ICS use trajectories in severe asthma patients on benralizumab: real-life data from 3-years follow-up

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Abstract

Background: Inhaled steroids dose reduction is a relevant goal in severe asthma management.

Research question: We aimed to investigate ICS use trajectories and their clinical impact in severe asthma patients on benralizumab over 36 months.

Study design and Methods: We conducted a retrospective real-life observational study including clinical and inflammatory parameters. Patients were stratified according to ICS dose trends over time: "stable" (same dose at ≥80% of visits), "decreasing" (≥50% of visits with lower ICS dose vs baseline), and "increasing" (≥50% of visits with higher ICS dose vs baseline).

Results: 92 patients were included. Post-bronchodilation FEV_1 significantly increased over 36 months, while pre-bronchodilation FEV_1 remained stable. An overall statistically significant improvement was observed also for ACT, ACQ, AQLQ and annual exacerbation rate. The probability of decreasing ICS dose was 19.0% at 12 months and 37.4% at 36 months. In the decreasing group (30% of the cohort), baseline blood eosinophil count (BEC) was higher than in the stable group, and BEC suppression over time was greater. The decreasing group was also less frequently treated with OCS at baseline. At 24 months, the stable group showed a greater reduction in OCS use compared to the decreasing group. Across all groups, OCS use dropped from 89.8% to 4.9% at 36 months.

Interpretation: The findings suggest that ICS tapering is feasible and safe in selected patients under benralizumab therapy.

Conclusions: To the best of our knowledge, this is the first real-life study specifically supporting the ICS-sparing effect of benralizumab over a 36-month period.

Key words

Benralizumab; inhaled corticosteroids; severe asthma; steroid sparing

ICS use trajectories in severe asthma patients on benralizumab: real-life data from 3-years follow-up

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Glossary

ACT Asthma Control Test

ACQ Asthma Control Questionnaire

AQLQ Asthma Quality of Life Questionnaire

BEC blood eosinophils count

BMI body mass index

CRSwNP chronic rhinosinusitis with nasal polyps

ICS inhaled corticosteroids

OCS oral corticosteroids

INTRODUCTION

Around 300 million people worldwide suffer from bronchial asthma that represents the most frequent non communicable respiratory condition (1). The severe form affects 3-5% of asthma patients (2) and is generally characterised by difficult symptom control and higher disease burden (3). Inhaled steroids (ICS) represent the cornerstone of asthma treatment according to the international recommendations (4,5); in fact, they are able to target bronchial inflammation and to reduce daily symptoms and exacerbations, showing an optimal safety profile. High dose ICS, namely a daily dose >500 mcg fluticasone or equivalent are currently suggested for the treatment of severe asthma forms (4,5). However, some recent evidence highlighted a not negligible systemic absorption of high-dose ICS (6-8) in terms of adrenal suppression, and generally speaking a similar risk of adverse events when compared to systemic steroids. According to a recently published UK observational nationwide report, moderate to high ICS doses were associated, although at a low frequency, with an increased riskof cardiovascular events, pulmonary embolism, and pneumonia (9). Similarly, data from a large study from the Swedish asthma registry highlighted an association between the exposure to high-dose (≥800-1599 µg budesonide) and very high dose (≥1600 µg budesonide) ICS and an increased hazard ratio for cardiovascular disease, type 2 diabetes mellitus, osteoporosis, and pneumonia (10).

In addition, both the historical UK cohort study mentioned above (9) including patients with asthma and conducted on electronic medical records pointed out that stepping-up to high-dose ICS did not result in reducing time to first moderate/severe asthma exacerbations and was instead associated with higher rates of relapse and antibiotic prescriptions related to lower respiratory tract conditions .

Although further investigations are needed to confirm the findings reported above, the evidence on sub-optimal safety profile of high-dose ICS and their limited clinical efficacy when compared to lower doses suggests: i) to explore alternative options, including biologic drugs, to increased daily doses of inhaled treatment in the case of poor control under moderate ICS dose; ii) to consider ICS reduction as a major goal in asthma management, especially in severe asthma patients who are eligible for biologic therapy and who are commonly exposed to higher ICS daily intake (7).

However, even though OCS sparing effect has been often explored as a relevant outcome of monoclonal antibodies in severe asthma (11), ICS tapering under biologic therapy has been poorly investigated so far. In fact, the currently available evidence comes from clinical trials (12), whose data need to be confirmed in a more heterogeneous real-life setting, and from studies not specifically designed for that purpose (13). In addition, long term data on sustainability over time in terms of safety and efficacy of stepping down from high dose ICS in patients under biologic treatment are lacking. We aimed to investigate the trajectories of ICS use in severe asthma patients on benralizumab treatment, and to explore the trend of clinical and inflammatory parameters over a three years follow-up by comparing patients on stable or variable ICS dose. The present report represents a focused analysis of the results from a published real-life study (14).

METHODS

This is a secondary analysis of previously collected data. Study design and methodology are reported in detail elsewhere (14). In brief, data from 9 Referral Centres for severe asthma, part of our national Severe Asthma Network Italy (SANI), were retrospectively collected between January 2018 and February 2021. Consenting patients prescribed with benralizumab for severe asthma according to current regulatory requirements (15) were included. Patients' characteristics—namely age, gender, body mass index (BMI), smoking habit, age at asthma diagnosis, and comorbidities—were considered for the analysis. Inflammatory (blood eosinophil count - BEC), functional (pre- and post-bronchodilator FEV_1), and clinical (Asthma Control Test - ACT; Asthma Control Questionnaire - ACQ; Asthma Quality of Life Questionnaire - AQLQ; Annual Exacerbation Rate) parameters were analysed at baseline and at 6, 12, 24, and 36 months after benralizumab initiation. Inhaled therapy and systemic corticosteroid use were evaluated at the same time points. ICS dose was expressed as mcg fluticasone or equivalent daily.

