

# Green Light for Response: Clinical Stratification of Response to Biologic Therapy in Severe Asthma

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**Background:** Biologic therapies have transformed the management of severe asthma; however, treatment response remains heterogeneous and difficult to anticipate in routine practice. Conventional biomarkers alone have limited ability to identify patients who will achieve complete or sustained clinical benefit. This study aimed to explore baseline clinical and inflammatory thresholds associated with response to biologic therapy and to propose an exploratory, clinically oriented stratification framework.

**Methods:** We conducted a secondary analysis of a real-world, single-center, ambispective cohort of adults with severe uncontrolled asthma treated with biologic therapies and followed for at least 12 months. Clinical response was assessed at 6 and 12 months using the multidimensional EXACTO and FEOS scales. Baseline clinical and biological variables were analyzed using exploratory ROC curve analyses to identify thresholds associated with complete clinical response.

**Results:** Among 64 patients, the proportion of complete responders increased from 14% at 6 months to 32.1% at 12 months. No significant differences in response were observed between biologic agents. Higher baseline blood eosinophil counts and a history of frequent exacerbations were associated with improved outcomes. Exploratory eosinophil thresholds of approximately 440 and 435 cells/ $\mu$ L were identified at 6 and 12 months, respectively. Female sex and nasal polyposis were also associated with higher response rates. Based on these findings, three exploratory response profiles reflecting different likelihoods of response were identified.

**Conclusion:** Baseline clinical and inflammatory characteristics may support response stratification in severe asthma. Given that maximal benefit may be achieved over longer treatment periods, extended follow-up should be considered before modifying biologic therapy. The proposed framework is exploratory and provides a basis for future prospective validation.

**Keywords:** severe asthma, biological therapy, clinical thresholds, biomarkers, super-responders

## Introduction

The development of biologic therapies targeting specific components of type 2 inflammation has significantly improved the management of severe asthma. These therapies have led to better symptom control, fewer exacerbations, reduced reliance on systemic corticosteroids, and are increasingly used in clinical practice, particularly in patients with persistent eosinophilic or allergic inflammation.<sup>1,2</sup> However, the clinical response to biologic treatments remains heterogeneous and difficult to predict. While biomarkers such as peripheral blood eosinophil count, total immunoglobulin E (IgE), and fractional exhaled nitric oxide (FeNO) are helpful for guiding therapeutic decisions, their ability to predict a complete or sustained clinical response is limited. A substantial proportion of patients who meet the eligibility criteria still fail to achieve key treatment goals.<sup>2-4</sup>

Efforts have been made to standardize the definition of clinical response to biologics, including objective criteria such as exacerbation reduction or corticosteroid withdrawal. For example, a  $\geq 75\%$  reduction in annual exacerbation rate has been proposed as an optimal response threshold, with reductions of 50–74% representing a moderate response.<sup>5</sup> Recent real-world studies have shown that certain clinical features, such as elevated eosinophil levels or the presence of nasal polyps, may be associated with improved outcomes, beyond conventional biomarkers. Moreover, multidimensional tools

such as the EXACTO and FEOS scales have enabled a more comprehensive and reproducible assessment of clinical response.<sup>1,2,6</sup>

Despite previous efforts to propose response indices or predictive markers in severe asthma, most available approaches focus on single biomarkers or post hoc responder definitions and are not easily translated into pragmatic clinical stratification tools. Moreover, there is no consensus regarding the definition of complete response or remission in real-world settings, further complicating early treatment evaluation. Previous real-world registries and response-prediction studies have largely focused on single biomarkers or post hoc responder classifications, often without integrating multidimensional clinical outcomes. In contrast, the present study adopts a threshold-based, clinically oriented approach combining inflammatory and clinical variables to support pragmatic response stratification in routine practice.

In this context, the aim of the present study was to explore baseline clinical and inflammatory thresholds associated with response to biologic therapy and to propose an exploratory, clinically intuitive stratification framework based on multidimensional response assessment. To achieve this, we conducted a real-world, single-center ambispective analysis integrating both retrospective and prospective data, allowing longitudinal evaluation of treatment response in routine clinical practice using the EXACTO and FEOS scales.

