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ORIGINAL RESEARCH

Feasibility of a 50% Dosing Interval Extension of Anti–IL-5 Biologics in Patients with Severe Asthma in Clinical Remission: A Real-World Validation Study

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Video Abstract

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Background: Initiation criteria for biologic therapies for severe asthma are well established, but guidance on dose reduction or discontinuation remains limited. Sustained clinical remission presents an opportunity to evaluate biologic dose tapering strategies.

Objective: To validate a down-titration algorithm by assessing the feasibility and safety of extending the dosing interval of anti–IL-5 biologics (mepolizumab, benralizumab) by 50% in patients with severe asthma in clinical remission.

Methods: In this single-center, real-world, longitudinal study, 31 patients with severe asthma and sustained four-component remission for >12 months were enrolled. The biologic dosing interval was extended by 25% at baseline and by 50% at 6 months if four-component remission was maintained. Remission was assessed at 26 and 52 weeks using established three- and four-component criteria. Bayesian logistic and mixed-effects models were used to evaluate clinical and biomarker outcomes.

Results: Over the 12-month study period, a 50% dose interval extension was successfully achieved in 28 out of 31 patients (90%). At study end, 18 patients (58%) remained in four-component remission, while 25 (81%) met three-component remission criteria. Acute exacerbations occurred in 3 patients (10%). Comparison between benralizumab and mepolizumab showed no significant differences. While peripheral eosinophil counts increased slightly, mean levels remained below 300 cells/μL. FeNO levels showed no significant change.

Conclusion: Following a 50% extension of anti–IL-5 biologic dosing intervals, full four-component clinical remission was maintained in 58% of patients, while 81% preserved three-component remission with a low exacerbation rate. These findings indicate that a uniform 50% interval extension cannot be applied universally without risk of partial loss of disease control. However, the high proportion of patients maintaining clinically meaningful 3-component remission supports the feasibility of a structured, stepwise dosing-interval extension strategy in selected patients with severe asthma, emphasizing the need for individualized implementation.

Keywords: asthma, severe asthma, biological therapy, anti-IL-5 therapy, biological therapy titration

Introduction

The efficacy of biologic agents in patients with severe asthma is well established.[1] Comprehensive meta-analyses of numerous randomized clinical trials (RCTs) have demonstrated that licensed asthma biologics significantly improve key asthma-related outcomes: they reduce exacerbation and hospitalization rates, improve lung function, asthma control, and quality of life, and limit the need for systemic corticosteroids.[2,3] These benefits have also been confirmed in a similar

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extent in real-world studies.[4,5] Notably, the therapeutic effects of biologic agents are most pronounced in patients with Th2–high severe asthma inflammation.[1–4]

While the criteria for initiating biologic therapy in severe asthma are generally well defined, subsequent clinical decisions (such as treatment duration, switching agents, or discontinuation) remain largely unclear. These decisions often depend on the magnitude of the initial clinical response, which can vary considerably among individuals and is typically assessed using non-standardized and inconsistent measures. Accordingly, numerous publications have sought to define treatment response in patients with severe asthma receiving biologics.[6–10] Various outcomes have been analyzed, and several composite measures have been proposed. However, methodological inconsistencies, differences in outcome selection, and heterogeneous follow-up durations have limited comparability and clinical applicability.[6]

Based on improvements in asthma-related outcomes, some researchers, particularly in studies on anti-IL-5/anti-IL-5R agents, have categorized patients as super-responders, partial responders, or non-responders.[7–9] Super-responders exhibit profound, though heterogeneous, improvements in clinical, biological, and functional outcomes. Baseline characteristics predictive of a favorable long-term response to anti-IL-5/anti-IL-5R therapies in super-responders typically include higher blood eosinophil count (BEC) and exhaled nitric oxide (FeNO) levels, earlier onset and shorter duration of asthma, less severe disease, absence of nasal polyps and obesity, and relatively preserved lung function.[7–10]

However, definitions of super-responders are not standardized. In some studies, stringent criteria were used, requiring no residual asthma symptoms over extended periods, essentially equating super-response with asthma remission, which is increasingly viewed as a key therapeutic target.[10]

The concept of clinical remission represents a multidimensional and ambitious approach that has shifted the paradigm of asthma management.[10–13] Proposed criteria generally include a ≥12-month period with no significant symptoms or exacerbations, stable and optimized lung function, and no systemic corticosteroid use (the four-component definition). Some studies have adopted a less comprehensive three-component definition that omits the lung function criterion.[14] According to the Spanish consensus, complete remission builds on these criteria by also requiring absence of inflammation, bronchial hyperresponsiveness, and airway remodeling, maintained for at least three years.[15] More recently, the MODIASTHMA consensus has further expanded this framework by introducing the concept of disease modification. In this multidisciplinary consensus, disease modification is defined as the sustained achievement of complete clinical improvement, normalization of biological activity, reversal of bronchial hyperresponsiveness, improvement or stabilization of structural airway abnormalities, and the long-term maintenance of this state for at least three years.[16]

The clinical remission rate achieved in patients with severe asthma treated with biologics ranges from 14% to 44%, depending on the specific biologic used and the composite outcomes applied (eg., variations in symptom thresholds, lung function interpretation, and follow-up duration).[17] However, the core components of remission definitions are generally accepted. In a recent systematic review of 25 studies involving 5196 patients, Shackleford et al found that one-third of the studies used at least one three-component definition of remission, and 89% employed at least one four-component definition.[18]

Once long-term remission is achieved, it presents an opportunity to reconsider treatment strategies. Reducing the biologic dose appears to be a logical next step. According to Cohn, there are at least four potential scenarios in which biologic dose reduction may be effective: (a) the biologic target may be less active after prolonged therapy, (b) the disease may be directly modified by the treatment, (c) comorbid conditions may improve and indirectly affect the disease course, and (d) the natural course of the disease may change independently of therapy.[19]

Previous work, notably the OPTIMAL study, proposed a dose-tapering algorithm for anti–IL-5 biologics aimed at identifying the lowest effective dosing interval before loss of asthma control.[20] However, this algorithm has not been extensively validated in real-world clinical settings. Building on these findings, our study aims to validate the OPTIMAL dose reduction algorithm by assessing the feasibility and safety of extending the dosing interval by 50% in patients with severe asthma who are in clinical remission. As the biologics were administered via prefilled syringes, dose reduction was implemented by extending the dosing interval.

