

LETTER TO THE EDITOR

Adherence to inhaled corticosteroids and clinical outcomes following a year of benralizumab therapy for severe eosinophilic asthma

To the Editor,

Asthma is a common inflammatory airways disorder for which inhaled corticosteroids (ICS) are the cornerstone of treatment.¹ Whilst the majority of patients can be successfully managed by optimization of ICS therapy, some require frequent courses of systemic corticosteroids or indeed maintenance oral corticosteroids (mOCS), leading to significant OCS-related morbidity.² Biologic agents targeting type-2 inflammatory pathways facilitate reduced OCS exposure in the treatment of severe eosinophilic asthma (SEA). Amongst these is benralizumab, a humanized monoclonal antibody to interleukin (IL)-5 receptor- α (IL5R α), use of which leads to a reduction in asthma exacerbations and mOCS requirements, alongside improvements in lung function and subjective symptom control.³

Despite its benefits, non-adherence to ICS therapy is highly prevalent amongst asthma patients and may lead to worse disease control and unnecessary escalation to high cost biologic agents.^{4,5} We have previously described the association of poor ICS adherence with worse clinical outcomes in mOCS dependent SEA patients receiving mepolizumab⁶; herein we report the relationship of ICS adherence with outcomes in a similar cohort commenced on benralizumab at Guy's Severe Asthma Centre, Guy's and St Thomas' Hospitals, London, UK.

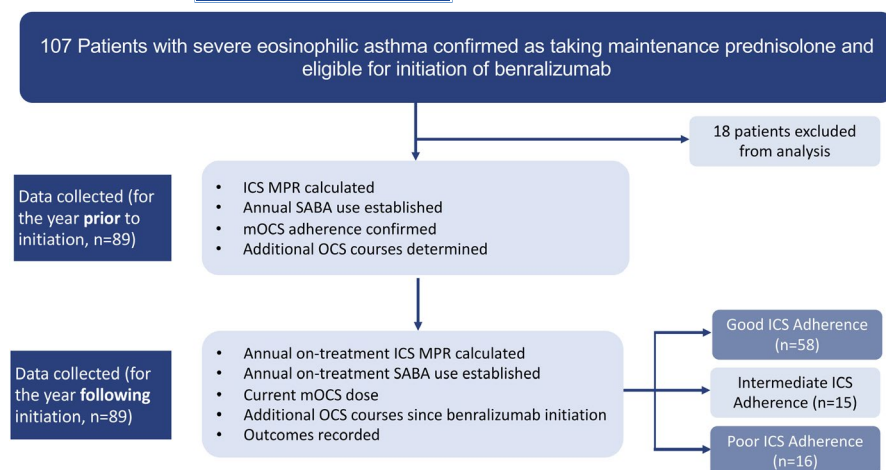
We retrospectively assessed patients who commenced benralizumab for the treatment of mOCS dependent SEA between May 2018 and March 2019. As per our national eligibility criteria, all of these patients were prescribed a high dose ICS (at 1,000 mcg of beclomethasone dipropionate-HFA equivalent daily); required ≥ 5 mg prednisolone (or equivalent) daily for at least 6 months prior to initiation, had adherence to their oral steroids confirmed using matched blood prednisolone and cortisol levels⁷ and had a blood eosinophil count of ≥ 300 cells/mcl in the preceding 12 months. We excluded those with a confounding diagnosis and those who did not complete 12 months of benralizumab. All patients underwent a full multi-disciplinary team review, including asthma education and assessment of prior ICS adherence via analysis of prescribing data. It was confirmed with the patient that the treating physician would adjust the patient's mOCS dose according to clinical need at each visit, but that the background therapies would be left unchanged. Any changes to the ICS regimen can therefore be regarded as patient-led.