In all centres, ICS dose adjustments were made by the treating physicians as part of routine clinical decision making, based on comprehensive individual assessment of clinical symptoms, pulmonary function, and inflammatory biomarkers in accordance to the step up/down approach suggested by GINA recommendations. No study-related protocol or predefined algorithm guided ICS tapering, and no external incentive or expectation was introduced that could have influenced the choice to reduce ICS dose, thereby minimizing potential bias in ICS management strategies. The retrospective design of the study also excludes the awareness of the study outcome as a potential source of bias.

Three groups of patients were identified based on ICS dose evolution during the follow-up: “stable” (same dose in at least 80% of the assessed time points); “decreasing” (at least 50% of follow-up assessments with lower ICS dose compared to baseline, or both final two time points showing a dose reduction from baseline); “increasing” (at least 50% of follow-up assessments with higher ICS dose compared to baseline, or both final two time points showing an increase). To avoid misclassification, patients who required escalation of oral corticosteroid (OCS) therapy during follow-up were not considered part of the ICS-decreasing group, even if ICS dose was lowered.

Statistical analysis

Baseline characteristics were analysed using descriptive statistics. Categorical variables were expressed as frequencies and percentages, and continuous variables as medians with interquartile ranges (IQR). Between-group comparisons at baseline were assessed using Fisher’s exact test or Mann–Whitney U test, as appropriate.

Longitudinal analysis of ICS trajectories and their association with clinical outcomes was conducted using generalized linear mixed-effect models with subject-specific random intercepts and follow-up time points as independent variables. Differences in the predicted probabilities of ICS dose reduction and of OCS treatment over time were evaluated using the same model framework.

Inflammatory, functional, and clinical parameters (BEC, FEV_1, ACT, ACQ, AQLQ, annual exacerbation rate) were modelled using linear or generalized mixed-effect models for longitudinal data, adjusted for potential confounders including sex, age, BMI, smoking habit, age at asthma diagnosis, and the presence of chronic rhinosinusitis with nasal polyps (CRSwNP).

All analyses were conducted using R software version 4.3. A *p*-value <0.05 was considered statistically significant.

RESULTS

Study population characteristics at baseline are reported in Table 1. Detailed data on baseline inhaled therapy was available for 92 out of 108 patients (85.2%) included in the study, and for 80 of them (87.0%) ICS doses were assessed at least two times during the follow-up (Figure 1). At baseline evaluation, 46 patients (50.0%) were on 500-1000 mcg inhaled fluticasone or equivalent, followed by 40 (43.5%) of them taking > 1000 mcg. Only 6 patients (6.5%) used < 500 mcg per day. No differences between the different ICS groups were found based on sex (p = 0.542), age (p = 0.282), BMI (p = 0.727), smoking history (p = 0.974), age at diagnosis (p = 0.272), or CRSwNP (p = 0.985). Patients in the ICS decreasing group were less frequently treated with OCS at baseline compared to the other subgroups (p = 0.019). When looking at the ICS use trajectories over the follow-up, slightly more than half of patients (n=53, 66.3%) remained on a stable ICS dose; 30.0% (n=24) of patients moved to a lower daily intake, being the number of patients on < 500 mcg dose almost three times higher at the end of the observation (n=20, 27.8%, p <0.001) compared to the baseline proportion. Only 3.7% (n=3) increased the ICS dose during follow-up period (Figure 1).

When considering the whole population, predicted probability of decreasing ICS dose was higher at 12 months follow-up compared to 6 months visit (p = 0.043), and at 36 months assessment compared to 6 (p<0.001), 12 (p = 0.041) and 24 (p = 0.010) months evaluation (Figure 2 panel A). More in detail, the overall probability of decreasing ICS dose in the whole sample was 19.0% (95%CI 9.0-35.4) at 12 months and 37.4% (95%CI 21.7-56.4) at 36 months. A similar trend characterized the decreasing group as defined in the *Methods*, showing a higher probability to reduce ICS dose at 12 and 36 months when compared to 24 (p = 0.033, p = 0.026) months assessment (Figure 2 panel B). In particular, the probability to decrease inhaled therapy intake was 87.1% (95%CI 63.9-96.3) and 88.0% (95%CI 65.3-96.6) at 12- and 36-months follow-up respectively.

The potential "cost" of ICS dose reduction in terms of OCS use was also explored (Figure 2 panel C). Predicted probability of being treated with OCS dropped down at 6 months (p < 0.001, 16.1%, 95%CI 8.2-29.0) and then remained stable with significant lower values at 12 (8.1%, 95%CI 3.2-18.9), 24 (27.6%, 95%CI 14.7-45.6) and 36 months (4.9%, 95%CI 1.7-13.0) compared to baseline (89.8%, 95%CI 78.6-95.4). No statistically significant differences were found based on ICS group at 6 (p = 0.350), 12 (p = 0.556) and 36 (p = 0.861) months follow up. At 24 months, ICS stable group showed a greater decrease in OCS probability compared to ICS decreasing group (p = 0.032).

