Adherence to inhaled corticosteroids and clinical outcomes in mepolizumab therapy for severe asthma

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Poor adherence to ICS is common in severe asthma patients receiving mepolizumab, and is associated with increased oral corticosteroid exposure and exacerbation risk <http://bit.ly/2v9hdAi>

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ABSTRACT

Introduction: Inhaled corticosteroids (ICS) achieve disease control in the majority of asthmatic patients, although adherence to prescribed ICS is often poor. Patients with severe eosinophilic asthma may require treatment with oral corticosteroids (OCS) and/or biologic agents such as mepolizumab. It is unknown if ICS adherence changes on, or alters clinical response to, biologic therapy.

Methods: We examined ICS adherence and clinical outcomes in OCS-dependent severe eosinophilic asthma patients who completed 1 year of mepolizumab therapy. The ICS medicines possession ratio (MPR) was calculated (the number of doses of ICS issued on prescription/expected number) for the year before and the year after biologic initiation. Good adherence was defined as MPR >0.75, intermediate 0.74–0.51 and poor <0.5. We examined outcomes after 12 months of biologic therapy, including OCS reduction and annualised exacerbation rate (AER), stratified by adherence to ICS on mepolizumab.

Results: Out of 109 patients commencing mepolizumab, 91 who had completed 12 months of treatment were included in the final analysis. While receiving mepolizumab, 68% had good ICS adherence, with 16 (18%) having poor ICS adherence. ICS use within the cohort remained similar before (MPR 0.81±0.32) and during mepolizumab treatment (0.82±0.32; *p*=0.78). Patients with good adherence had greater reductions in OCS dose (median (interquartile range) OCS reduction 100 (74–100)% *versus* 60 (27–100)%; *p*=0.031) and exacerbations (AER change −2.1±3.1 *versus* 0.3±2.5; *p*=0.011) than those with poor adherence. Good ICS adherence predicted the likelihood of stopping maintenance OCS (adjusted OR 3.19, 95% CI 1.02–9.94; *p*=0.045).

Conclusion: ICS nonadherence is common in severe eosinophilic asthma patients receiving mepolizumab, and is associated with a lesser reduction in OCS requirements and AER.

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Introduction

Inhaled corticosteroids (ICS) have been the cornerstone of asthma care since the 1970s [1]. Although ICS use is sufficient to control airway inflammation in the majority of asthma patients, a significant minority will have poor disease control despite ICS [2], potentially necessitating the persistent or recurrent use of oral corticosteroids (OCS), thus exposing patients to significant treatment-related morbidity [3]. The past 20 years have seen a revolution in our understanding of asthma biology, and particularly of the role of type 2 inflammation within the asthmatic airway. With this has come the development of targeted biologic therapies, aimed at specific components of relevant inflammatory pathways [4]. Mepolizumab is a humanised monoclonal antibody which blocks interleukin (IL)-5 signalling, thereby reducing eosinophilic inflammation [5]. In a series of phase 3 randomised controlled trials, mepolizumab was shown to reduce OCS dependence and exacerbation frequency [6, 7], and improve health-related quality of life measures and lung function, in patients with severe eosinophilic asthma [8]. Current Global Initiative for Asthma guidelines recommend that high-dose ICS be continued alongside mepolizumab [9], but little is known about the impact of ICS withdrawal in patients receiving biologic therapy.

Adherence to prescribed treatments is an important consideration in chronic disease management, and severe asthma appears to be no exception. Low levels of adherence to prescribed ICS, and to maintenance OCS, have been identified in patients attending severe asthma clinics, including those being considered for initiation of high-cost biologic therapy [10, 11]. Poor adherence may be of clinical relevance in these patients: it is associated with impaired lung function and increased airway inflammation compared with those who are adherent to ICS, and with an increased likelihood of having previously required critical care admission [12]. However, very little is known about what happens to ICS adherence when patients are commenced on biologic therapy, or indeed if ICS adherence remains relevant once a biologic agent has been started.

In a cohort of patients being commenced on mepolizumab for OCS-dependent severe eosinophilic asthma, we assessed adherence to prescribed ICS over the course of 12 months of mepolizumab therapy, and examined its relationship with clinical outcomes, including exacerbation frequency and OCS withdrawal.