Methods

Study Design

This single-arm, longitudinal study was conducted under real-world conditions at the University Hospital Dubrava, Zagreb, Croatia. The study was approved by the Institutional Ethics Committee (2024/1003-3), and all participants provided written informed consent.

Study Population

Eligible participants were adults who had been receiving mepolizumab or benralizumab for more than 12 months and had documented four-component remission lasting longer than 12 months at the time of enrollment. Four-component remission was defined as the absence of exacerbations, no need for oral corticosteroids, an asthma control test (ACT) score consistently ≥20, and stable lung function, defined as no decline in forced expiratory volume in one second (FEV_1) greater than 15% and/or 200 mL on routine six-month evaluations during the previous year. Patients with concomitant eosinophilic granulomatosis with polyangiitis (EGPA) were excluded from the study.

Visits and Down-Titration Algorithm

The down-titration algorithm was developed to assess whether, and to what extent, the dose of biologics could be reduced by gradually extending the interval between individual drug administrations while maintaining disease control.

The study included three primary visits: a baseline visit at enrollment, followed by two follow-up visits at 26 and 52 weeks. At each visit, both three- and four-component remission criteria were assessed, along with biomarkers of type 2 inflammation (FeNO and BEC). Four-component remission was defined as previously described, while three-component remission was defined as the absence of exacerbations, no need for oral corticosteroids (OCS), and either stable symptoms or preserved lung function.

At the baseline visit, which coincided with the patient's regularly scheduled anti-IL-5 biologic injection, the interval to the next administration was extended by 25%. For patients on mepolizumab, the interval was extended to five weeks, and for those on benralizumab, to ten weeks. At the 26th week, disease control was reassessed. If four-component remission was maintained, the interval between doses was further extended to six weeks for mepolizumab and twelve weeks for benralizumab (50% increase from standard dosing). At the final visit (52nd week), disease control was again evaluated based on three- and four-component remission rates and the occurrence of acute exacerbations.

If disease control was lost at visit 2 (26th week), the participant resumed their original dosing schedule, and no further attempts at dose reduction were made. At the end of the study (52nd week), patients who shifted from 4-component to 3-component remission were returned to their previous dosing interval. Those who remained in 4-component remission either continued with the same dosing interval or extended it further, based on their personal preference. At each scheduled visit for drug administration, patients were seen by a physician to ensure objective assessment of disease control and patient safety.

Statistical Analyses

Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were reported as medians with minimum and maximum values, due to the unknown distribution and small sample size, which precluded assumptions of normality. Categorical variables were summarized as counts and percentages. Data were analyzed across dosing interval timepoints (0, 26th and 52nd week), with additional stratification by remission status at 52nd week.

To assess whether the impact of dosing interval prolongation differed between mepolizumab and benralizumab, three clinical benchmarks were evaluated: a relapse probability below 15%, and probabilities of achieving three- and four-component remission above 85%. The 15% margin was set based on the control-arm of the OPTIMAL trial in which 17% of patients experienced exacerbations.[20] Due to perfect separation—where some levels of interval prolongation yielded no observed relapses—standard logistic mixed-effects models produced unstable estimates with inflated standard errors. Consequently, Bayesian logistic regression was employed as a more robust alternative.

The Bayesian model included dosing interval ratio (1.0, 1.25, and 1.5) and therapy type (benralizumab vs. mepolizumab) as fixed effects, with subject identifier included as a random intercept. Binary outcomes (relapse, three-component remission, and four-component remission) were modeled using a Bernoulli distribution. Weakly informative priors were specified: normal (0, 10) for fixed effects and half-normal (0, 10) for random effects. The model was fitted using a Hamiltonian Monte Carlo algorithm with tuning parameters adjusted to ensure convergence. Posterior distributions were summarized using 95% highest posterior density intervals, and clinically relevant contrasts were assessed within the Bayesian framework.

Biomarker outcomes, including fractional FeNO and peripheral blood eosinophil counts, were analyzed to assess differences by dosing interval ratio and therapy type. Due to right-skewness, FeNO values were log-transformed and analyzed using linear mixed-effects models. Eosinophil counts were modeled using a generalized linear mixed-effects model with a Poisson distribution, appropriate for count data. In both models, dosing interval and therapy type were treated as fixed effects, while subject identifier was modeled as a random intercept to account for repeated measures.

Estimated marginal means (EMMs) with 95% confidence intervals were computed on the response scale. Comparisons between each extended dosing interval and the approved interval (ratio = 1) were conducted using Dunnett's post hoc test. Results were reported both as marginal means and as ratios relative to the approved interval, with statistical significance assessed using adjusted p-values.