In terms of inflammation assessment, baseline BEC was higher in the decreasing group (median=675, IQR 462-960) than in the stable one (median = 420, IQR 0-658) (p = 0.011). Eosinophil count decreased significantly from 570.0 (0.95CI: 505.3-634.8) to 2.4 (0.95CI: -66.4-71.3) cells/microliter over the whole follow-up time frame (p < 0.001) (Figure 3 panel A). BEC improvement from baseline assessment was significantly more apparent in the decreasing group (from 678.0, 0.95CI: 571-784 to 1.3, 0.95CI: -109.7-112.2) compared to the stable group (from 462.2, 0.95CI: 388.1-536.3 to 3.6, 0.95CI: -78.3-85.5, p < 0.001).

Regarding lung function, no differences in pre- and post-bronchodilator FEV_1% could be described at baseline by ICS dose group (p = 0.588, p = 0.187 respectively). The pre-bronchodilator FEV_1% showed a substantial stability over the observation time frame, without significant differences at any point during the follow-up period (t6 p = 0.090, t12 p = 0.194, t24 p = 0.592, t36 p = 0.979) even when considering the decreasing group (p = 0.440) (Figure 3 panel B). The post-bronchodilator FEV_1% had a significant improvement from baseline (74.6, 0.95CI: 68.1-81.2) to 36 (87.8, 0.95CI 91.1-94.6, p = 0.007). There were no differences based on ICS group (p=0.333) (Figure 3 panel C).

Patient reported outcomes values were fully comparable at baseline in the increasing, stable and decreasing subgroups (ACT: p = 0.972, ACQ: p = 0.265, AQLQ: p = 0.161)

The ACT score increased from 15.2 (0.95CI: 14.2-16.1) to 22.8 (0.95CI: 21.9-23.8) at 36 months follow-up (p < 0.001). Males reported higher score compared to females (p=0.033), but no significant differences were found based on ICS group (p=0.577) (Figure 4 panel A).

The ACQ score changed from 2.4 (0.95CI: 2.0-2.8) to 0.6 (0.95CI: 0.2-1.1) at 36 months follow-up (p<0.001) and the trend was comparable in the three ICS subgroups (Figure 4 panel B).

The AQLQ score increased from 4.4 (0.95CI: 3.7-5.1) to 5.5 (0.95CI: 4.7-6.2) at 36 months follow-up (p = 0.019), without remarkable differences based on ICS dose trend (p = 0.181) (Figure 4 panel C). Male reported higher score compared to females (p = 0.044), unrelated to ICS trajectory.

The annual exacerbation rate score was comparable in the different ICS subgroups (p = 0.101) at baseline and over the whole follow-up period. It decreased from 2.7 (0.95CI: 2.4-3.1) to 0.2 (0.95CI: -0.1-0.6) at 36 months follow-up (p < 0.001) (Figure 4 panel D).

Discussion

Our study investigated the trends of ICS use in severe asthma patients on benralizumab treatment over a three-years follow-up in real-life. According to our findings, patients on stable ICS dose represented the predominant subgroup (66.3%), and around 1 out of 3 (30.0%) demonstrated a decreasing trend, in most cases recorded at the 36 months follow-up. Of note, no differences were detected overtime when comparing the stable and decreasing subgroups by BEC, lung function, patient reported outcomes, and asthma exacerbation rate. These results align with the emerging notion that, in the context of biologic therapy, ICS dose can be modulated without compromising disease stability. The inhaled therapy modulation did not result in increased OCS use; in fact, a rapid and maintained OCS sparing-effect could be observed. Generally speaking this represents an expected achievement related to the biologic treatment that has been specifically demonstrated for benralizumab as well (11,14). The additional contribution of our findings highlight how benralizumab might exert a broader corticosteroid-sparing effect beyond OCS, supporting an ICS step-down strategy that prioritizes safety and reduction in inhaled corticosteroid-related side effects. Notably, stable and stepping-down patients did not significantly differ in terms of sex, age, BMI, smoking history, age at diagnosis, or concomitant CRSwNP, suggesting that a successful ICS tapering can be performed regardless of the presence of known determinants of potential poor asthma control or worse disease evolution in patients under benralizumab. This observation reinforces the generalizability of our findings and suggests that clinicians should not exclude ICS tapering a priori based on baseline demographic or comorbidity profiles. When looking at baseline clinical profile, patients in the ICS decreasing group were less frequently treated with OCS at baseline, suggesting that feature as a reasonable predictor of successful inhaled corticosteroid step-down strategies),. In the light of the recent data showing an increased risk of steroid-related adverse events associated with prolonged use of high-dose ICS (6-10), GINA recommendations identify the inhaled therapy reduction as a priority in the management of severe asthma patients well responding to biologic treatment (4). The potential benefits of reducing corticosteroid exposure may extend beyond chronic toxicity, potentially impacting infection risk and disease outcomes in comorbid conditions. This has been recently emphasized in the context of SARS-CoV-2 infection, where patients on biologic treatments such as mepolizumab maintained good asthma control and experienced favourable infection courses despite immunomodulation (16). Beyond clinical effectiveness, inhaled corticosteroid reduction and the associated lower need for OCSmay also translate into significant health economic benefits. Real-world data have already shown that biologic therapies, such as mepolizumab, can yield cost savings in severe eosinophilic asthma through reduced exacerbations and healthcare utilization (17).

