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Editorial

Expanding Horizons in Severe Asthma: Anti-IgE Biosimilars and the Redefinition of Patient Selection

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Severe asthma is a debilitating disease associated with substantial morbidity, including frequent exacerbations, progressive loss of lung function, corticosteroid-related complications, impaired quality-of-life, and increased mortality.[1-3] While the introduction of biological therapies has been a major breakthrough—mitigating future health risks and improving clinical outcomes—a critical gap remains between the availability of these agents and their actual accessibility.[1,4,5] In many countries including Korea, patients face substantial barriers to biological treatment owing to high costs and overly restrictive reimbursement criteria. In this context, the phase 3 trial published in this issue of *Allergy, Asthma & Immunology Research* presents timely evidence on the efficacy and safety of an anti-immunoglobulin E (IgE) biosimilar, CMAB007.[6] This study by Lai and colleagues[6] is beyond merely demonstrating equivalence, offering the potential to narrow the gap between innovation and accessibility.

These findings provide several important insights into the landscape of severe asthma management: (1) the potential role of biosimilars in improving treatment accessibility, (2) the need to reconsider and potentially broaden the indications for anti-IgE therapy, and (3) implications for forthcoming Korean guidelines on biologic therapy in adults with severe asthma.

To anticipate the impact of these findings, parallels can be drawn from the experience with anti-tumor necrosis factor biosimilars in the fields of rheumatology and gastroenterology.[7,8] The introduction of these agents initiated a 'virtuous cycle' of market expansion, reshaping the treatment paradigms by enabling earlier biological intervention for a broader patient population.[9] A similar transition may now be emerging in the field of asthma and allergy.[10] Recent data on omalizumab biosimilars, including the CT-P39 study (Omlyclo)[11] and the current CMAB007 trial,[6] confirm that therapeutic equivalence can be achieved without compromising safety. Currently, biologic therapies are largely confined to the most severe end of the asthma spectrum (e.g., GINA Step 5), primarily because of cost constraints. However, the budgetary savings afforded by cost-effective biosimilars may allow healthcare systems to reallocate resources, facilitating earlier biological intervention—potentially before irreversible airway remodeling or corticosteroid-related adverse effects develop.[12] Such

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a paradigm shift would extend beyond symptomatic control to achieve long-term disease control and remission.

From a global perspective, regional and socioeconomic disparities remain a challenge in the management of severe asthma. In many low- and middle-income countries, biologics remain largely unavailable, excluding most patients from optimal care. Even in high-income nations where these drugs are reimbursed, high acquisition costs compel payers to implement overly stringent eligibility criteria as a gatekeeping mechanism.[13-16] Consequently, patients are often forced to prove 'sufficient severity,' such as exceedingly frequent severe exacerbations (requiring multiple oral corticosteroid bursts per year), poor lung function, or mandatory failure of maximal inhaler therapies (e.g., the addition of long-acting muscarinic antagonists), to eventually qualify for funding and coverage. The availability of cost-effective biosimilars may offer an opportunity to dismantle these financial and administrative barriers, moving towards a standard paradigm in which treatment decision is guided by clinical necessity rather than economic consideration.

Another notable aspect of the current trial[6] is its broader definition of allergic asthma. Unlike pivotal omalizumab trials, which mandated documented sensitization to perennial aeroallergens via skin prick testing or specific IgE (sIgE) measurement,[17-19] the present study[6] defined eligibility solely based on elevated total IgE levels (60–1,500 IU/mL). This departure from conventional criteria prompts a re-evaluation of how we conceptualize allergic asthma and select patients who may benefit from anti-IgE therapy.