Methods

Patients

We retrospectively assessed consecutive patients commencing mepolizumab for the treatment of OCS-dependent severe eosinophilic asthma at Guy's Severe Asthma Centre (Guy's & St Thomas' Hospitals, London, UK) between April 2017 and June 2018. All patients met the UK National Institute for Health and Care Excellence criteria for initiation of mepolizumab: all had confirmed severe asthma requiring ≥ 5 mg prednisolone daily for ≥ 6 months, and had a peripheral blood eosinophil count of ≥ 300 cells μL^{-1} in the preceding 12 months [13]. All patients had adherence to maintenance OCS confirmed by matched prednisolone and cortisol levels, and prior to commencing biologic therapy, all patients underwent inhaler technique optimisation and asthma education consultations with a consultant pharmacist (GdA) or nurse specialist (CR, LG, MF and LT), during which the importance of ICS adherence was emphasised.

Following initiation of mepolizumab, patients attended on a 4-weekly basis for administration of the medication. Maintenance OCS doses were reviewed during each visit and adjusted as deemed appropriate by the treating physician. At baseline and at each visit, clinical data including exacerbation history, OCS dose, forced expiratory volume in 1 s (FEV_1) and fractional exhaled nitric oxide (F_{ENO}) levels were recorded, along with Asthma Control Questionnaire (ACQ)-6 and Asthma Quality of Life Questionnaire (AQLQ) scores [14, 15]. An ACQ-6 score ≥ 1.5 is suggestive of poor asthma control, with higher scores indicative of worse symptoms. Conversely, higher scores on the AQLQ indicate better quality of life. The minimal clinically important difference for both scores is 0.5.

Adherence assessment

Adherence to prescribed ICS was measured *via* assessment of monthly prescription issues recorded on a number of National Health Service sources including summary care records, local care records, general practice recording system and/or hospital pharmacy dispensing system. Adherence was quantified according to the medicines possession ratio (MPR), which is calculated for an individual drug by comparing the number of prescriptions issued with the number that would be expected to be issued. This study investigated the ICS MPR over a 2-year period [16], 1 year before initiation of a biologic, and 1 year after. Three levels of adherence were defined depending on the MPR over the preceding year: poor (<0.5), intermediate (0.5 – 0.74) and good (≥ 0.75) adherence. Patients with an MPR <0.75 were considered to be suboptimally adherent.

We excluded patients who did not complete 12 months of mepolizumab therapy, and those where ICS adherence data could not be obtained, along with patients with confounding diagnoses such as eosinophilic granulomatosis with polyangiitis.

Outcomes and statistical analysis

Using the pre-mepolizumab and on-treatment MPR, we assessed baseline ICS adherence and changes in adherence following initiation of biologic therapy. We then assessed outcomes after 12 months of mepolizumab therapy, stratifying analyses according to levels of ICS adherence. Outcomes assessed included changes in annual exacerbation rate (AER), daily OCS dose, FEV₁, F_{ENO} level and ACQ-6 and AQLQ scores. In addition, the likelihood of successfully stopping maintenance OCS was compared between the three levels of ICS adherence.

Nominal variables were compared using Chi-squared analysis, and continuous variables by paired or independent t-test or ANOVA or nonparametric equivalents as appropriate. To assess the likelihood of stopping OCS according to level of ICS adherence, a regression model was built with cessation of OCS as the dependent variable, and good adherence (MPR ≥ 0.75), OCS baseline dose, sex, FEV₁ <65% predicted, baseline AER, smoking history, body mass index and pre-mepolizumab peak peripheral blood eosinophil count as independent variables. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS (v25; IBM, Chicago, IL, USA).

Results

109 patients requiring daily OCS for severe eosinophilic asthma were commenced on mepolizumab between April 2017 and June 2018. Of these, 91 completed 12 months of treatment and had primary care prescription records available for review. Patients were predominantly middle-aged, with a slight female predominance and required a median (interquartile range (IQR)) daily prednisolone dose of 10 (10–15) mg (table 1). Despite OCS, patients had poorly controlled asthma, as manifested by recurrent exacerbations, impaired lung function and impaired patient-reported outcome measures (table 1). At baseline, despite evidence of good OCS adherence, 22% of patients had prior poor ICS adherence, with an MPR <0.5 over the preceding 12 months.