However, the evidence supporting that approach is quite limited so far, especially in real-life settings and over long-term follow-up. The recently published SHAMAL study has investigated the safety and clinical efficacy of ICS tapering in patients achieving disease control under benralizumab treatment (12). Within the frame of a phase 4, multicentre, randomised, open-label, active-controlled, clinical trial, the authors explored exacerbation rate, lung function, FeNO values, and patient reported outcomes over 48 weeks follow-up by comparing the treatment reduction group with the reference one maintaining a stable ICS dose. At the end of the study, a decreased FEV_1 and higher FeNO values were detected in patients, reducing their inhaled steroid therapy to as-needed only, but no differences were observed when comparing the treatment reduction group, including low, medium, and high-dose ICS, to the reference one. However, as a major result, the study demonstrated that 92% of patients safely tapered their inhaled therapy and 87% of them remained exacerbation free during the whole observation time frame. The key findings of our study substantially confirm the SHAMAL main message, although in the different frame of a real-world setting and with a lower proportion of patients reducing their ICS dose. The relevance of ICS tapering in the biologic era has been further reinforced by recent trials on long-acting anti-IL-5 therapies, such as depemokimab, showing sustained disease control with reduced dosing schedules in eosinophilic asthma (18). Our analysis adds value by showing that even outside a structured protocol-driven environment, ICS tapering may occur with sustained control, provided that patients are carefully monitored and biologic response is confirmed. Of note, ICS tapering was part of the longitudinal protocol in SHAMAL study, of course in well controlled patients. On the opposite our retrospective data reflect the real-life behaviour of clinicians variably following the step-down approach suggested by international recommendations (4); in addition, a not negligible proportion of patients were on medium ICS dose already at baseline, so that a further decrease was less likely, and no patients in our study resulted in reducing their inhaled steroid therapy to as-needed only. This may partially explain the lower rate of ICS reduction observed in our cohort compared to SHAMAL, highlighting how real-world barriers, such as clinical inertia or uncertainty regarding tapering criteria, can impact the translation of guideline recommendations into practice. Similarly to SHAMAL, our data confirm no differences in ICS stable and decreasing subgroups in terms of FEV_1 (% of predicted), exacerbation rate, and patient reported outcomes, being the same trend sustained over the whole three-years study time frame. This finding is particularly relevant as it strengthens the concept that ICS reduction is not only feasible but also safe in the long term. Of note, the post-bronchodilator FEV_1%, that was not evaluated in SHAMAL, demonstrated a significant improvement from baseline to 36 months in both ICS stable and decreasing groups, suggesting that even in the case of tapered ICS the known benralizumab effect on lung function and potentially on bronchial remodelling (19) is maintained. Differently from SHAMAL, no data on FeNO were available in our dataset, which might represent a limitation. Nevertheless, the sustained eosinophil suppression in both ICS stable and decreasing groups, with a significantly greater depletion in the latter, supports the interpretation of successful biologic response and corroborates the feasibility of ICS tapering in selected patients. In terms of inflammation markers, we relied on blood eosinophil count that showed a rapid and maintained depletion with no difference in the population subgroups. Although the present study focused on BEC as a primary inflammatory marker, recent investigations suggest that biologic therapy may also modulate the broader immunological landscape, including regulatory T cell populations, that could further support corticosteroid sparing strategies (20). However, the specific relevance of FeNO as a predictor of poor control or asthma exacerbations cannot be neglected (21). The long-term follow-up duration in our study, without asthma exacerbations regardless of the different ICS-dose trajectory, seems to sustain a full benralizumab ICS-sparing effect even without confirmatory FeNO values.

These observations suggest that baseline BEC may serve as a potential predictor of ICS tapering success, as patients in the decreasing group showed significantly higher eosinophil counts at baseline, and this marker could be considered when selecting candidates for corticosteroid reduction. Regarding real world setting, a few data have been generated on the specific topic so far, none of them related to benralizumab. When considering other anti-IL-5 agents, a retrospective study analysed the administrative claims information related to 351 severe asthma patients prescribed with mepolizumab (22). Around half of the patients (49%) within 12 months follow-up and 68.2 % at 24 months follow-up were able to reduce or discontinue ICS for at least 1 quarter that represents a higher rate when compared to our study. The greater proportion of patients on high ICS-dose at baseline compared to our population (100% vs 50%) might account for that difference. The authors also reported no statistically significant differences in terms of exacerbation rate and reliever therapy when comparing patients who discontinued ICS and those who maintained ICS treatment over the 24-month follow-up period (). These findings align with our observation that asthma control was preserved regardless of ICS modulation, further supporting that biologics may decouple disease control from ICS dependence in responsive patients. In our study no patients completely discontinued the inhaled therapy, but we also observed a similar disease control in patients on stable ICS and in the decreasing subgroup, which is quite coherent with the evidence that stepping-up from medium to high dose ICS does not significantly improve disease control (9). Of note, differently from our study, the retrospective analysis of mepolizumab treated asthma patients limited the follow-up to 24 months of observation, and no information were provided in terms of lung function and BEC.

This highlights the added value of our analysis, which extends the observational period to 36 months and provides a multidimensional assessment of outcomes, including lung function, symptoms, quality of life, and inflammation. A retrospective cohort study evaluating data from a commercial claims database reported about the ICS sparing effect of mepolizumab in 346 adult severe asthma patients over 12 months follow-up (23). At the end of the observation frame, the proportion of patients on high-dose ICS was 16% lower than at baseline. However, no comparative analysis about disease control in patients reducing the inhaled therapy and on stable ICS dose was performed. This gap in comparative effectiveness is addressed in our study, that explicitly examined the clinical equivalence of the two groups across multiple endpoints, confirming that tapering ICS is a safe and realistic objective in patients achieving control under benralizumab.To the best of our knowledge, our report provides the first real-life focused analysis on ICS-sparing effect of benralizumab in severe asthma patients, over a long-term follow-up (36 months). Our findings support that tapering ICS dose over biologic treatment is achievable in real-life without any impact on the diseases overall control and should be considered as a main goal to minimize the potential side effects related to high-dose ICS. As a major limitation, besides the retrospective design of the study, the lack of data on FeNO measurement must be acknowledge. Although it is considered by international recommendations as a required biomarker for asthma assessment and pheno-endotyping, especially in the case of severe forms, the missing information from some centres collaborating to our study and the lack of regular assessment in other sites, forced us to exclude it from the analysis to avoid bias related to incompleteness. The absence of a systematic and standardised assessment of treatment adherence represents a further limitation . However, it reflects the real-life setting, where adherence rate is always complex to evaluate and cannot rely on completely accurate tools (24).