Inhaler prescription issue data were extracted from primary care and hospital records. ICS adherence was quantified using the Medicines Possession Ratio (MPR), a method by which the number of prescriptions issued is compared with those expected to be issued, and calculated the MPR for the year prior to benralizumab initiation and the year immediately after.⁸ We compared 12-month outcomes in patients stratified by on-treatment ICS MPR into *poor* adherence (defined as $\text{MPR} \leq 0.5$), *intermediate* adherence ($\text{MPR} 0.51\text{--}0.74$) and *good* adherence ($\text{MPR} \geq 0.75$); we also compared patients who reduced their ICS MPR on benralizumab by $\geq 25\%$ with those who maintained consistent ICS use throughout. Data collection time points are summarized in Figure 1.

89 of 107 patients commenced on benralizumab were included in the final analysis. Patients were principally middle-aged, with a slight female predominance, and just under half had previously been treated with another biologic agent for their asthma (Table S1). Despite confirmed adherence to mOCS, patients continued to have frequent exacerbations, had impaired lung function and reported poor symptom control. Whilst on benralizumab, 58 (65%) of patients had good adherence to ICS, 15 (16.8%) intermediate and 16 (18%) poor adherence. Patients with intermediate or poor adherence were younger than those with good adherence, but no other significant differences were seen in baseline characteristics, including prior poor ICS adherence, baseline exacerbation rate or asthma control scores (Table S1).

Treatment with benralizumab led to improvements in the overall cohort: there were significant reductions in annual exacerbation rate (AER) and mOCS requirements (54% of patients could stop their mOCS), alongside better asthma control and quality of life (Table 1), and reductions in SABA use (Table S2). No significant differences were observed in clinical outcomes including AER, mOCS dose reduction and patient reported outcomes across the ICS adherence categories (Figure 2 and Table 1).

Over the 12 months of benralizumab therapy, 27 (30%) patients reduced their ICS MPR by $\geq 25\%$ (Table S3). These patients had fewer exacerbations ($\text{AER } 0.4 \pm 0.6$ vs 1.1 ± 1.5 ; $p = 0.038$), greater reductions in exacerbation frequency (AER reduction 4.4 ± 4.6 vs 2.5 ± 3.0 ; $p = 0.021$) and numerically greater, but statistically non-significant, improvements in mOCS requirements,

**FIGURE 1** A timeline illustrating the study data collection

	All patients	Good ICS adherence	Intermediate ICS adherence	Poor ICS adherence	p value
N	89	58	15	16	
ACQ reduction	0.86 (1.44)	0.63 (1.45)	1.22 (1.18)	1.37 (1.54)	0.114
AQLQ change	0.96 (1.51)	0.96 (1.38)	0.47 (1.95)	1.31 (1.59)	0.389
FEV1 change (l/sec)	0.12 (0.41)	0.14 (0.34)	0.02 (0.40)	0.18 (0.61)	0.352
FeNO reduction (ppb)	4.3 (47.8)	1.3 (45.4)	14.2 (35.8)	5.9 (65.0)	0.648
OCS reduction (mg/day)	9.1 (7.8)	8.2 (5.9)	9.3 (10.0)	12.4 (10.5)	0.157
OCS % reduction	100 (50–100)	100 (50–100)	60 (0–100)	100 (75–100)	0.16
>50% OCS reduction	73 (82)	48 (82.8)	11 (73.3)	14 (87.5)	0.76
Stopped OCS	48 (53.9)	32 (55.2)	6 (40)	10 (62.5)	0.67
AER (events/year)	0.9 (1.3)	0.95 (1.41)	0.93 (1.34)	0.6 (0.8)	0.57
Reduction in AER	3.1 (3.6)	2.8 (3.7)	4.7 (4.3)	2.9 (3.8)	0.223
Treatment failure	4 (4.5)	4 (6.9)	0	0	0.49

TABLE 1 Patient outcomes on benralizumab stratified according to ICS adherence

Note: Data expressed as n (%), mean (SD), or median (IQR) as appropriate. Treatment failure was defined as not achieving a $\geq 50\%$ reduction in mOCS dose or annualised exacerbation rate after 1 year of benralizumab therapy.