Over 12 months of mepolizumab therapy, 62 (68%) patients maintained good adherence to prescribed ICS, with 29 (32%) having suboptimal adherence, 16 of whom (18% of the study population) had poor levels of ICS use. Patients with poor ICS adherence while on mepolizumab were more likely to be smokers and more likely to have been poorly adherent to ICS at baseline. No other significant differences were identified in baseline characteristics across categories of ICS adherence during mepolizumab therapy (table 1).

TABLE 1 Patient baseline characteristics stratified by inhaled corticosteroid adherence while on mepolizumab

	Adherence				p-value
	Overall	Good	Intermediate	Poor	
Subjects	91	62 (68)	13 (14)	16 (18)	
Age years	53.7±14.4	55.8±13.3	49.9±16.1	48.8±16.4	0.13
Female	50 (54.9)	32 (51.6)	9 (69.2)	9 (56.3)	0.51
BMI kg·m⁻²	30.2±6.1	29.6±5.2	29.9±6.22	32.7±8.4	0.21
Smokers	3 (3.3)	0	0	3 (18.8)	0.001
Ex-smokers	25 (27.5)	20 (32.3)	1 (7.7)	4 (25)	0.191
AER events·year⁻¹	2.7±2.7	3.2±2.9	1.9±2.3	1.8±2.2	0.1
Median prednisolone dose mg·day⁻¹	10 (10–15)	10 (10–15)	12 (10–15)	10 (10–15)	0.582
FEV₁ L	1.91±0.83	1.84±0.87	1.84±0.64	2.23±0.73	0.246
FEV₁ % predicted	65.8±22.2	64.4±22.8	63.3±20.7	73.3±20.8	0.33
F_{ENO} ppb	56.7±44.3	56.8±42.0	74±57	42.4±38.9	0.161
Peak eosinophil count ×10⁹ cells·L⁻¹	0.67±0.47	0.61±0.44	0.72±0.41	0.88±0.60	0.11
ACQ-6	2.69±1.33	2.80±1.39	2.79±1.09	2.17±1.20	0.24
AQLQ	3.86±1.38	3.79±1.45	3.82±1.37	4.17±1.12	0.61
Prior poor adherence	20 (22)	8 (12.9)	2 (15.4)	10 (62.5)	<0.001

Data are displayed as n, n (%), mean±SD or median (interquartile range), unless otherwise stated. BMI: body mass index; AER: annual exacerbation rate; FEV₁: forced expiratory volume in 1 s; F_{ENO}: exhaled nitric oxide fraction; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire.

TABLE 2 Inhaler use changes over 12 months on mepolizumab

	Baseline	Mepolizumab	p-value
ICS MPR	0.81±0.32	0.82±0.32	0.786
ICS n	9.8±3.9	9.9±3.8	0.796
SABA n	10.2±12.1	7.9±9.9	0.013
SABA daily doses	5.7±6.6	4.3±5.5	0.009

Data are presented as mean±SD, unless otherwise stated. ICS: inhaled corticosteroid; MPR: medicines possession ratio; SABA: short-acting β_2 -agonist.

Overall levels of ICS use within the cohort remained similar before and after initiation of mepolizumab (table 2). The ICS MPR was 0.81±0.32 at baseline, compared with 0.82±0.32 on mepolizumab ($p=0.786$). Within this there was significant intra-individual change: 23 (25.3%) of patients had a reduction of ≥ 0.25 in their ICS MPR, with nine (15.4%) of those with prior good ICS adherence having an ICS MPR <0.75 while receiving mepolizumab. There was a significant reduction in short-acting β_2 -agonist (SABA) inhaler usage overall, with the number of SABA issues reducing from 10.2±12.1 to 7.9±9.9 ($p=0.013$) in the year following initiation of mepolizumab. This equated to a reduction in daily SABA doses from 5.7±6.6 to 4.3±5.5 ($p=0.009$).