It has been previously described that adherence to inhaled treatment before and after a biologic treatment start is substantially comparable (24).

Further real-word evidence is needed to confirm our results and to explore whether the best candidate for a safe and effective ICS tapering can be identified in advance relying on a specific baseline profile. Additional research should also support how to define the minimal ICS dose in each individual patient still able to maintain the optimal disease control.

CRediT authorship contribution statement

Laura Pini: Supervision-Equal, Validation-Equal. **Marco Caminati**: Conceptualization-Equal, Investigation-Equal, Writing - original draft-Equal. **Matteo Maule:** Data curation-Equal, Investigation-Equal. **Diego Bagnasco** Investigation-Equal, Validation-Equal. **Bianca Beghé:** Investigation-Equal, Validation-Equal. **Benedetta Bondi:** Investigation-Equal. **Fulvio Braido:** Data curation-Equal, Supervision-Equal. **Paolo Cameli:** Data curation-Equal, Investigation-Equal. **Cristiano Caruso:** Investigation-Equal. **Claudia Crimi:** Data curation-Equal, Investigation-Equal. **Yehia El Masri:** Investigation-Equal **Jordan Giordani:** Data curation-Equal, Investigation-Equal, Writing - Review & Editing-Equal. **Gabriella Guarnieri:** Investigation-Equal, Validation-Equal. **Manuela Latorre:** Investigation-Equal. **Andrea Mastrototaro:** Data curation-Equal, Investigation-Equal. **Francesco Menzella:** Investigation-Equal. **Claudio Micheletto:** Supervision-Equal, Validation-Equal. **Alessandro Pini:** Investigation-Equal. **Stefano Piras:** Investigation-Equal. **Antonio Spanevello:** Supervision-Equal, Validation-Equal. **Andrea Vianello:** Data curation-Equal, Supervision-Equal, Validation-Equal. **Dina Visca:** Investigation-Equal, Validation-Equal. **Martina Zappa:** Investigation-Equal. **Marco Zurlo:** Data curation-Equal, Investigation-Equal. **Pierluigi Paggiaro:** Supervision-Equal, Validation-Equal. **Francesco Blasi:** Supervision-Equal, Validation-Equal. **Giorgio Canonica:** Supervision-Equal, Validation-Equal. **Gianenrico Senna:** Investigation-Equal, Validation-Equal. **Roberto Benoni:** Data curation-Equal, Formal analysis-Equal.

Ethics statements

The SANI registry was constructed according to the Declarations of Helsinki and Oviedo.

The study was approved by the Central Ethics Committee for the SANI Network (protocol number: 1245/2016, protocol ID: 73714).

Data availability statement

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of interest statements

All authors reported no financial interests or potential conflicts of interest related to this study. L.P. received grants for educational events from AstraZeneca, Chiesi Farmaceutici, Glaxo Smith Kline and speaker fees from AstraZeneca, Chiesi Farmaceutici S.p.A, Glaxo Smith Kline, Guidotti, Grifols, Menarini, Novartis AG; M.C. received financial grants from AstraZeneca, GSK and Sanofi; D.B, B.Be, F.Br, D.V. received speaker fees from AstraZeneca, Chiesi Farmaceutici S.p.A, Glaxo Smith Kline, Guidotti, Grifols, Menarini, Novartis AG, Sanofi;

P.C. received grants and speaker fees from AstraZeneca and GSK; C.Cr. received honoraria for lectures from AZ, GSK, Sanofi, Novartis, Resmed, F&P; C.M. received fees as a speaker in national and international congress from Astrazeneca, Sanofi, Novartis, GSK, Menarini, Guidotti, Firma, Roche, Berlin Chemie, Chiesi, Zambon; G.S. received financial grants from AstraZeneca, GSK, Novartis and Sanofi; P.P. received grants for educational events from AstraZeneca, Chiesi Farmaceutici, Glaxo Smith Kline, Guidotti and Sanofi and grants for participation to Advisory Board from Chiesi Farmaceutici, Glaxo Smith Kline, and Sanofi; F.Bl. received financial grants from AstraZeneca, Chiesi Farmaceutici S.p.A and Insmed Inc. and speaker fees from AstraZeneca, Chiesi Farmaceutici S.p.A, Glaxo Smith Kline, Guidotti, Grifols, Insmed Inc., Menarini, Novartis AG, Sanofi-Genzyme, Viatris Inc., Vertex Pharmaceuticals and Zambon; G.W.C. recceived research grants from A. Menarini, Allergy Therapeutics, AstraZeneca, Chiesi Farmaceutici, Faes, Firma, Glaxo Smith Kline, Guidotti-Malesci, Hal Allergy, Innovacaremd, Novartis, OmPharma, RedMaple, Sanofi-Aventis, Sanofi-Genzyme, Stallergenes-Greer, Uriach Pharma, ThermoFisher, Valeas.

B.B., G.G, M.L., A.M., M.M, Y.E.M, F.M., J.G., A.P., S.P., A.S., A.V. M.Z., R.B. have nothing to disclose

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Table 1 – Baseline characteristics of the overall sample and stratified by inhaled corticosteroids (ICS) group.

