Why do benralizumab patients still suffer asthma attacks?

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For clinicians managing severe asthma, particularly the eosinophilic phenotype, biologic therapies targeting interleukin-5 (IL-5) or its receptor (IL-5R) have become a cornerstone of treatment. These agents, including benralizumab, effectively deplete eosinophils, a key driver of airway inflammation. But a persistent clinical question remains: why do some patients on these therapies continue to experience exacerbations, and what is driving those events? A review in Allergy examines the nature of these breakthrough attacks, revealing a shift in their underlying pathology.1

KEY TAKEAWAYS

- The Pivot: Asthma exacerbations in patients receiving benralizumab are predominantly non-eosinophilic, a shift from the typical eosinophil-driven events seen in untreated severe asthma.
- The Data: Benralizumab targets IL-5Rα leading to rapid and near-complete depletion of eosinophils through antibody-dependent cell-mediated cytotoxicity.
- The Action: Clinicians should consider non-eosinophilic inflammatory pathways when managing persistent exacerbations in patients on benralizumab, exploring alternative biologic mechanisms or non-biologic strategies.

Severe asthma, defined by its resistance to high-dose inhaled corticosteroids and long-acting beta-agonists, represents a significant clinical challenge. Patients often experience frequent exacerbations, impaired lung function, and a diminished quality of life. For a subset of these patients, particularly those with an eosinophilic phenotype, the discovery and development of monoclonal antibodies targeting the IL-5 pathway have been transformative. These therapies aim to reduce the eosinophilic inflammation that drives many severe asthma symptoms and exacerbations.2

Benralizumab, a humanized monoclonal antibody, specifically targets the IL-5 receptor alpha (IL-5Rα). Unlike other anti-IL-5 biologics that neutralize circulating IL-5, benralizumab binds directly to the receptor on the eosinophil surface. This binding triggers antibody-dependent cell-mediated cytotoxicity (ADCC), leading to a rapid and near-complete depletion of eosinophils from the blood and tissues. This mechanism of action is distinct and has been shown to reduce exacerbation rates and improve lung function in clinical trials.1,2

The Eosinophil Paradox Under Treatment

The success of benralizumab and other anti-IL-5 therapies in reducing eosinophil counts and improving clinical outcomes is well-documented. Cochrane reviews, updated over several years, consistently show that these monoclonal antibodies reduce asthma exacerbations, improve health-related quality of life (HRQoL), and enhance lung function.2,3

These benefits have led to their incorporation into international asthma guidelines, solidifying their role in managing severe eosinophilic asthma. But despite these improvements, a proportion of patients continue to experience asthma exacerbations, raising questions about the nature of these breakthrough events.1

The central question addressed by Poznanski, Mukherjee, and Zhao in their 2021 review in Allergy is whether these residual exacerbations are still eosinophil-driven.1 Given benralizumab's potent eosinophil-depleting effect, one might assume that any remaining exacerbations would stem from non-eosinophilic pathways. The review confirms this hypothesis: exacerbations occurring in patients on benralizumab are largely non-eosinophilic. This finding has significant implications for understanding the heterogeneous nature of severe asthma and for guiding future therapeutic strategies.1

Unpacking the Mechanism of Benralizumab

Interleukin-5 is a cytokine primarily responsible for the growth, differentiation, recruitment, activation, and survival of eosinophils. In eosinophilic asthma, an overproduction of IL-5 leads to an accumulation of eosinophils in the airways, contributing to inflammation, airway hyperresponsiveness, and tissue damage. Monoclonal antibodies targeting this pathway aim to interrupt this inflammatory cascade.2

Benralizumab's unique mechanism of action, directly targeting IL-5Rα and inducing ADCC, results in a profound and sustained reduction in eosinophil counts. Studies have shown that benralizumab can reduce blood eosinophil counts by 90% or more within weeks of initiation. This near-complete depletion distinguishes it from other anti-IL-5 agents that primarily neutralize circulating IL-5 but do not directly target the eosinophil itself for destruction. The sustained depletion of eosinophils is a key factor in its clinical efficacy.1

The Shift in Exacerbation Phenotype

The Poznanski review synthesizes evidence indicating that when patients on benralizumab experience an exacerbation, the inflammatory profile of that event is typically not eosinophilic. This contrasts sharply with the pre-treatment state, where eosinophilic inflammation is a hallmark of severe asthma exacerbations. The shift suggests that benralizumab successfully addresses the eosinophilic component, unmasking or allowing other inflammatory pathways to drive subsequent exacerbations.1