Abbreviations: ACQ, asthma control questionnaire; AER, annual exacerbation rate; AQLQ, asthma quality of life questionnaire; FEV1, forced expiratory volume in 1 second; OCS, oral corticosteroids.

and ACQ and AQLQ scores than patients who maintained consistent ICS use.

In this study of mOCS dependent SEA patients, many patients decreased their ICS use during the year of benralizumab treatment, but this suboptimal ICS adherence did not have a statistically significant or clinically important impact on exacerbation frequency, ability to withdraw mOCS, or symptoms reported. Moreover, patients who tapered their ICS appeared to have better outcomes than those who maintained their ICS use over the study period.

We have previously described worse outcomes associated with poor ICS adherence in a similar cohort of SEA patients who received mepolizumab.⁶ The reason for this difference between these groups is unclear, but whereas airway eosinophilia persists with licensed doses of mepolizumab, benralizumab leads to the almost complete depletion of airway eosinophils and eosinophil precursor cells⁹; consequently, one may speculate that some SEA patients treated with mepolizumab may require concomitant suppression of residual eosinophilic airway inflammation with an ICS to achieve

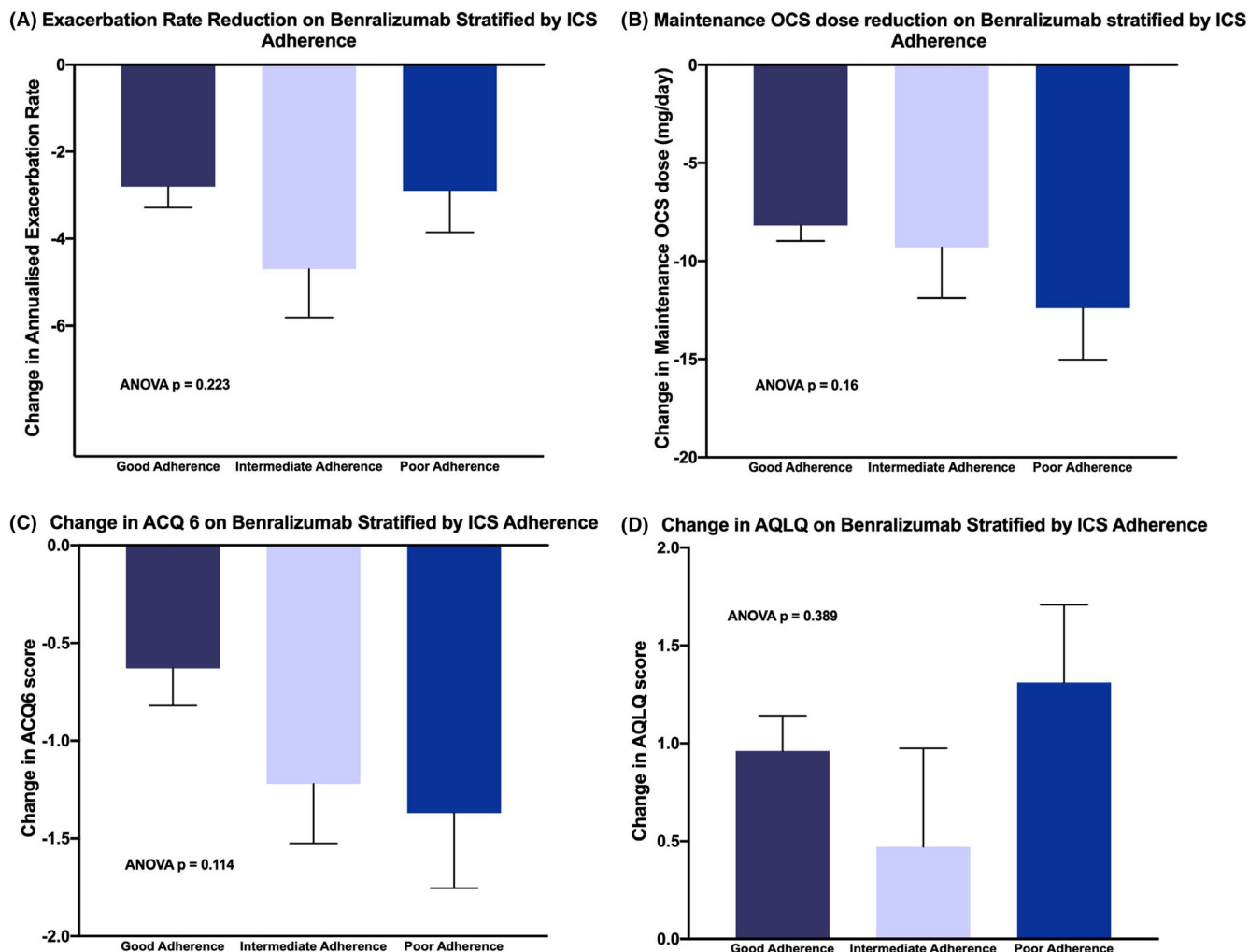


FIGURE 2 Clinical outcomes stratified by ICS adherence following 12 months of Benralizumab therapy. A, Exacerbation rate reduction. B, Maintenance OCS dose reduction. C, Change in ACQ6. D, Change in AQLQ. All figures compare outcome measures prior to, and following 12 months of treatment with benralizumab. OCS, oral corticosteroids; ACQ6, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire. A change of 0.5 is considered to be the minimal clinically important difference for both ACQ6 and AQLQ, with a reduction in ACQ6 and an increase in AQLQ indicative of improved asthma symptom burden. Data shown as mean (Standard Error of the Mean)

satisfactory disease control. Our data also suggest that some patients who successfully respond to benralizumab therapy may tolerate a degree of ICS dose reduction, a hypothesis that will be tested in the upcoming SHAMAAL phase 4 RCT (ClinicalTrials.gov Identifier: NCT04159519).¹⁰ However, in the absence of prospective data from a properly controlled trial examining reductions in ICS dosage, patients receiving benralizumab should continue to be encouraged to maintain adherence to their prescribed ICS therapy.