## Methods

This was a single-center, ambispective, observational real-world study conducted at the Department of Allergology of Hospital Universitario A Coruña. Patients were  $\geq 18$  years old, met criteria for severe uncontrolled asthma (GEMA 5.4),<sup>7</sup> and completed at least 12 months of follow-up, with clinical and inflammatory biomarkers assessed at baseline, 4–6 months, and 12 months with omalizumab, mepolizumab, benralizumab, dupilumab, or tezepelumab. Retrospective data collection was restricted to baseline demographic, clinical, and inflammatory variables routinely recorded at treatment initiation. Follow-up assessments at 6 and 12 months were conducted prospectively using standardized clinical visits and predefined response criteria, thereby ensuring consistency in outcome evaluation. We analyzed baseline clinical and biological variables to identify cut-off points associated with treatment response, as assessed by the EXACTO and FEOS scores at 6 and 12 months. Baseline inflammatory biomarkers were measured at treatment initiation as part of routine clinical care and analyzed in the same hospital laboratory using standardized and quality-controlled assays. Asthma exacerbations were defined as episodes of worsening respiratory symptoms requiring systemic corticosteroid treatment (oral corticosteroid bursts and/or parenteral corticosteroids) and/or leading to emergency department visits or hospitalization. Analyses were conducted using a complete-case approach. No data imputation was performed. Differences in the number of evaluable patients at 6 and 12 months were due to missed follow-up visits or incomplete assessments.

The FEOS score (based on FEV<sub>1</sub>, exacerbations, oral corticosteroid use, and symptom control via the ACT) ranges from 0 to 100 and reflects the patient's overall clinical improvement. The EXACTO score has two versions depending on corticosteroid use, incorporating the number of exacerbations, clinical control (asthma control test (ACT)), and FEV<sub>1</sub>, with a total score ranging from 0–7 (without corticosteroids) or 0–10 (with corticosteroids). For clarity, Table 1 summarizes both the original definitions of the EXACTO and FEOS scales and the study-specific categorization applied for the present analyses. Both scores were classified into three response levels (non-response, partial/good response, and complete response) and then dichotomized (complete vs non-complete response) for ROC curve analysis. ROC curves and non-parametric tests were applied to determine optimal cut-off values and stratify patients into three response categories: non-responders, partial responders, and super-responders. The classification criteria for the EXACTO and FEOS scales, including categorical and dichotomized levels used for ROC analysis, are summarized in Table 1.

Continuous and categorical variables were analyzed using appropriate parametric or non-parametric tests, including Chi-square/Fisher's exact, paired *t*-test/Wilcoxon signed-rank, and Mann–Whitney U/Kruskal–Wallis, as applicable. Logistic regression analyses were conducted exclusively for exploratory purposes to assess unadjusted associations between selected baseline variables and clinical response. Given the limited number of outcome events, multivariable modeling was intentionally restricted to avoid overfitting, and no variables were interpreted as independent predictors. Results from regression analyses were therefore considered descriptive and hypothesis-generating. A  $p < 0.05$  was considered statistically significant. Analyses were performed with R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

**Table 1** Stratification of Clinical Response to Biologic Therapies Using the EXACTO and FEOS Scales

| Variable                              | Category                  | Description                                                                                                                                                                                                    |
|---------------------------------------|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>FEOS</b>                           | Continuous numerical      | 0–100 scale integrating objective and patient-reported components, including FEV <sub>1</sub> , exacerbation frequency, oral corticosteroid use, and symptom control assessed by the Asthma Control Test (ACT) |
|                                       | Categorized into 3 levels | 0–89 = <b>No or minimal response</b><br>90–99 = <b>Partial/good response</b><br>100 = <b>Complete response</b>                                                                                                 |
|                                       | Dichotomized for ROC      | 0–99 = Non-complete response<br>100 = <b>Complete response</b>                                                                                                                                                 |
| <b>EXACTO without corticosteroids</b> | Categorized into 4 levels | 0–1 = No response<br>2–4 = Partial<br>5–6 = Good<br>7 = Complete                                                                                                                                               |
| <b>EXACTO with corticosteroids</b>    | Categorized into 4 levels | 0–2 = No response<br>3–6 = Partial<br>7–9 = Good<br>10 = Complete                                                                                                                                              |
| <b>EXACTO combined</b>                | Categorized into 3 levels | <b>No or partial response</b><br><b>Good response</b><br><b>Complete response</b>                                                                                                                              |
|                                       | Dichotomized for ROC      | No, partial, or good response = Non-complete<br><b>Complete response = Complete</b>                                                                                                                            |