The rationale behind this approach, while not explicitly stated in the paper, likely reflects a pragmatic recognition of clinical complexity. Conventional allergen testing—whether through skin prick tests or sIgE panels—focuses on a set of common perennial aeroallergens, thereby underestimating the burden of IgE sensitization to seasonal or non-classical allergens that may drive severe asthma.[20] A prime example is staphylococcal enterotoxin-sIgE, which has emerged as a relevant biomarker of disease severity.[21-23] Similarly, fungal sensitization beyond *Aspergillus* species and sensitization to occupational or environmental allergens not included in standard panels may be missed.[24]

In clinical practice, we encounter severe asthmatic patients with distinct allergic features—such as markers of type 2 inflammation or comorbid allergic rhinitis, nasal polyps, or atopic dermatitis—who paradoxically test negative for common aeroallergens yet exhibit elevated total IgE. These patients, traditionally excluded from anti-IgE therapy under strict 'allergic asthma' criteria, may nonetheless derive benefit from anti-IgE biologics.[25,26] The current trial's inclusive approach, therefore, may serve to broaden the treatment indications, potentially capturing patients with unconventional or 'hidden' allergic sensitization profiles that evade standard testing panels.

As we are currently developing Korean guidelines for biologic therapy in severe asthma, it is important to reconcile these findings with established paradigms. Since the EXTRA study by Hanania and colleagues,[27] elevated eosinophils and fractional exhaled nitric oxide (FeNO) have been regarded as major predictors of omalizumab response among patients with allergic asthma. Current international guidelines reflect this, recommending anti-IgE therapy for patients with severe 'eosinophilic' asthma.[28,29] This 'eos/FeNO-centric' framework indicates that high downstream activity is a prerequisite for treatment benefit.

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However, the current trial[6] challenges the concept. The findings rather suggest the possibility of decoupling of therapeutic efficacy from downstream inflammatory markers. While Hanania *et al.*[27] correctly identified eosinophils or FeNO as dynamic effectors of disease activity, the current data[6] demonstrate that blocking the stable upstream driver (IgE) can still provide significant protection effects even when downstream effectors (eosinophils) are low (< 150 cells/μL), although the findings were obtained from subgroup analyses.

Although the precise origins of this divergence remain speculative, it is likely attributable to two factors. First, difference in population characteristics may play a role: whereas the study by Hanania *et al.*[27] was strictly limited to the patients with 'confirmed allergic asthma' within a limited IgE range, the current trial by Lai *et al.*[6] defined its population more broadly by total IgE levels, potentially capturing a distinct 'high-IgE burden' phenotype, including unconventional allergic sensitization. Second, the divergence may reflect the fundamental differences in the nature of the biomarkers themselves. Unlike total IgE, which represents a relatively stable upstream driver, blood eosinophil counts are dynamic downstream effectors subject to significant fluctuations, including diurnal variation and treatment effects. Consequently, a single 'snapshot' measurement of blood eosinophils may have failed to accurately reflect the true inflammatory status of the so-called 'low eosinophil' responders in the current trial.

Given the emerging evidence, the optimal indication for anti-IgE therapy warrants reconsideration. Total IgE (reflecting the global atopic burden) should be the primary criterion for identifying eligible patients. In this framework, eosinophils and FeNO are no longer binary or strict gatekeepers, but rather indicators of the specific inflammatory pathway involved. Strict reliance on these biomarkers can be risky, as a single 'snapshot' measurement may fail to capture the fluctuating nature of these volatile markers. Consequently, the absence of elevated eosinophils at a single visit should not preclude therapeutic intervention if the upstream atopic driver—IgE—is clearly present at high levels.

In summary, the publication of this phase 3 trial evaluating an anti-IgE biosimilar, CMAB007, represents a meaningful step toward narrowing the accessibility gap in severe asthma care. As we face the ongoing challenge of translating scientific advancements into real-world practice, the emergence of biosimilars offers a timely and welcome opportunity. The study also provides a valuable perspective by demonstrating clinical efficacy across patients with varying biomarker profiles, thereby prompting a re-examination of how allergic asthma is defined and how optimal patients are selected for anti-IgE therapy. We hope that these insights may support greater flexibility in clinical decision-making, ultimately ensuring that therapeutic innovations reach those who need them most.

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