This study has important limitations. We describe a relatively small patient cohort from a single centre. ICS MPR is an imperfect method of measuring adherence as it assumes all doses issued are taken as directed with optimal technique. It overestimates actual usage and represents the best case scenario of adherence behaviour. Instead, a real-time electronic inhaler assessment could provide more robust verification of adherence, and would also facilitate better assessment of total ICS dosage taken, as well as temporal associations between periods of non-adherence and clinical outcomes.¹¹ Although we defined

good, intermediate and poor adherence by MPR cut offs consistent with previous published data in this area,^{4,5,12} these are not based on prospective clinical trial data, and are inherently arbitrary in nature. We included only patients receiving mOCS at baseline, so our results should be interpreted with caution in benralizumab patients who do not require mOCS. Similarly, our patient population had a marked type 2 high severe asthma phenotype, as reflected by elevation in peripheral blood eosinophils and FeNO levels at baseline despite mOCS use, hence our results may be of less relevance in severe asthma populations with less evidence of type 2 inflammation. We excluded 18 patients from our final analysis, including 10 who did not complete a full year of benralizumab therapy. This was necessary due to the adherence metric we used, but it is conceivable that the inclusion of these patients may have altered our results. Finally, although all patients were prescribed the highest licensed dose of their ICS baseline, we did not record which patients received which ICS, and thus cannot comment on whether choice of ICS could have influenced outcomes.

In conclusion, in this real-world cohort of patients who required mOCS for SEA, we found that non-adherence to high dose ICS whilst receiving benralizumab was not associated with worse clinical outcomes in terms of exacerbation frequency, ability to wean mOCS, or symptoms reported. Patients who reduced their ICS usage had more significant reductions in AER than those who did not, with numerically greater reductions in mOCS dose and improvements in patient reported outcome measures. We suggest that prospective, controlled studies examining the effects of weaning ICS in patients who have achieved satisfactory control of their SEA with benralizumab are needed.