		Stable (n=53)	Decrease (n=24)	Increase (n=3)	Not assigned (n=28)	Overall (n=108)
Sex						
	Female	34 (64,2%)	12 (50,0%)	2 (66,7%)	16 (57,1%)	64 (59,3%)
	Male	19 (35,8%)	12 (50,0%)	1 (33,3%)	12 (42,9%)	44 (40,7%)
Age (years)						
	median (IQR)	60 (56-67)	59 (50-64)	73 (64-73)	64 (52-69)	60 (54-68)
Smoking						
	yes	0 (0,0%)	0 (0,0%)	0 (0,0%)	1 (3,6%)	1 (0,9%)
	no	37 (69,8%)	18 (75,0%)	2 (66,7%)	21 (75,0%)	78 (72,2%)
	ex	16 (30,2%)	6 (25,0%)	1 (33,3%)	6 (21,4%)	29 (26,9%)
Poliposis						
	no	19 (35,8%)	9 (37,5%)	1 (33,3%)	14 (50,0%)	43 (39,8%)
	yes	34 (64,2%)	15 (62,5%)	2 (66,7%)	14 (50,0%)	65 (60,2%)
Age at diagnosis						
	median (IQR)	38 (26-49)	32 (19-38)	30 (27-35)	39 (25-54)	36 (23-49)
Body mass index (kg/m2)						
	median (IQR)	24,9 (22,0-28,0)	26,1 (21,3-28,4)	22,7 (22,0-24,4)	26,6 (25,0-29,0)	25,8 (22,1-28,1)
OCS use at baseline						
	No	0 (0,0%)	7 (29,2%)	0 (0,0%)	3 (10,7%)	16 (14,8%)
	Yes	34 (64,2%)	8 (33,3%)	3 (100,0%)	22 (78,6%)	67 (62,0%)
	NA	13 (24,5%)	9 (37,5%)	0 (0,0%)	3 (10,7%)	25 (23,1%)
ICS dosage (mg) baseline						
	<500	6 (11,3%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	6 (5,6%)
	500-1000	26 (49,1%)	14 (58,3%)	0 (0,0%)	0 (0,0%)	40 (37,0%)
	>1000	21 (39,6%)	10 (41,7%)	3 (100,0%)	12 (42,9%)	46 (42,6%)
	NA	0 (0,0%)	0 (0,0%)	0 (0,0%)	16 (57,1%)	16 (14,8%)
ICS dosage (mg) 6th month						
	<500	7 (13,2%)	7 (29,2%)	0 (0,0%)	1 (3,6%)	15 (13,9%)
	>1000	25 (47,2%)	4 (16,7%)	1 (33,3%)	0 (0,0%)	30 (27,8%)
	500-1000	20 (37,7%)	11 (45,8%)	2 (66,7%)	11 (39,3%)	44 (40,7%)
	NA	1 (1,9%)	2 (8,3%)	0 (0,0%)	16 (57,1%)	19 (17,6%)
ICS dosage (mg) 12th month						
	<500	7 (13,2%)	9 (37,5%)	1 (33,3%)	1 (3,6%)	18 (16,7%)
	>1000	20 (37,7%)	1 (4,2%)	1 (33,3%)	0 (0,0%)	22 (20,4%)
	500-1000	21 (39,6%)	11 (45,8%)	1 (33,3%)	0 (0,0%)	33 (30,6%)
	NA	5 (9,4%)	3 (12,5%)	0 (0,0%)	27 (96,4%)	35 (32,4%)
ICS dosage (mg) 24th month						
	<500	4 (7,5%)	8 (33,3%)	0 (0,0%)	1 (3,6%)	13 (12,0%)
	>1000	23 (43,4%)	6 (25,0%)	3 (100,0%)	1 (3,6%)	33 (30,6%)
	500-1000	21 (39,6%)	8 (33,3%)	0 (0,0%)	(0,0%)	29 (26,9%)
	NA	5 (9,4%)	2 (8,3%)	0 (0,0%)	26 (92,9%)	33 (30,6%)
ICS dosage (mg) 36th month						
	<500	9 (17,0%)	12 (50,0%)	0 (0,0%)	2 (7,1%)	23 (21,3%)
	>1000	18 (34,0%)	0 (0,0%)	2 (66,7%)	0 (0,0%)	20 (18,5%)
	500-1000	20 (37,7%)	10 (41,7%)	1 (33,3%)	0 (0,0%)	31 (28,7%)
	NA	6 (11,3%)	2 (8,3%)	0 (0,0%)	26 (92,9%)	34 (31,5%)