**Notes:** The FEOS scale ranges from 0 to 100 and integrates lung function (FEV<sub>1</sub>), exacerbations, oral corticosteroid use, and symptom control (ACT). The EXACTO scale includes two versions depending on oral corticosteroid use and incorporates exacerbation frequency, ACT score, and FEV<sub>1</sub>. For the purposes of this study, both scales were categorized into response levels and subsequently dichotomized (complete vs non-complete response) to enable ROC curve analysis.

**Abbreviations:** ACT, Asthma Control Test; FEV<sub>1</sub>, forced expiratory volume in 1 second; OCS, oral corticosteroids.

The study was approved by the Fundación Jiménez Díaz Ethics Committee (CEIm-FJD; Ref. 22/23) as part of the MEGA Project (PI18/01016). All participants provided written informed consent for participation and for the use of their clinical data for research purposes. Retrospective chart review was conducted under this approval and did not require a separate waiver of informed consent. Procedures complied with the Declaration of Helsinki and applicable data protection regulations.

It is worth noting that the FEOS scale includes oral corticosteroid use as a component of clinical response, which may lead to an underestimation of response in patients not receiving corticosteroids—particularly when their discontinuation reflects clinical improvement rather than therapeutic need. Nevertheless, because corticosteroid use was consistently documented and the scale was applied uniformly across all patients, the potential for bias was minimized. In addition, the complementary use of the EXACTO score—which allows assessment both with and without corticosteroid use—helped contextualize and validate the findings.

## Results

In an initial analysis of this cohort, treatment with biologics was associated with clinical improvement in most patients. Factors associated with a better clinical response included female sex ( $p = 0.001$ ) and the presence of nasal polyps ( $p = 0.027$ ), while aspirin-exacerbated respiratory disease (AERD), emerged as a clinically relevant factor, although not statistical differences were found ( $p = 0.075$ ). Baseline demographic and clinical characteristics of the cohort are presented in [Table 2](#).

Clinical response to biologic treatments was evaluated at 6 and 12 months using the FEOS and EXACTO scales. To enhance clinical interpretability, response was stratified into three categories: no or partial response, good response, and

**Table 2** Baseline Demographic and Clinical Characteristics of the Study Population (N = 67)

| N (67)                    |            | Female Sex, No. (%)        | 43(64,2)                 |
|---------------------------|------------|----------------------------|--------------------------|
| Age, mean (SD)            | 47,4(12,2) | Phenotype                  | 13(19,4)                 |
| BMI (SD)                  | 27,2(7,1)  | • T2 allergic, no. (%)     | 12(18)                   |
| • Rhinitis, no. (%)       | 65(97)     | • T2 eosinophilic, no. (%) | 42(62,6)                 |
| • CRSwPN, no.(%)          | 26(38,9)   | • Mixed, no. (%)           |                          |
| • AERD, no. (%)           | 22(32,8)   |                            |                          |
| Biologic                  | 22(31,4)   | Score                      | 12(4,9)-21(4,5)          |
| • Omalizumab, no. (%)     | 12(17,1)   | ACT, mean (SD) pre-post    | 1,4(1,9)-7,3(3,1)        |
| • Mepolizumab, no. (%)    | 12(17,1)   | VAS, mean (SD) pre-post    | 63,1(20)-25(20,2)        |
| • Benralizumab, no. (%)   | 3(4,4)     | SNOT, mean (SD) pre-post   |                          |
| • Reslizumab, no. (%)     | 15(21,4)   |                            |                          |
| • Dupilumab, no. (%)      | 6(8,6)     |                            |                          |
| • Tezepelumab, no (%)     |            |                            |                          |
| Global clinical remission | 27,3(0,4)  | N° ex prev/year, mean (SD) | 3,2(2,6)-0,4(0,7)        |
| Complete global remission | 12,7(0,3)  | ICS p.year mg, mean (SD)   | 1123,6 (1036,7)-379(383) |