CONFLICT OF INTEREST

GdA reports advisory board and/or speaker fees from Astrazeneca, Chiesi, GSK, Napp, Boehringer Ingelheim and Teva. JK reports travel support from Teva. CR reports advisory board and/or speaker fees Astrazeneca, Chiesi, Napp, Novartis and Teva. AMN reports advisory board and/or speaker fees from Astrazeneca. DJJ reports advisory board and/or speaker fees from Astrazeneca, Chiesi, GSK, Napp, Novartis and Teva. BDK reports advisory board and/or speaker fees from Astrazeneca, Chiesi, GSK, Napp, and Novartis. No COIs are reported by the remaining authors.

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REFERENCES

1. GINA Science Committee. *Global Strategy for Asthma Management and Prevention*. 2020.
2. Volmer T, Effenberger T, Trautner C, Buhl R. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. *Eur Respir J*. 2018;52:1800703.
3. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115-2127.
4. Lee J, Tay TR, Radhakrishna N, et al. Nonadherence in the era of severe asthma biologics and thermoplasty. *Eur Respir J*. 2018;51:1701836.
5. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med*. 2009;180:817-822.
6. d'Ancona G, Kavanagh J, Roxas C, et al. Adherence to inhaled corticosteroids and clinical outcomes in mepolizumab therapy for severe asthma. *Eur Respir J*. 2020;55:1902259.
7. Mansur AH, Hassan M, Duffy J, Webster C. Development and clinical application of a prednisolone/cortisol assay to determine adherence to maintenance oral prednisolone in severe asthma. *Chest*. 2020;158:901-912.
8. Lam WY, Fresco P. Medication adherence measures: an overview. *Biomed Res Int*. 2015;2015:217047.
9. Sehmi R, Lim HF, Mukherjee M, et al. Benralizumab attenuates airway eosinophilia in prednisone-dependent asthma. *J Allergy Clin Immunol*. 2018;141:1529.e8-1532.e8.
10. Jackson DJ, Kent BD, Humbert M, et al. Enabling reductions in maintenance ICS/LABA therapy using as needed anti-inflammatory reliever for patients with severe eosinophilic asthma controlled with benralizumab: SHAMAL phase IV clinical study. B31 Asthma Clinical Trials: American Thoracic Society. 2020:A3020-A.
11. Sulaiman I, Greene G, MacHale E, et al. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. *Eur Respir J*. 2018;51:1701126.
12. Murphy AC, Proeschal A, Brightling CE, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax*. 2012;67:751-753.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Benralizumab treatment Regimen

Patients received 30mg of benralizumab subcutaneously at 4-weekly intervals for 3 doses, then every 8 weeks as per EU licence <https://www.medicines.org.uk/emc/product/8918/smpc>

Statistical analysis

Nominal variables were compared using Chi-square analysis, and continuous variables by paired or independent t-test or ANOVA, or non-parametric equivalents as appropriate. A p value of <0.05 was considered statistically significant. All analyses were performed using SPSS v25 (IBM, Chicago USA).

Results

18 patients were excluded from analysis. Of them, 8 of had a concomitant EGPA diagnosis, while 10 did not complete 1 year of treatment due to lack of efficacy (n=6), apparent medication related adverse events (n=1; headache), failure to attend clinic appointments (n=2) or becoming pregnant (n=1).