All analyses were performed in R version 4.5.0.[21] Mixed-effects models were fit using the lmer() and glmer() functions from the lme4 package,[22] and estimated marginal means and contrasts were computed using the emmeans package.[23] Bayesian models were fit using brms,[24,25] which interfaces with Stan.[26] Visualizations were created using ggplot2.[27]

Potential bias results in the discrepancy between frequencies of mepolizumab and benralizumab dosing was mitigated by performing visits at fixed time points at 26th and 52nd week from study initiation.

Results

Of the 58 patients receiving anti-IL-5 therapy at our institution at the time of study initiation, 33 met the inclusion criteria. Two patients declined to participate, resulting in 31 patients who completed the study between January 2024 and February 2025 and were included in the analysis (Figure 1). Thirteen patients (42%) were treated with benralizumab and 18 (58%) with mepolizumab. Participants' demographic data are presented in Table 1.

During the 12-month course of anti-IL-5 biologic therapy, the dosing interval was successfully extended by 50% in 25 of 31 patients (90%). Three patients were not eligible for further extension at Visit 2 (26th week) due to loss of 4-component disease control; all three experienced a decline in lung function. At this time point (Visit 2), all patients remained free of exacerbations and did not require oral corticosteroids (Bayes factor [BF]: 8.0×10^4; posterior probability [PP]: 100%; see Figure 2 and Table 2), thereby fulfilling the criteria for 4-component remission. Following Visit 2, three patients (10%) experienced acute exacerbations requiring systemic corticosteroids. Consequently, the final remission status was analyzed in 25 patients (at 52nd week). Of these, 18 (58% of all participants) maintained 4-component clinical remission (BF: 1.5; PP: 59.9%; see Figure 2 and Table 2). In seven patients, disease control declined to the 3-component level: five experienced reduced lung function, and two reported worsening asthma symptoms, as assessed by the ACT questionnaire. Overall, 25 patients (81% of all participants) maintained 3-component disease control (BF: 2.7×10^4; PP: 98.29%), regardless of whether the impairment was in lung function or symptom control, Figure 3.

Comparison between benralizumab and mepolizumab across these monitoring points revealed no significant differences in outcomes (Figure 4 and Table S1). FeNO levels increased during the study, though not significantly (p-values for mean FeNO score ratio: 0.074 and 0.746 for 25% and 50% dosing interval extensions, respectively, Figure 5 and Table S2). Peripheral blood eosinophil counts increased over the course of the study ($p < 0.01$ for mean eosinophil count ratios at both 25% and 50% interval extensions, Figure 5 and Table S2). However, mean eosinophil counts remained below 300 cells/μL at all monitoring points.