**Notes:** Data are presented as mean (standard deviation) or number (percentage), as appropriate. Baseline characteristics include sex, age, body mass index (BMI), asthma-related comorbidities (rhinitis, chronic rhinosinusitis with nasal polyps [CRSwNP], and aspirin-exacerbated respiratory disease [AERD]), inflammatory phenotype, biologic therapy received, clinical scores, exacerbation history, and inhaled corticosteroid (ICS) use. Asthma inflammatory phenotypes were classified as type 2 (T2) allergic, T2 eosinophilic, or mixed, according to clinical and biomarker assessment at baseline. Clinical scores are shown as pre-treatment and post-treatment values and include the Asthma Control Test (ACT), visual analog scale (VAS) for symptom burden, and Sino-Nasal Outcome Test (SNOT). Global clinical remission refers to the proportion of patients achieving complete global remission during follow-up, as defined by the combined clinical response criteria used in this study.

**Abbreviations:** ACT, Asthma Control Test; AERD, aspirin-exacerbated respiratory disease; BMI, body mass index; CRSwNP, chronic rhinosinusitis with nasal polyps; ICS, inhaled corticosteroids; SD, standard deviation; SNOT, Sino-Nasal Outcome Test; VAS, visual analog scale.

very good or complete response. At 6 months, among the 50 patients with available data, 18 (36%) showed no or partial response, 25 (50%) had a good response, and only 7 (14%) achieved a very good response. At 12 months (n = 53), the distribution improved, with an increase in patients classified as having a very good response (17 patients, 32.1%). No significant differences in treatment response were observed between biologic agents at 6 or 12 months. However, the study was not powered to perform comparative effectiveness analyses, and these findings should not be interpreted as evidence of equivalence between agents. Biologic choice was not adjusted for baseline eosinophil levels.

When analyzing baseline variables associated with response levels, blood eosinophil count showed a significant difference between groups both at 6 months ( $p = 0.033$ ) and at 12 months ( $p = 0.017$ ), with higher levels in patients with better response. The number of previous exacerbations was also significantly associated with response at 6 months ( $p = 0.036$ ), with patients experiencing more exacerbations tending to respond better. In addition, female sex was significantly associated with higher response rates ( $p = 0.001$ ), while male patients were mostly concentrated in the non- or partial response group.

The FEOS and EXACTO scales were subsequently dichotomized into complete response (1) vs non-complete response (0) for exploratory ROC curve analysis, enabling the assessment of associations between baseline variables and complete clinical response.

Exploratory ROC curve analyses were performed to evaluate the association between baseline blood eosinophil counts and complete clinical response. Given the limited number of patients achieving complete response, these analyses were intended to identify clinically plausible thresholds rather than to establish definitive cut-off values. Exploratory eosinophil thresholds of approximately 440 cells/ $\mu$ L at 6 months and 435 cells/ $\mu$ L at 12 months were identified and are presented as hypothesis-generating findings ( $p = 0.008$  at 12 months). In addition, a threshold of  $\geq 3$  exacerbations in the previous year, commonly used in clinical practice and supported by previous literature, was identified as clinically relevant and included in the exploratory binary response analysis.

**Table 3** Clinical Profiles Associated with Response to Biologic Therapy in Severe Asthma

|                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Lower Likelihood of Response:</b> <ul style="list-style-type: none"> <li>• Blood eosinophils &lt; 300 cells/<math>\mu</math>L</li> <li>• &lt; 2 exacerbations p/y</li> <li>• Male</li> <li>• Absence of nasal polyposis</li> </ul> | <b>Intermediate Likelihood of Response:</b> <ul style="list-style-type: none"> <li>• Blood eosinophils between 300–435 cells/<math>\mu</math>L</li> <li>• 2–3 exacerbations p/y</li> <li>• Female without nasal polyposis or male with nasal polyposis</li> </ul> | <b>Higher Likelihood of Response:</b> <ul style="list-style-type: none"> <li>• Blood eosinophils <math>\geq</math> 435 cells/<math>\mu</math>L</li> <li>• <math>\geq</math> 3 exacerbations p/y</li> <li>• Presence of nasal polyposis</li> <li>• Female</li> </ul> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

