

Super-Responders to Severe Asthma Treatments: Defining a New Paradigm



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“My life has been transformed.” Hearing patients with severe asthma utter these words is intensely satisfying. They remind us that targeting biological pathways through precision medicine can offer a new lease of life.

Since omalizumab was licensed almost 2 decades ago, other monoclonal biologics targeting the type 2 inflammatory cascade in severe asthma have followed suit. Clinical trials and real-world studies show that in general, biologic initiation in appropriate patients who meet specified biomarker thresholds can improve symptom control and halve exacerbation frequency, with a corresponding reduction in oral corticosteroid (OCS) bursts. Several biologics also facilitate tapering of maintenance OCS.

Notably, there is substantial heterogeneity in clinical response. As for most other medications, a few patients derive no benefit from biologics or may even deteriorate clinically during treatment. Many more respond but continue to manifest some disease activity. Finally, at the other end of the spectrum, some individuals achieve exceptional levels of asthma control and are termed super-responders. These are the ones for whom such therapy is truly transformational.

Clinicians have long recognized the super-responder phenomenon, but pinning down a definition of this term has proved challenging owing to the multidimensional nature of severe asthma and the broad range of disease outcomes. In this issue of the Journal, Upham and colleagues¹ report a consensus definition of a severe asthma super-responder. Consensus was achieved through a modified Delphi process that included 81 severe asthma experts, undertook three iterative online voting rounds, and used a cutoff of 70% for panel member agreement. (The writers of this editorial participated in the Delphi rounds and can attest to their rigor.) The final consensus definition requires three criteria to be met, two of which must be major criteria. Major criteria are exacerbation

elimination, cessation of maintenance OCS, and improvement in asthma control by twice or more the minimal clinically important difference of the questionnaire used. Minor criteria are a 75% reduction in exacerbations, 500 mL or greater improvement in FEV₁, and well-controlled asthma. No double counting of criteria is permitted within the same domain, and clinical improvement must be durable over 12 months.

The domains defining super-responders reflect central challenges in severe asthma care.

First, a reduction in OCS reliance, for both continuous and intermittent use, features heavily in the proposed super-responder definition. Is this appropriate? Absolutely. For too long, OCS have been the only available way to treat those with the most severe disease, exposing them to numerous adverse effects inherent in their use, yet failing to achieve adequate disease control.²

Second, reduction or elimination of exacerbations is a critical outcome, particularly given the propensity for type 2 inflammation—the target for biologics—to trigger frequent exacerbations.

Third, substantial weight has been given to patients’ subjective symptom response. It is true that patient-reported outcome measures are subjective and influenced by patient expectations, perceptions, and comorbidities. However, their inclusion is critical for shared decision-making and setting of expectations between clinicians and patients, both before and after initiating biologic treatment. The authors point out that inclusion of quality-of-life measures would also be helpful if and when such measures become easier to perform routinely in clinical practice.

Fourth, although it was important to include substantial lung function improvement as a criterion, the authors acknowledged that the magnitude of FEV₁ improvement proposed was arbitrary and open to debate.

Publication of this super-responder definition immediately raises several questions. How frequently are these criteria met in clinical practice? That remains to be determined, but previous data yield insights. In real-world severe asthma cohorts, Kavanagh and colleagues³ found that 36% of patients were exacerbation-free after 52 weeks of mepolizumab treatment, and likewise 44% after 48 weeks of benralizumab.⁴ In randomized controlled trials, the odds ratio for 100% reduction in OCS dose was 1.67 (95% confidence interval, 0.49-5.75) for mepolizumab⁵ and 4.19 (95% confidence interval, 1.58-11.12) for benralizumab.⁶ In real-world cohorts, 50% to 70% of patients were able to discontinue maintenance OCS completely or wean to the lowest dose achievable in the setting of adrenal insufficiency.^{3,4,7}

What might the underlying biologic mechanisms be in super-responders? The gradient of type 2 inflammation is consistently

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associated with the magnitude of response to many biologics.⁸ Lower comorbidity burden has also been associated with a greater response to mepolizumab.⁷ This super-responder definition may help elucidate these and other mechanisms at play.

Could the super-responder definition be applied beyond biologics? Upham and colleagues¹ suggest that the definition could evaluate effects of other add-on therapies such as azithromycin and bronchial thermoplasty, although such marked clinical responses seem anecdotally less common with those treatments. The definition could also be used to assess complex interventions addressing a range of severe asthma treatable traits, including those outside the lower airways.^{9,10}

Finally, where to from here? First, existing trial and real-world data could be readily reanalyzed using these criteria. Of course, future studies should incorporate the definition as a therapeutic outcome. Precise characterization of super-responder populations to individual therapies, or classes of therapies, should help clinicians choose between targeted therapies for patients, and get it right first time.

Second, identifying super-responder characteristics may yield new mechanistic insights regarding the mode of action of targeted therapies, with potential for new drug discovery.

Third, the super-responder definition represents a fresh metric for therapeutic outcomes and provides a tangible way to raise the therapeutic bar in severe disease, from *asthma control* to the far more ambitious paradigm of *asthma remission*.¹¹ The super-responder definition by Upham and colleagues¹ is an important step toward making asthma remission possible for all patients with severe asthma.

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