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Comment on: Eosinophilic granulomatosis with polyangiitis across the eosinophilic spectrum: from molecular mechanisms to practical differential diagnosis and targeted therapy

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Dear Editor,

We read with interest the recently published article in *Reumatologia* addressing eosinophilic granulomatosis with polyangiitis (EGPA), which provides a comprehensive overview of current concepts in disease mechanisms, diagnostic complexity, and evolving therapeutic approaches, including biologic therapies [1]. The authors underscore the heterogeneity of EGPA, a feature that is increasingly recognized as central to understanding both disease biology and treatment response.

This work underscores complexity by placing EGPA within a group of eosinophilic disorders, reflecting overlapping distinct pathomechanisms rather than a single, homogeneous entity [2, 3]. Eosinophilic granulomatosis with polyangiitis ranges from mainly eosinophil-driven inflammation to immune-mediated vasculitis, with variability in anti-neutrophil cytoplasmic antibody status and organ involvement [2, 4].

Therefore, eosinophils are not only effector cells but also active in immune regulation. By releasing cytotoxic granules and cytokines and by interacting with endothelial and immune cells, they influence tissue inflammation and systemic immune responses [5]. This understanding implies that therapies targeting eosinophils should be selected based on their specific molecular mechanisms, rather than being grouped under one pharmacological label [6].

Indeed, benralizumab illustrates this point very well. Benralizumab targets the alpha subunit of the interleukin (IL)-5 receptor (IL-5Rα) expressed on eosinophils and basophils [6]. Its afucosylated Fc region enhances binding to FcγRIIIa receptors on natural killer cells, resulting in potent antibody-dependent cell-mediated cytotoxicity and rapid eosinophil apoptosis [6, 7]. As a consequence, benralizumab induces near-complete depletion of eosinophils not only in peripheral blood but also in tissues and bone marrow, distinguishing it mechanistically from IL-5-neutralizing agents that primarily interfere with eosinophil survival signals [8].

At the molecular level, strong eosinophil depletion reduces inflammation by limiting eosinophil-derived mediators such as major basic protein, eosinophil cationic protein, and transforming growth factor-β [5]. Reducing the eosinophil burden may indirectly influence adaptive immune responses by limiting antigen presentation, Th2 polarization, and tissue remodeling associated with chronic eosinophilic inflammation [9]. These mechanisms are particularly relevant in EGPA patients, as manifestations such as asthma, sinonasal disease, pulmonary infiltrates, and cardiac involvement closely correlate with eosinophil activation [2].

By contrast, anti-IL-5 monoclonal antibodies such as mepolizumab reduce eosinophil survival through cytokine neutralization but do not induce direct cytotoxicity, resulting in a generally less profound and more indirect reduction in eosinophil numbers [6]. This mechanistic distinction supports the view that IL-5 neutralization and IL-5Rα-mediated cell depletion should not be regarded as pharmacologically interchangeable within the eosinophilic spectrum model [10].

In this context, available real-world evidence from eosinophilic diseases includes case reports describing clinical responses to benralizumab in patients with an insufficient or absent response to mepolizumab [11, 12]. Such observations also include our own published clinical experience [12].

Moreover, recent clinical trials have shown that benralizumab can effectively control disease activity and reduce the need for glucocorticoids in EGPA, likely reflecting the depth and persistence of eosinophil depletion [13]. Post hoc analyses further suggest that rapid suppression of eosinophil-driven inflammation may lead to improved control of respiratory and systemic manifestations [14]. Taken together, these findings suggest that the treatment response in EGPA should be understood in terms

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of the underlying molecular mechanisms rather than traditional disease labels alone [2].

From this perspective, benralizumab may be particularly well suited for patients whose disease manifestations cluster toward the eosinophil-dependent end of the spectrum, while alternative immunomodulatory strategies may be more appropriate for vasculitic-dominant phenotypes [10]. Incorporating these mechanistic considerations into discussions of biologic therapies may further enrich the educational and clinical value of the reviewed article [4].

We hope that these reflections are valuable to the ongoing discussion on mechanism-based, individualized treatment strategies in EGPA [1, 4].

Disclosures

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