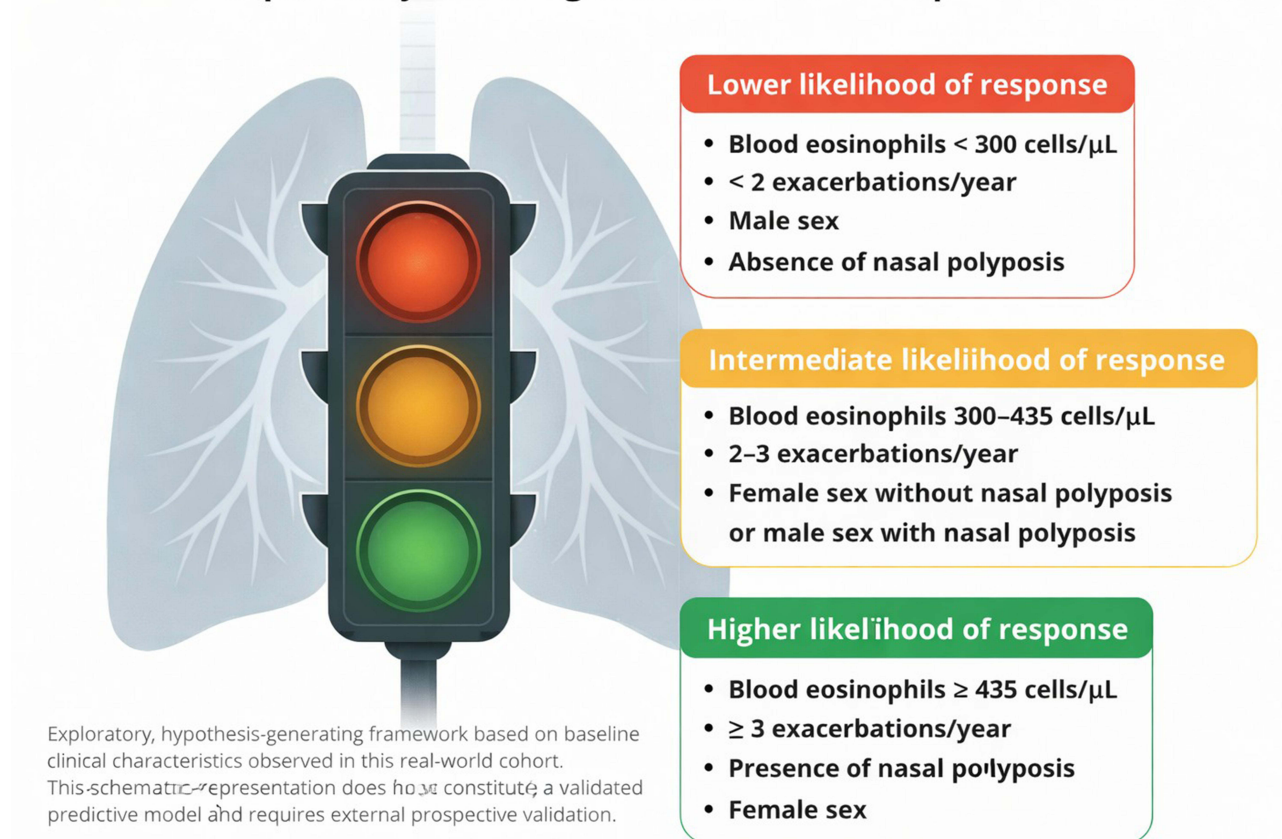
**Notes:** Clinical profiles were derived from exploratory analyses of baseline clinical and inflammatory characteristics associated with treatment response in this real-world cohort. These profiles represent a conceptual stratification framework and should be interpreted as hypothesis-generating rather than as a validated predictive model.