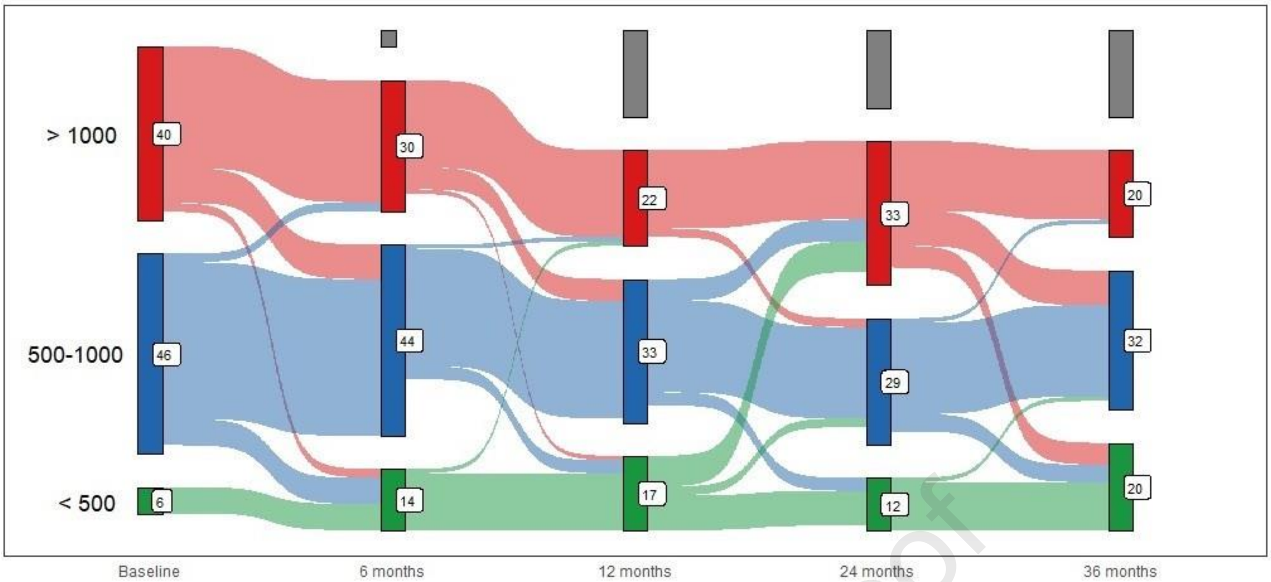

Figure 1 – Sankey plot of the number of patients at each follow-up time point based on Inhaledcorticosteroids dosage. Grey bars represent the missing values.

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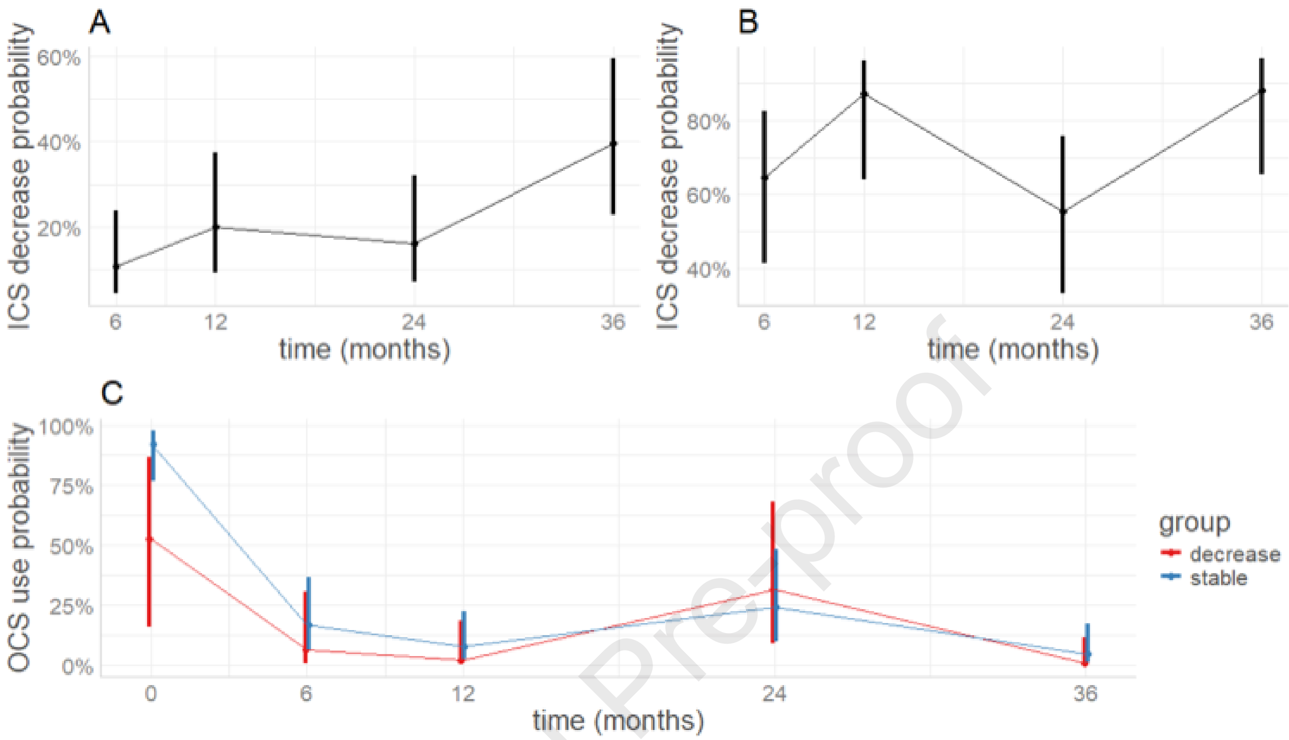

Figure 2 - – Predicted probabilities of decrease in ICS dosage compared to baseline, time 0, (panelA=overall sample, panel B=decreasing group) and of being treated with oral corticosteroids (panelC) from generalized linear mixed-effects models fitted on time points of the follow-up period