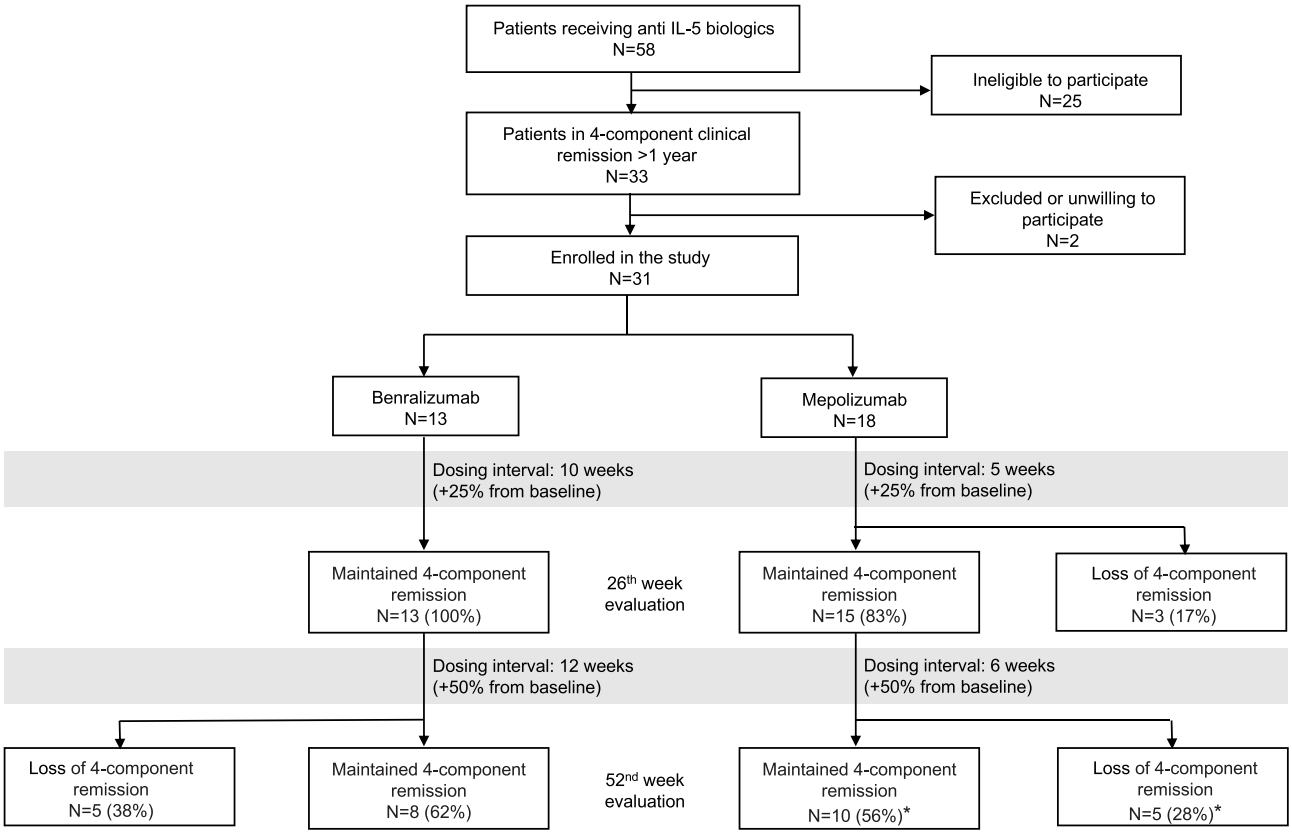

Figure 1 Study flowchart showing patient selection, treatment allocation, dosing schedule prolongation, and clinical outcomes during follow-up. Among 58 patients receiving anti–IL-5 biologics, 31 patients with sustained four-component clinical remission for >1 year were enrolled. Patients were treated with benralizumab (n=13) or mepolizumab (n=18). Dosing intervals were progressively prolonged by 25% and subsequently by 50% relative to baseline. Maintenance or loss of four-component clinical remission was assessed at week 26 and week 52. *percentage calculated from the 18 patients on mepolizumab.

Discussion

The results of the present study show that in some patients with severe asthma treated with anti-IL-5 biologics (mepolizumab, benralizumab) who had achieved clinical remission, it is possible to maintain clinically relevant control with a lower dose of the drug (ie. by extending the period between individual applications).

Firstly, during the initial six months of the study, when the dosing interval was increased by 25%, the loss of four-component remission was not statistically significant for the overall cohort. This was defined as a relapse probability below 15% and a probability of achieving four-component remission above 85%, based on the control arm of the OPTIMAL trial, in which 17% of patients experienced exacerbations.[20] However, during the second phase of the study, when the dosing interval was increased by 50%, there was a statistically significant decline in four-component remission, with only 58% of patients remaining in full remission.

Surprisingly few studies have investigated dose reduction of biologics in severe asthma. It is similar with global guidelines, Global Initiative for Asthma (GINA), for example, does not explicitly address discontinuation. It acknowledges that some patients may achieve sustained asthma control with biologics and could potentially be candidates for stepping down or discontinuing treatment, but it does not provide guidance on how to do so.[28] Accordingly, Hamada et al believe that discontinuation of a biologic is a feasible option in carefully selected patients. Their algorithmic approach discussed mostly the eligibility of some patients for treatment discontinuation (super-responders with controlled comorbidities and proven suppression of T2 inflammation) but does not discuss gradual dose reduction.[29] This lack of interest can be explained by the fact that in several earlier clinical trials, gradual loss of asthma control was found after discontinuation of biological agents, especially mepolizumab, which may have discouraged further research.[30–33]

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Table 1 Participants' Demographic Data, Including Basic Demographic Factors and Key Asthma-Specific Characteristic at the Time of Study Initiation

Variable	Overall N = 31[a]	Benralizumab N = 13[a]	Mepolizumab N = 18[a]	p-value[b]
Sex (or Gender)				0.701
Male	10 (32%)	5 (38%)	5 (28%)	
Female	21 (68%)	8 (62%)	13 (72%)	
Age (years)	64 (35, 81)	66 (50, 81)	59 (35, 77)	0.062
Charlson Comorbidity Index	2.00 (0.00, 7.00)	2.00 (1.00, 5.00)	1.50 (0.00, 7.00)	0.110
Smoking status				0.284
Current Smoker	1 (3.2%)	0 (0%)	1 (5.6%)	
Former Smoker	4 (13%)	3 (23%)	1 (5.6%)	
Never Smoked	26 (84%)	10 (77%)	16 (89%)	
BMI (kg/m^2)	29.0 (17.9, 44.0)	29.0 (22.1, 34.3)	28.2 (17.9, 44.0)	0.968
FEV1 (% predicted)	86 (48, 125)	98 (71, 125)	85 (48, 120)	0.180
FEV1 (L)	2.17 (0.90, 3.48)	2.11 (1.63, 3.41)	2.23 (0.90, 3.48)	0.589
BEC (cells/mm^3)	50 (0, 230)	0 (0, 60)	70 (23, 230)	<0.001
FeNO (ppb)	36 (5, 144)	56 (5, 94)	29 (7, 144)	0.253
Duration of remission before the start of the study (months)	14 (12, 52)	13 (12, 31)	14 (12, 52)	0.264
Total IgE (before biological therapy)	264 (17, 3000)	147 (22, 813)	444 (17, 3000)	0.055
Fungal sensitization (A. fumigatus)	4 (15%)	1 (9.1%)	3 (20%)	0.614
Acetylsalicylic acid-exacerbated asthma	2 (6.5%)	0 (0%)	2 (11%)	0.497

Notes: [a]N(%); Median (Min, Max). [b]Fisher's exact test; Wilcoxon rank sum test; Wilcoxon rank sum exact test.
Abbreviations: N, number of participants; BEC, blood eosinophil account; FEV1, Forced Expiratory Volume in 1 second; FeNO, Fractional Exhaled Nitric Oxide.

Our approach differed in that, rather than discontinuing treatment, we gradually reduced the biologic dose by extending the interval between administrations - targeting a 50% dose reduction. The ultimate goal was to maintain remission with the lowest effective biologic dose, in line with strategies used in the management of rheumatic diseases with biologic therapies.[34]

To our knowledge, dose reduction of anti-IL-5 biologics in severe asthma has only been examined in two clinical trials.[20,35] In the first study, the period between mepolizumab injections was extended to 6 or 8 weeks in 18 patients. During the one-year follow-up, pulmonary function and ACT score, selected parameters of persistence of disease control, remained unchanged. Further downward titration had not been tested.[35] The second study, the OPTIMAL trial, was an open-label, randomized controlled trial that tested a dose-tapering algorithm designed to identify the longest possible dosing interval before loss of asthma control occurred.[20] Given the similar hypothesis and clinical setting, after study completion, we analyzed our results in the context of the OPTIMAL study.