**Abbreviation:** Cells/ $\mu$ L, cells per microliter.

Beyond biomarkers, several clinical factors were associated with improved response to biologic therapy, including nasal polyposis, female sex, and peripheral eosinophilia. This multidimensional exploratory approach highlights clinically relevant features that may help inform response stratification in routine practice.

Based on baseline clinical and inflammatory characteristics associated with treatment response, three exploratory response profiles were identified, Table 3. To facilitate clinical interpretation, these profiles are also summarized using a conceptual, color-coded “traffic-light” framework, Figure 1.

### Exploratory traffic-light framework for response stratification



**Figure 1** Conceptual “traffic-light” framework for stratifying likelihood of response to biologic therapy in severe asthma. This schematic figure illustrates an exploratory, color-coded stratification framework based on baseline clinical and inflammatory characteristics associated with treatment response in this real-world cohort. The framework categorizes patients into three groups reflecting a lower, intermediate, or higher likelihood of achieving a complete clinical response, according to blood eosinophil count, exacerbation history, sex, and presence of nasal polyposis. This stratification is intended as a conceptual, hypothesis-generating tool and does not represent a validated predictive model. External validation in larger, prospective cohorts is required before clinical implementation.

**Abbreviation:** cells/ $\mu$ L, cells per microliter.



## Discussion

Our findings reinforce the heterogeneity of clinical response to biologic therapy in severe asthma, which likely reflects the dynamic nature of underlying endotypes rather than fixed phenotypic categories. In line with previous literature, female sex and nasal polyposis were more frequently observed among patients achieving a favorable response, consistent with recent high-impact studies investigating type 2 eosinophilic phenotypes in omalizumab and benralizumab treated cohorts.<sup>8</sup> This observation is biologically plausible, as sex hormones have been shown to modulate type 2 immune responses and eosinophilic inflammation, potentially influencing treatment response; however, no causal inference or effect size estimation can be drawn from the present data. The observed trend toward a better response in patients with AERD further supports emerging evidence suggesting dupilumab efficacy in this subgroup, likely related to modulation of type 2 inflammatory pathways.<sup>9</sup>

Notably, the proportion of patients achieving a very good response increased substantially at 12 months (32.1%), suggesting that some individuals may require longer treatment periods to reach maximal clinical benefit. This delayed improvement may reflect time-dependent immunomodulation, including suppression of chronic mucosal inflammation, or downstream effects on airway remodeling. Such mechanisms are unlikely to be fully captured within the conventional 4–6 months evaluation window, and premature discontinuation may therefore underestimate true response, especially in partially improved patients. This observation is consistent with real-world studies reporting progressive clinical benefit over time in a subset of patients with severe eosinophilic asthma.<sup>6</sup>

Our findings highlight the potential value of individualized evaluation timelines and extended follow-up in treatment algorithms, especially in patients with clinical improvement but incomplete biomarker resolution. In clinical practice, a more flexible evaluation approach may improve therapeutic persistence and avoid inappropriate switching between biologics.

Regarding inflammatory markers, our ROC-based thresholds of 440 and 435 cells/ $\mu$ L for complete response at 6 and 12 months align with recent real-world evidence. Bleecker et al reported that baseline eosinophil counts  $\geq 400$  cells/ $\mu$ L were associated with a robust response to benralizumab and mepolizumab.<sup>10</sup> Similar associations have been described by Padilla-Galo et al and Hekking et al<sup>2,5</sup> Additionally, a history of frequent exacerbations emerged as a significant predictor—reinforcing longitudinal analyses in which the combination of exacerbation history and eosinophil levels enhances prognostic precision.<sup>11</sup> These findings were further corroborated by Gómez-Chávez et al in a large multinational registry.<sup>12</sup> Importantly, these thresholds should be interpreted as exploratory and hypothesis-generating rather than as definitive cut-off values.