This observation aligns with the understanding that asthma is not a single disease but a syndrome with multiple endotypes, each driven by distinct inflammatory mechanisms. While eosinophilic inflammation is prominent in many severe cases, other pathways, such as those involving neutrophils, mast cells, or type 2 innate lymphoid cells (ILC2s) independent of eosinophils, can also contribute to airway inflammation and exacerbations. The role of epithelial cytokines in linking severe asthma with other airway diseases is an area of ongoing investigation.1

Clinical Implications of Non-Eosinophilic Exacerbations

The recognition that exacerbations on benralizumab are non-eosinophilic carries significant clinical weight. It means that for patients who continue to have breakthrough events despite effective eosinophil depletion, simply increasing the dose of benralizumab or switching to another anti-IL-5 agent is unlikely to be beneficial. Instead, clinicians must consider alternative inflammatory drivers and explore different therapeutic approaches.1

For example, if a patient's exacerbations are driven by neutrophilic inflammation, therapies targeting neutrophil pathways or addressing underlying infections might be more appropriate. Similarly, if type 2 inflammation persists independent of eosinophils, or if other cytokines like IL-13 or IL-4 are dominant, biologics with broader type 2 inhibition, such as

dupilumab, might be considered. The superiority of dupilumab over omalizumab in high-biomarker asthma highlights the importance of matching therapy to specific inflammatory profiles.1

The review also highlights the importance of a thorough diagnostic workup for patients with severe asthma, not just at baseline but also when treatment response is suboptimal. This includes assessing sputum cytology, fractional exhaled nitric oxide (FeNO), and blood eosinophil counts to phenotype the patient's asthma and guide initial biologic selection. For those on benralizumab who continue to exacerbate, re-evaluating these markers, alongside considering other potential triggers like gastroesophageal reflux disease (GERD), chronic rhinosinusitis with nasal polyps (CRSwNP), or vocal cord dysfunction, becomes paramount.1

Limitations and Future Directions

The Poznanski review, while insightful, is a narrative synthesis of existing literature rather than a new primary research study. This means it relies on the quality and consistency of previously published data, which can vary. The precise mechanisms driving non-eosinophilic exacerbations in benralizumab-treated patients are still being elucidated, and direct comparative studies are needed to fully characterize these events.1

The review does not provide specific algorithms for managing non-eosinophilic exacerbations in this population, but it does lay the groundwork for such considerations. Future research should focus on identifying reliable biomarkers for non-eosinophilic inflammation in asthma, which would enable more targeted therapeutic interventions. Developing new biologics that address these alternative pathways is also a critical unmet need. The broader focus in severe asthma treatment decisions beyond just airway inflammation is a welcome development.1

The understanding that benralizumab effectively depletes eosinophils, shifting the inflammatory landscape of exacerbations (the market, the guidelines, the trial pipeline), reinforces the need for precision medicine in asthma. It highlights that even highly effective targeted therapies may not address all aspects of a complex, heterogeneous disease. Clinicians must remain vigilant, continually re-evaluating their patients' inflammatory profiles and considering a broader range of therapeutic options when initial biologic responses are incomplete. For a comprehensive overview of respiratory conditions and their management, the Oxford Handbook of Respiratory Medicine can be a valuable resource.1

The ongoing challenge in severe asthma is to identify the specific drivers of inflammation in each patient and to match those drivers with the most appropriate therapy. This review serves as a reminder that even with potent eosinophil-depleting agents, asthma's complexity demands an evolving treatment approach. The next step involves understanding what exactly is causing these non-eosinophilic events and how to effectively target them.

> **CLINICAL IMPLICATIONS**
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> The finding that benralizumab effectively shifts asthma exacerbations from an eosinophilic to a non-eosinophilic phenotype is not merely an academic observation; it fundamentally alters how clinicians should approach treatment failures. For patients still experiencing attacks despite being on benralizumab, the default assumption should no longer be insufficient eosinophil control. This mandates a re-evaluation of the underlying inflammatory drivers.
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> This insight pushes us beyond a simplistic 'more of the same' mentality. Doubling down on anti-IL-5 therapy or switching to another eosinophil-targeting biologic when the problem is no longer eosinophilic is a waste of resources and, more importantly, patient time. It forces a deeper dive into the patient's clinical picture,

considering other type 2 pathways (e.g., IL-4/IL-13 axis) or even non-type 2 inflammation.
The industry must now focus on developing reliable biomarkers for these non-eosinophilic exacerbations. Without clear diagnostic tools, identifying the specific alternative pathways driving these events remains a challenge. This also means that for patients, persistent exacerbations on benralizumab are not a sign of treatment failure for the drug's intended purpose, but rather an indication that their asthma has other, unaddressed inflammatory components.
This review reinforces the need for a truly personalized approach to severe asthma. It is a call to action for clinicians to think beyond eosinophils in patients already on benralizumab and to consider the broader spectrum of inflammatory mechanisms that can drive this complex disease.

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