In both studies, patients were classified as being in clinical control for over one year; however, the definitions of control differed. In the OPTIMAL study, eligibility required no exacerbations or need for oral corticosteroids (OCS) in the preceding 12 months and BEC ≤300 cells/μL, with no requirements on lung function or symptoms scores. In contrast, our study applied a widely accepted four-component definition, including absence of exacerbations, no OCS use, an ACT score ≥ 20, and stable lung function, defined as no decline in FEV_1 >15% or 200 mL over the prior year. Symptom

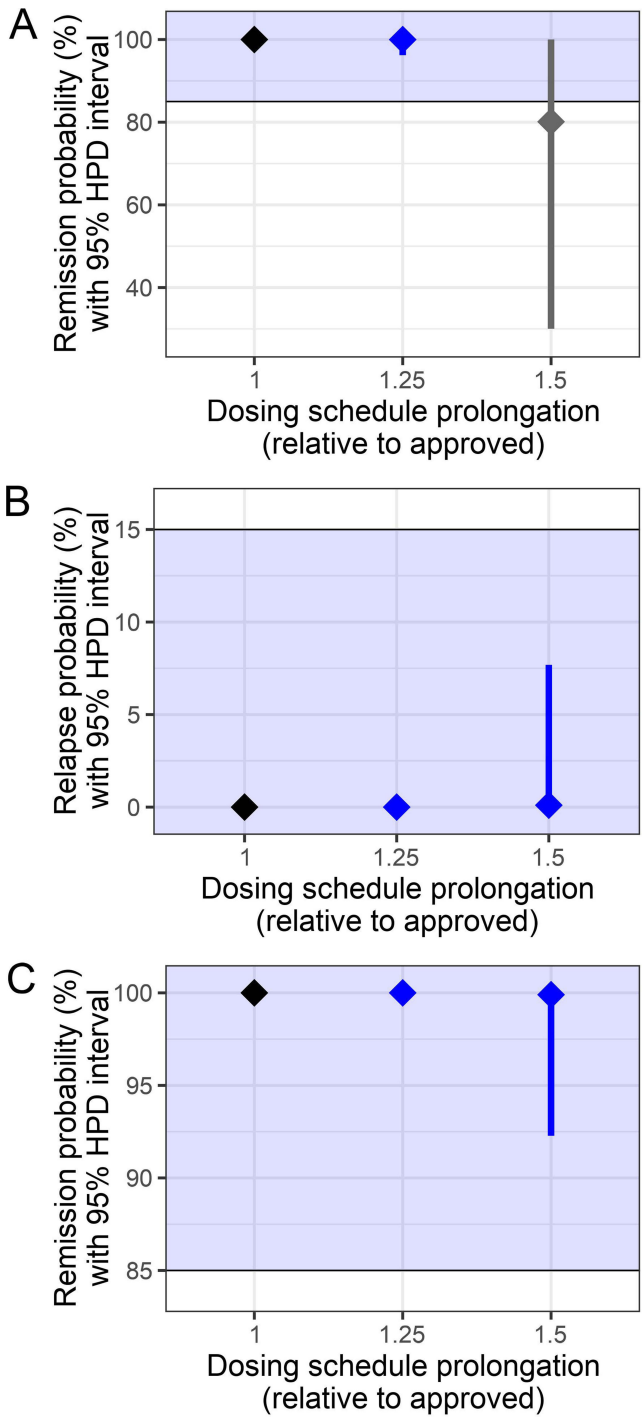

Figure 2 Posterior probabilities of four-component remission (**A**) relapse (**B**) and three-component remission (**C**) according to dosing interval prolongation. Estimates were obtained using a Bayesian logistic regression model. Dosing interval prolongation (ratios 1, 1.25, and 1.5) was included as a fixed effect, with subject identifier as a random intercept. Diamonds represent posterior means and vertical error bars denote 95% highest posterior density (HPD) intervals.

Notes: The blue shaded areas represent the predefined non-inferiority margins, defined as ±15% around the posterior mean estimated for the approved dosing interval (ratio 1). Prolonged dosing intervals (1.25 and 1.5) were tested for non-inferiority versus the approved interval. Results meeting the non-inferiority criterion are presented in blue; those not meeting the criterion are presented in gray; black diamond symbols indicate that non-inferiority was not assessed.

stability is a key patient-centered measure of asthma control, capturing important real-world burdens such as night-time awakenings, rescue medication use, and activity limitations. For this reason, it is included in nearly all proposed definitions of asthma remission.[18] The role of lung function monitoring in severe asthma remains debated. A post-bronchodilator $FEV_1 \geq 80\%$ predicted, previously proposed as a remission target, is often unachievable due to

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Table 2 Non-Inferiority Analysis: The Non-Inferiority Margin Is Established at 15% Based on the Estimated Probability of Relapse/Remission During the Approved Dosing Schedule