Table S1. Baseline patient characteristics stratified by ICS adherence on Benralizumab

	Overall	Good adherence	Intermediate adherence	Poor adherence	p value
N (%)	89	58 (65)	15 (17)	16 (18)	
Age (years)	52.7 (14.8)	55.4 (15.0)	50.3 (14.9)	45.1 (11.4)	0.035
Female n (%)	58 (65.2)	35 (60.3)	13 (86.7)	10 (62.5)	0.157
BMI (kg/m ²)	30.6 (6.7)	30.0 (6.4)	31.2 (8.2)	32.3 (5.8)	0.431
Smoker n (%)	3 (3.4)	2 (3.4)	1 (6.7)	0	0.127
Ex-smoker n (%)	21 (23.6)	12 (20.7)	2 (13.3)	7 (43.8)	0.24
Prior biologic n (%)	41 (46.1)	27 (46.6)	6 (40)	8 (50)	0.85
Prior Omalizumab n (%)	12 (13.5)	8 (13.8)	1 (6.7)	3 (18.8)	0.82
Prior anti-IL5 n (%)	39 (43.8)	26 (44.8)	6 (40)	7 (43.8)	0.95
Atopic n (%)	64 (71.9)	38 (65.5)	12 (80)	14 (87.5)	0.29
Childhood onset n (%)	40 (44.9)	24 (41.4)	7 (46.7)	9 (56.3)	0.71
AER (events/year)	3.9 (3.5)	3.7 (3.3)	5.4 (4.0)	3.4 (3.8)	0.204
mOCS dose (mg prednisolone/day)	12.4 (9.4)	11 (7.5)	15 (12.5)	14.8 (11.9)	0.178
FEV ₁ (L/sec)	1.72 (0.66)	1.66 (0.61)	1.50 (0.57)	2.11 (0.79)	0.022
FEV ₁ % predicted	64.5 (21.6)	62.9 (21.5)	64.1 (24.8)	70.9 (19.2)	0.428
FeNO (ppb)	60.1 (51.2)	55.8 (40.1)	61.5 (63.7)	74.4 (70.7)	0.435
Peak Eosinophil count (x10 ⁹)	0.68 (0.36)	0.69 (0.38)	0.70 (0.35)	0.60 (0.30)	0.621
ACQ-6	2.94 (1.42)	2.78 (1.53)	3.11 (1.27)	3.38 (1.03)	0.285
AQLQ	3.52 (1.44)	3.52 (1.46)	3.76 (1.7)	3.36 (1.25)	0.792
Poor ICS adherence prior to benralizumab n (%)	10 (11.2)	6 (10.3)	1 (6.7)	3 (18.8)	0.63

Data displayed as n (%), mean (SD) or median (IQR) as appropriate. BMI: body mass index; AER: annual exacerbation rate; mOCS: maintenance oral corticosteroid expressed as prednisolone equivalent dose; FEV₁: forced expiratory volume in 1 second; FeNO: fractional exhaled nitric oxide; ppb: parts per billion; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire

Table S2. Inhaler use changes before and after 1 year of Benralizumab

	Year prior to benralizumab	On benralizumab	p value
MPR	0.90 (0.39)	0.81 (0.34)	0.084
ICS devices prescribed	10.7 (4.6)	9.7 (4.1)	0.084
SABA devices prescribed	13.3 (13.4)	9.3 (8.8)	0.001
SABA daily doses	7.3 (7.4)	5.2 (4.8)	0.001

MPR: medicines possession ratio; ICS: inhaled corticosteroid; SABA: short acting B-agonist; data expressed as mean (SD)

Table S3. Patient outcomes on benralizumab stratified by change in ICS usage behaviour

	MPR reduced by ≥ 0.25	MPR preserved	p value
N	27	62	
AER	0.4 (0.6)	1.1 (1.5)	0.038
Reduction in AER	4.4 (4.6)	2.5 (3.0)	0.021
OCS change	11.3 (9.0)	8.2 (7.0)	0.087
ACQ reduction	1.08 (1.58)	0.76 (1.39)	0.346
AQLQ change	1.15 (1.57)	0.86 (1.49)	0.439
FEV1 change (l/sec)	0.09 (0.49)	0.13 (0.38)	0.71

AER: annualised exacerbation rate; OCS: oral corticosteroids; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; FEV1: forced expiratory volume in 1 second