by dupilumab [5]. In the current study we demonstrate, for the first time to our best knowledge, that dupilumab reduces iEos in NP tissue; additionally, iEos in tissue appear to be a more suitable marker than total tissue eosinophils, considering that the latter does not correlate with both SNOT-22 and SST-16. This takes on greater importance as the clinical and endoscopic outcomes improvement paralleled the reduction of iEos, but not total tissue eosinophils.

In agreement with other studies [6, 7], one third of our patients experienced a complete disappearance of polyps. Although the dupilumab treatment improves symptoms within 4 days of starting treatment [8], the relationship between treatment duration and endoscopic resolution we observed underpins the

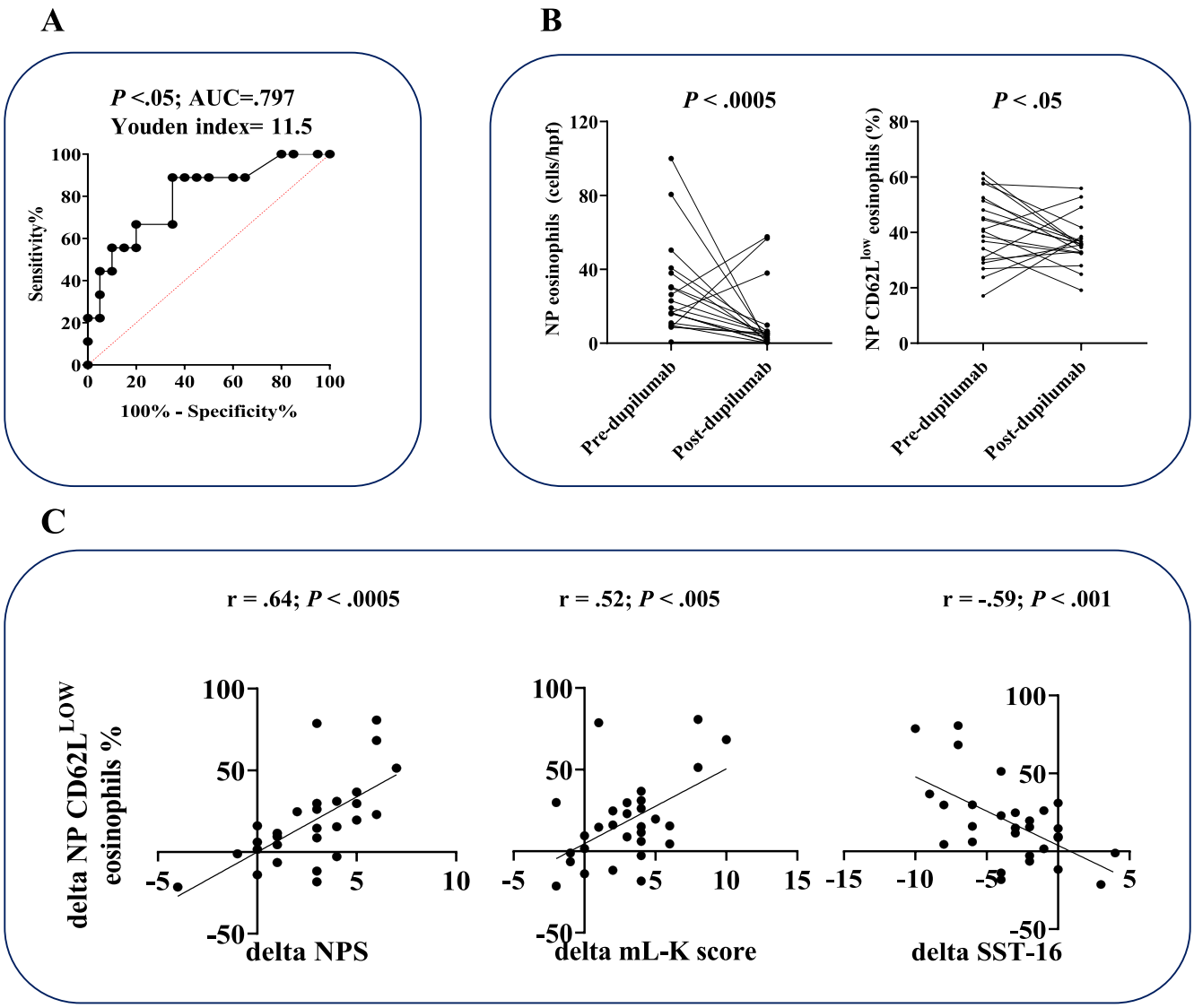

FIGURE 1 | (A) Treatment duration in patients with ($n = 10$) or without ($n = 20$) complete disappearance of nasal polyps (NPS = 0); ROC analysis performed according to CRSwNP remission (NPS = 0 vs. NPS > 0) after dupilumab treatment; (B) total tissue eosinophils, expressed as cells/hpf, and tissue CD62L^{low} inflammatory eosinophils percentage before and after dupilumab treatment ($n = 20$ patients); (C) analysis of the correlation between changes in the percentage of tissue CD62L^{low} eosinophils and the improvement of clinical and endoscopic scores of CRSwNP (delta NPS, delta mL-K, delta SST-16).

importance of prolonging treatment to reach the highest possible positive effect, even if SNOT-22 improvement occurred earlier, regardless of treatment duration. However, due to the limited number of patients, this exploratory analysis should be interpreted with caution.

Additional research would be desirable to better define the pathophysiological mechanisms, leading to incomplete NP disappearance, that can be observed in a proportion of patients, also after a long-lasting treatment, regardless of clinical symptom improvement, including olfactory dysfunction.

Some limitations of this study must be acknowledged. This is a single-centre retrospective study in a limited number of patients. The different treatment durations of our patients and the lack of a control group may represent further limitations. Finally, tissue analysis is limited to cell infiltration, globet cells and stroma characteristics. Considering that preliminary evidence from 3D spheroid cultures suggests that dupilumab treatment may improve epithelial organization in CRSwNP [9], more analysis are needed to deep into the tissue recovery after dupilumab treatment, including the evaluation of tissue cytokine expression, epithelial damage and tissue remodelling quantification.

Author Contributions

A.M., A.V., M.A., G.M., M.D., M.E.M., P.O., G.I., O.R., L.C., A.P., C.A., E.M.: acquisition of data. A.V., A.M., M.A., E.V.M.E.M.: conception and design. A.V., A.M., M.A., E.V.E.M.: analysis and interpretation. A.V., A.M., M.A., E.V., M.D. M.E.M.: manuscript writing. A.M., M.A., M.D., E.V., L.C., M.E.M., O.R., A.V.: approval and editing of the manuscript. A.V. and M.A. equally contributed to the article.

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Conflicts of Interest

A.M. received a fee for advisory board and speaker for GSK, Sanofi, Novartis, Astra Zeneca, CSL Boerhing Chiesi, Takeda; A.V. received a fee for advisory board and speaker for GSK, Sanofi, Novartis, AstraZeneca, Chiesi. O.R. received a fee for advisory board and speaker for GSK, Sanofi, Novartis, NOOS, Recordati, ALK-Abello; L.C. received a fee for advisory board and speaker for GSK, Novartis, ALK-Abello; G.D.M. received a fee as speaker for Sanofi, GSK, Novartis. P.P. received a fee as speaker for GSK, Novartis, Leopharma. The rest of the authors declare they have no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Zenodo at https://doi.org/10.5281/zenodo.19236051, reference number 19236051.

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