Hypothesis	log(OR) (95% CI)	Bayes Factor	Posterior Probability	Evidence for Hypothesis
Relapse				
25% dosing schedule extension is non-inferior to standard dosing	−18.9 (−33.7, −6.8)	8.0×10^4	100.0%	Decisive
50% dosing schedule extension is non-inferior to standard dosing	−6.6 (−15.6, −0.7)	59.4	98.3%	Very strong
Four-component remission				
25% dosing schedule extension is non-inferior to standard dosing	8.2 (1.7, 17.0)	2.7×10^2	99.6%	Decisive
50% dosing schedule extension is non-inferior to standard dosing	0.9 (−2.7, 5.7)	1.5	59.9%	None
Three-component remission				
25% dosing schedule extension is non-inferior to standard dosing	18.9 (6.8, 33.6)	2.7×10^2	100.0%	Decisive
50% dosing schedule extension is non-inferior to standard dosing	6.6 (0.7, 15.6)	54.4	98.2%	Very strong

irreversible airway remodeling. Stabilization, rather than normalization, of lung function has been suggested as a more realistic and clinically meaningful goal.[12,35] Accordingly, we incorporated both lung function stability and symptom control as complementary, though non-interchangeable, criteria for assessing clinical control and remission, thereby aiming to define remission in a more accurate and comprehensive manner. However, emerging evidence challenges this traditional view. Recently, the MESILICO study demonstrated that mepolizumab may reduce histological markers of

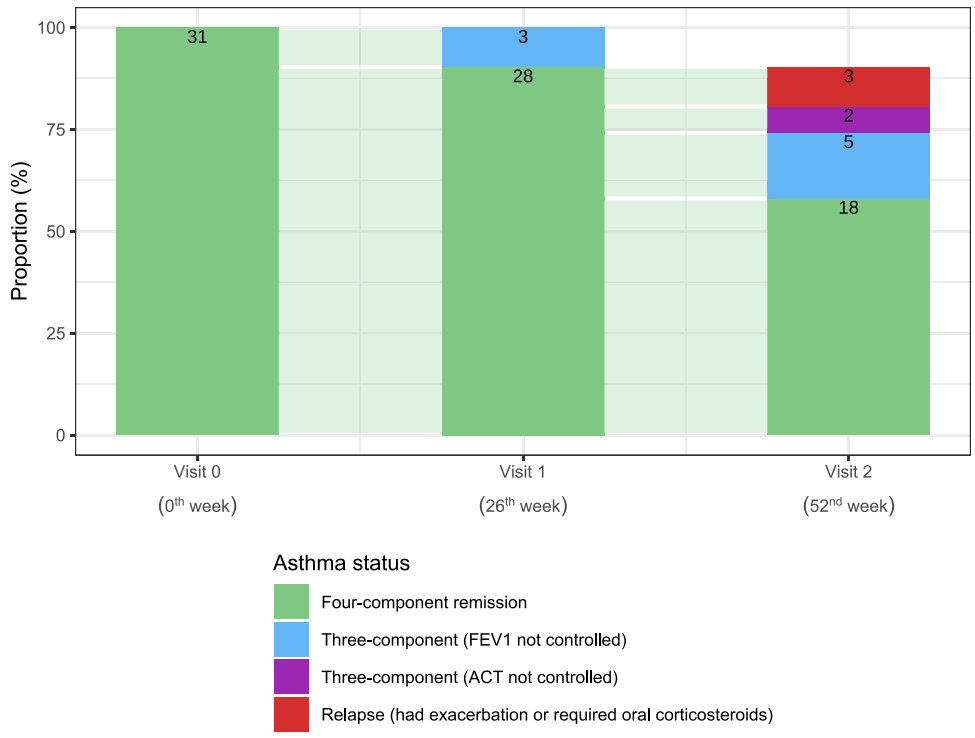

Figure 3 Transitions in asthma control status across study visits. Sankey diagram depicts patient flow between asthma status categories over three timepoints. Rectangle heights represent the number of participants in each asthma status category at a given visit, while ribbons show the number of individuals transitioning between categories over time. Asthma status includes four-component remission, three-component remission (with either ACT or FEV_1 decrease), and relapse (defined as exacerbation or need for oral corticosteroids).