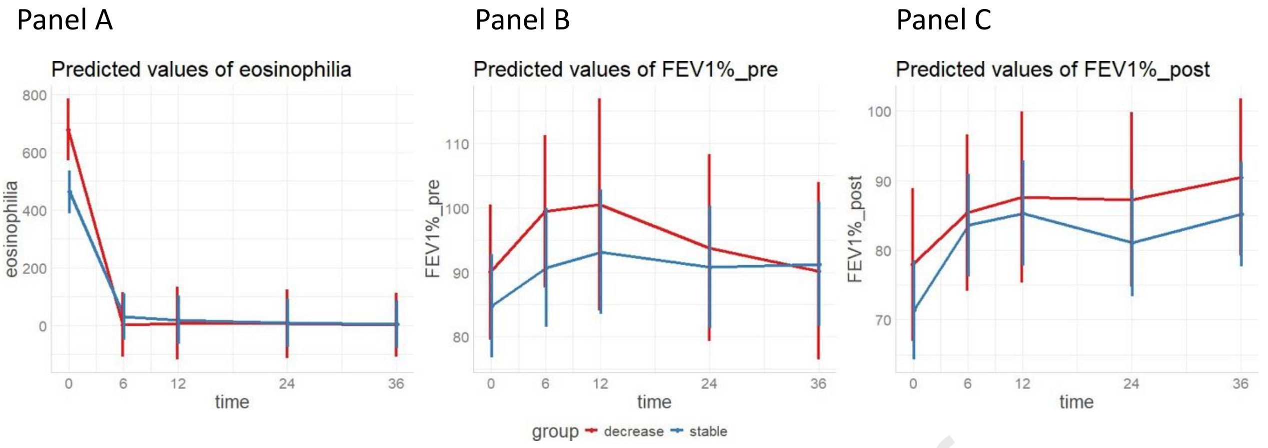

Figure 3 – Predicted values of eosinophilia (Panel A), pre (Panel B)- and post (Panel C)-bronchodilator FEV1% from linearmixed-effects models at each time point of the follow up period (in months) distinguished byinhaled corticosteroid dosage group. The 'increasing' group was not considered in the analysis asit comprised only 3 individuals.

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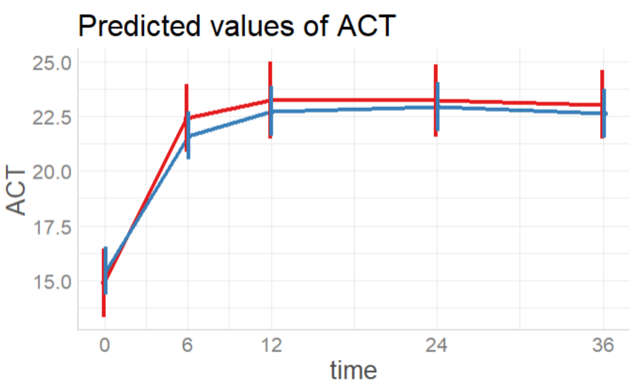
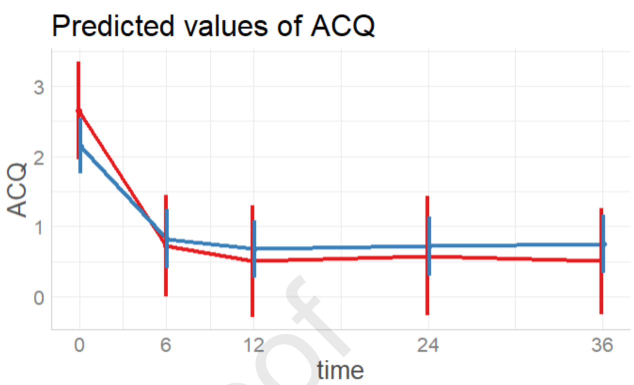
Panel A



Panel B



Panel C

Panel D

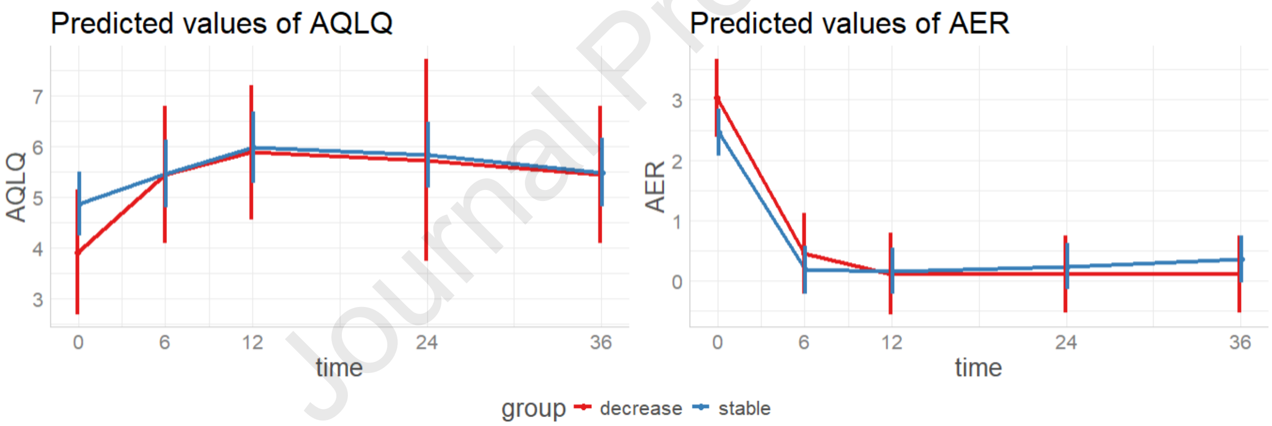


Figure 4 - Predicted values of ACT (Panel A), ACQ (Panel B), AQLQ (Panel C) and AER (Panel D) from linear mixed-effects models at each time point of the follow up period (in months) distinguished by inhaled corticosteroid dosagegroup. The 'increasing' group was not considered in the analysis as it comprised only 3 individuals

HIGHLIGHTS

- Benralizumab exerts a consistent inhaled corticosteroid sparing effect in real life.
- Benralizumab improves lung function and clinical outcomes over 36 months.
- 37.4% of patients reduced ICS dose after 3 years with benralizumab treatment.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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