In addition to biomarkers, several clinical characteristics—including nasal polyposis, female sex, and a history of frequent exacerbations—were associated with improved response. Taken together, these findings support a multidimensional, clinically oriented approach to response stratification. The exploratory response profiles presented in this study were derived post hoc as a conceptual synthesis of these associations and do not represent weighted or validated prediction models. This approach is supported by recent work from Damiński et al, who demonstrated that composite clinical-biomarker profiles outperform single-variable predictors in benralizumab-treated cohorts.<sup>6</sup>

The absence of significant differences in treatment response across biologics in our cohort suggests that this stratification model may have broad applicability across therapeutic classes. However, an apparent paradox arises: patients in the “green” category—those with higher baseline eosinophilia, more frequent exacerbations, and generally more inflamed clinical profiles—were more likely to achieve super-response or even remission. While this could appear to challenge the rationale for early intervention, it also exposes limitations in current response metrics, which may disproportionately favor improvements in severely symptomatic patients. In contrast, patients with milder disease may experience stabilization or slowed progression, outcomes that are clinically meaningful but less readily quantified using standard response criteria. This highlights the need for complementary response criteria, incorporating lung function trajectories, symptom control, and even patient-reported outcomes, to better capture the full spectrum of therapeutic benefit.

Although the single-center, real-life nature of our study may limit generalizability, the consistency of our observations with contemporary multicenter series lends robustness to our conclusions. Future research should focus on prospective

validation of these response profiles in larger cohorts and explore the inclusion of additional biomarkers—such as FeNO, periostin, or IL-5RA expression—to further refine predictive algorithms. Emerging candidates, including TSLP and epithelial-derived markers like DPP4, as well as multi-omic integration (transcriptomic, proteomic, microbiome), could provide further granularity in stratifying responders.

## Limitations

Several considerations should be considered when interpreting the present findings. First, the study was conducted in a single-center real-world cohort with a moderate sample size, which reflects routine clinical practice but may limit the direct generalizability of the results and precludes the development of a validated predictive model. In particular, the small number of patients achieving a complete clinical response, together with the absence of formal adjustment for multiple exploratory comparisons, may affect the stability of ROC-derived estimates and increase the risk of type I error; therefore, all associations should be interpreted with caution. Second, the observational and ambispective design may be associated with inherent sources of variability, including residual confounding by comorbidities and treatment-related factors. Although major comorbidities were systematically collected and explored in univariate analyses, they were not included as adjustment variables in multivariable models within the present exploratory framework. In addition, baseline inhaled corticosteroid dose, oral corticosteroid dependence, treatment adherence, smoking status, lung function, and other biomarkers were not systematically adjusted for and may have influenced the observed associations. However, baseline clinical and inflammatory characteristics were systematically collected, and standardized multidimensional response scales were used to ensure consistency in outcome assessment.

Third, biologic therapies with different mechanisms of action were analyzed together. While the study was not designed or powered to perform comparative effectiveness analyses, this approach was deliberately adopted to explore shared clinical and inflammatory features associated with treatment response across biologic classes in a real-world setting. The absence of statistically significant differences between biologics should be interpreted in the context of limited statistical power rather than as evidence of comparable effectiveness across agents. In addition, the lack of an external validation cohort limits the generalizability of the proposed thresholds and response profiles, which were derived post hoc and should be regarded as exploratory and hypothesis-generating. The possibility of regression to the mean, particularly among patients with a high number of prior exacerbations, cannot be excluded. Finally, missing data at the 6-month evaluation reduced the number of evaluable patients at this time point and may have introduced additional uncertainty.

Finally, the present findings should be viewed within the context of an exploratory, clinically grounded framework for response stratification rather than as a definitive predictive model. By highlighting the potential relevance of longer evaluation periods and more individualized treatment trajectories, this approach may help inform future research and support more nuanced therapeutic decision-making in routine clinical practice. In this sense, the proposed stratification framework may contribute to optimizing treatment persistence and avoiding premature biologic switching, while future prospective validation studies will be essential before considering broader implications for clinical guidelines or healthcare policy.

## Disclosure

RLR reports receiving payments for lectures and educational events from AstraZeneca and Leti Pharma. JAC reports receiving payments for lectures and educational events from AstraZeneca and GSK. MJR reports receiving payments for lectures and educational events from A-Z, Chiesi, Gsk, Menarini, Gebro, Leti pharma. The authors report no other conflicts of interest in this work.

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