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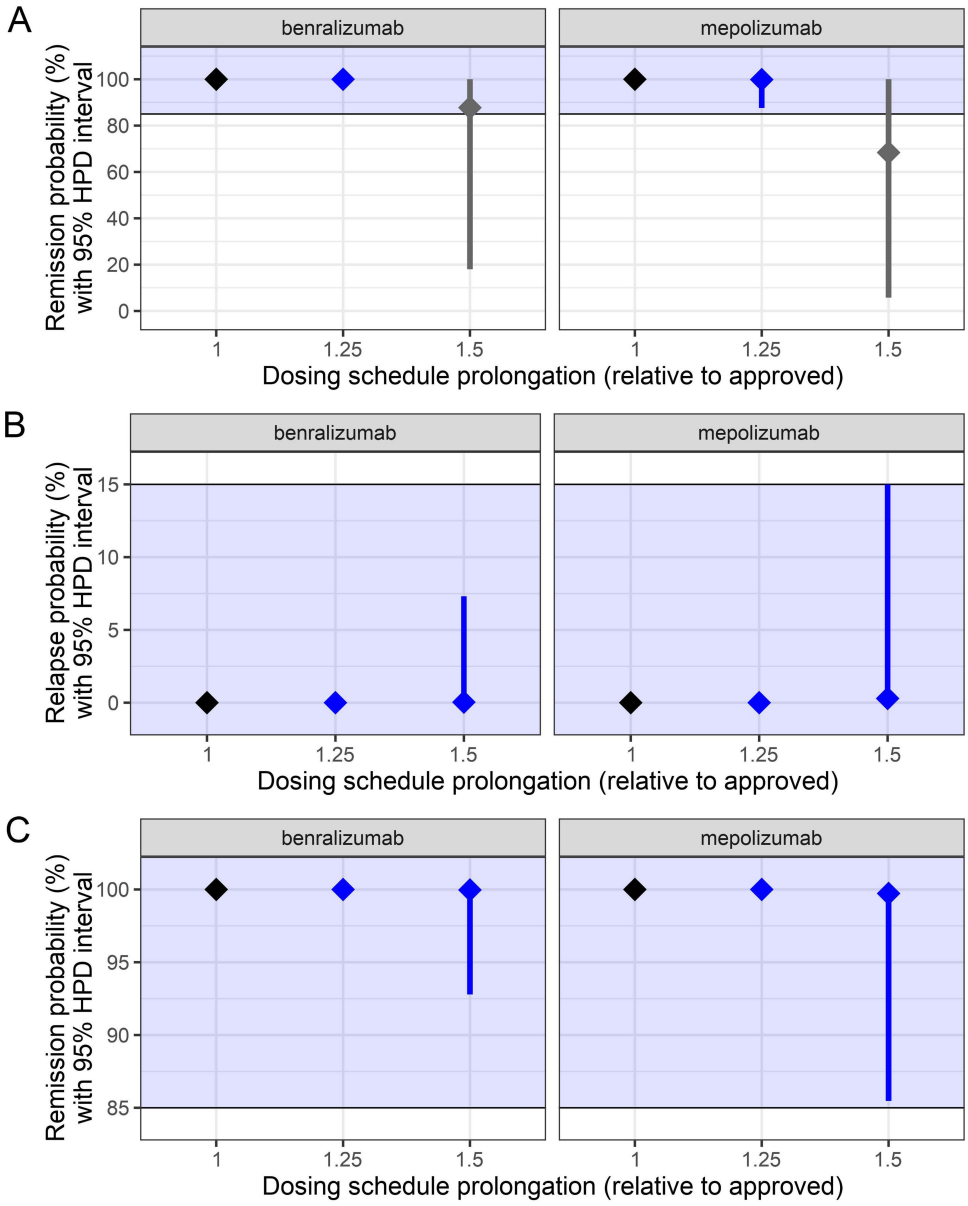

Figure 4 Comparison of posterior probabilities of four-component remission (**A**) relapse (**B**) and three-component remission (**C**) according to dosing interval prolongation and therapy type (benralizumab vs mepolizumab). Estimates were derived from a Bayesian logistic regression model including dosing interval prolongation (ratios 1 [approved interval], 1.25, and 1.5) and therapy type (benralizumab vs mepolizumab) as fixed effects, with subject identifier as a random intercept. Diamonds represent posterior means and vertical error bars denote 95% highest posterior density (HPD) intervals.

Notes: The blue shaded areas indicate the predefined non-inferiority margins, defined as ±15% around the posterior mean estimated for the approved dosing interval (ratio 1). Prolonged dosing intervals (1.25 and 1.5) were tested for non-inferiority versus the approved interval. Blue symbols denote intervals meeting the non-inferiority criterion; grey symbols indicate intervals not meeting the non-inferiority criterion; black symbols indicate that non-inferiority was not assessed.

airway remodeling, suggesting a potential reversibility of structural airway changes and, consequently, a disease-modifying effect.[36] These findings support the concept that biologic therapies, particularly when initiated early in appropriately selected patients, may influence the long-term trajectory of the disease. Nevertheless, until such disease-modifying effects are consistently confirmed and become clinically predictable, stability of lung function remains a pragmatic and clinically relevant target in routine care.

The criteria for loss of control also differed. In the OPTIMAL study, loss of control was defined by either a ≥15% reduction in FEV_1 from baseline, a blood eosinophil count ≥300 cells/μL, or an exacerbation requiring OCS: each assumed to reflect a surge in inflammation that would typically be suppressed by anti-IL-5 therapy. In contrast, our study defined loss of control as worsening of any component of remission, including symptoms. A key distinction lies in our

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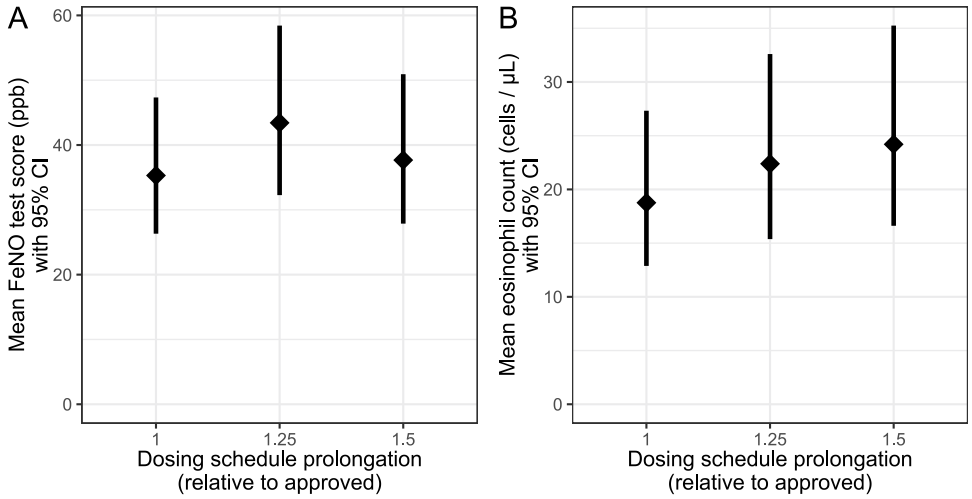

Figure 5 Estimated marginal means of (**A**) fractional exhaled nitric oxide (FeNO) and (**B**) peripheral blood eosinophil counts by dosing interval prolongation. A ratio of 1 corresponds to the approved dosing schedule, while ratios of 1.25 and 1.5 indicate prolonged dosing intervals. Estimated marginal means are displayed as black diamonds, with error bars indicating 95% confidence intervals (CI).

inclusion of symptom worsening as a valid indicator of loss of control. Symptom deterioration likely reflects a flare in underlying or confounding inflammation, potentially even preceding a measurable rise in blood eosinophils, particularly during the early phase of dose tapering, when biologic therapy may continue to suppress peripheral eosinophilia. We believe this approach enhanced the sensitivity of our criteria for detecting early loss of disease control.

Differences in the dose-tapering algorithms reflect distinct study objectives. The OPTIMAL study was a proof-of-concept trial aimed at developing an individualized dose-titration algorithm to determine the lowest effective biologic dose, including the possibility of complete discontinuation. In contrast, our study employed a slower reduction in biologic dosing designed to maintain disease control without full discontinuation. The primary objective was to evaluate a dose reduction strategy that could be broadly applicable to all patients with sustained asthma remission, avoiding the need for individualized titration protocols. We emphasize that complete discontinuation of biologic therapy is unlikely to be a feasible long-term goal for the majority of patients, as existing evidence consistently shows a gradual rebound in blood eosinophils and re-emergence of inflammation in most patients within 3 to 6 months of cessation (31,32). Thus, our protocol may be viewed as a pragmatic application of the OPTIMAL algorithm, adapted to support partial dose titration while prioritizing long-term disease stability.

Despite the differences in study protocols, we believe our findings are broadly consistent with those of the OPTIMAL study. In the OPTIMAL trial, 78% of patients tolerated a ≥50% extension in the dosing interval - the target dose reduction in our study, without loss of asthma remission, defined as absence of exacerbations, no need for OCS, and a BEC ≤300 cells/µL. Similarly defined clinical remission was observed in 81% of patients in our study. These patients remained in three-component remission, no exacerbations, no need for OCS, and ACT ≥ 20 or stable lung function, with a 50% extension of the dosing interval without an increase in mean blood eosinophil count. A more ambitious target, defined as four-component clinical remission with a 50% dose interval extension, was achieved in only 58% of patients (ie. 42% of patients lost at least one component of remission during the study period). The number of asthma exacerbations requiring systemic corticosteroids is difficult to compare across studies. In our study, this occurred in 3 patients (10%), while in the OPTIMAL study, it was reported in 32% of patients, mostly toward the end of the study, during the 125% dosing interval or after drug discontinuation.

The observation that loss of four-component remission was not accompanied by increases in Type 2 biomarkers suggests two possibilities: either that biomarker stability may better predict safe dose tapering than composite clinical scores such as the ACT, or that certain patients require tighter inflammatory control to maintain symptom remission despite "acceptable" biomarker levels. As Hirano and Matsunaga emphasize, asthma phenotypes require appropriate individualized management through precise assessment of pathophysiology based on age-related functional changes.[37]

This study has several limitations, the most notable being the absence of a control group. However, we believe that this did not significantly impact our findings. Due to the lack of a national severe asthma registry, the study was conducted at a single center with a relatively small pool of eligible patients. Based on findings from the OPTIMAL study, we believe it is reasonable to assume that the clinical status of a potential control group would have remained relatively stable over the one-year study period. Furthermore, any exacerbations occurring in such a control group would likely have only strengthened the significance of our results. We employed robust statistical analyses (Bayesian logistic and mixed-effects models), using an accepted probability threshold of <15% for exacerbations and >85% for achieving three- and four-component remission. Adherence to inhaled corticosteroids was not directly monitored; however, supplementary data indicate that the overall number of inhaled medications used did not increase during the study period. Although the one-year duration may be considered relatively short, the dose reduction was more gradual than in the OPTIMAL study, with changes implemented at six-month intervals. We consider this approach sufficient to assess the effects of dose reduction while prioritizing patient safety. Due to the limited sample size, we were unable to identify clinical or laboratory parameters that could distinguish patients in whom biologic dose reduction would be particularly effective.

Despite these limitations, our study provides important real-world evidence highlighting the possibility of dose reduction of anti–IL-5 biologics in some patients with severe asthma.

Conclusion

This study represents a first attempt to validate a previously proposed algorithm for dose reduction of anti–IL-5 biologics in patients with severe asthma who have achieved clinical remission. A gradual 50% extension of the dosing interval was feasible in a subset of patients; however, only 58% maintained full four-component clinical remission following dose reduction, while 42% experienced a partial loss of control in at least one remission component. Importantly, despite this loss of strict remission, the majority of patients preserved overall clinical stability, with more than 80% fulfilling three-component remission criteria and a low rate of exacerbations. These findings indicate that, although dose reduction may be achievable in selected patients, uniform application of a 50% interval extension carries a risk of compromising full remission. Further research is therefore needed to identify optimal candidates for treatment reduction, to evaluate the long-term sustainability of this approach, and to refine prolongation protocols. Incorporating additional pathophysiological assessments, such as Type 2 biomarkers and evaluation of bronchial hyperresponsiveness, may improve patient selection and enhance the safety and effectiveness of future interval-prolongation strategies. Ultimately, individualized tapering protocols may allow some patients to safely extend dosing intervals even beyond 50% while protecting others from premature dose reduction, emphasizing a personalized approach to biologic optimization in severe asthma.

Ethical Considerations

The study was approved by the Institutional Ethics Committee (Issue No. 2024/1003-3), and all participants provided written informed consent. This study was conducted in accordance with the Ethical Principles for Medical Research Involving Human Participants of the World Medical Association (Helsinki, 1964), and its subsequent amendments.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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