Treatment with mepolizumab led to significant improvements in clinical outcomes in the overall cohort, with reductions seen in AER, OCS dosage and ACQ-6 score, while 52% of patients were able to stop OCS completely (table 3). Generally, outcomes were not as good in patients with poor ICS adherence (table 3): nonadherent patients had lesser reductions in OCS dose than those with good adherence (median (IQR) OCS dose reduction 60 (27–100)% *versus* 100 (74–100)%; $p=0.031$), while adherent patients had a 66% reduction in AER, from 3.2±2.9 to 1.1±1.4 events ($p<0.001$), in contrast with patients with intermediate or poor ICS adherence, where no reductions in AER were observed (figure 1) (ANOVA $p=0.004$).

Patients with good ICS adherence appeared more likely to be able to stop OCS. In unadjusted analysis, the odds ratio for cessation of oral steroids in patients adherent to ICS was 2.8 (95% CI 1.1–7.1; $p=0.027$). Following adjustment for relevant confounding demographic and clinical factors, ICS adherence, along with baseline OCS dose, remained associated with the likelihood of stopping OCS (adjusted OR 3.19, 95% CI 1.02–9.94; $p=0.045$) (table 4). Treatment failure, defined as an inability to reduce OCS or exacerbation frequency by $\geq 50\%$, occurred in 14.3% of the cohort ($n=13$). Poor ICS adherence was more common in patients with treatment failure than in those who benefitted from mepolizumab therapy (46.2% *versus* 12.8%; $p=0.011$).

Discussion

In a real-world cohort of severe eosinophilic asthma patients being commenced on biologic therapy, we observed statistically significant and clinically important differences in the effect of mepolizumab on

TABLE 3 Outcomes in mepolizumab patients according to adherence

	All patients	ICS adherence			p-value
		Good	Intermediate	Poor	
Subjects	91	62	13	16	
ACQ-6 change	−0.63±1.26	−0.76±1.18	−0.63±1.1	−0.15±1.6	0.24
FEV ₁ % change	−2.3±14.4	0.7±11.2	−6.8±19.1	−4.9±18.8	0.28
Change in OCS dose mg·day ^{−1}	−8.4±5.4	−8.9±5.5	−9.0±5.5	−5.8±4.1	0.11
Median OCS reduction % baseline dose	100 (60–100)	100 (74–100)	93.3 (54–100)	60 (27–100)	0.031
>50% reduction in OCS dose	73 (80)	54 (87)	10 (77)	9 (57)	0.021
Stopped OCS	47 (52)	37 (60)	5 (39)	5 (31)	0.075
Treatment failure [#]	13 (14.3)	5 (8.1)	2 (15.4)	6 (37.5)	0.011
AER	1.4±1.8	1.1±1.4	1.8±1.6	2.1±2.7	0.06
Change in AER	−1.4±3.1	−2.1±3.1	−0.1±2.1	0.3±2.5	0.004

Data are presented as n, mean±SD, median (interquartile range) or n (%), unless otherwise stated. ICS: inhaled corticosteroid; ACQ: Asthma Control Questionnaire; FEV₁: forced expiratory volume in 1 s; OCS: oral corticosteroid; AER: annual exacerbation rate. [#]: inability to reduce either daily OCS dose or AER by $\geq 50\%$ after 12 months of mepolizumab therapy.

exacerbation frequency and OCS withdrawal with different levels of ICS adherence. Reported rates of adherence to ICS vary with clinical setting, measurement techniques used and criteria used to define nonadherence, but somewhere between 35% and 59% of patients attending severe asthma clinics seem to be nonadherent to prescribed ICS [10, 11, 17]. This appears to be equally true of patients being assessed for potential initiation of a biologic agent and patients receiving long-term treatment with omalizumab, at least half of whom were nonadherent to inhaled maintenance therapy [11, 18]. Similarly, an apparent requirement for maintenance OCS is no guarantee of adherence, with 45% of patients prescribed daily prednisolone for poorly controlled asthma failing to take their OCS [10]. In our cohort of patients commenced on mepolizumab for severe disease, all of whom had confirmed satisfactory adherence to maintenance OCS, rates of suboptimal ICS adherence remained high, with 32% having an MPR <0.75, and 18% having an MPR <0.5. Furthermore, ICS adherence had a degree of instability following initiation of mepolizumab: although the overall mean ICS MPR within the cohort remained unchanged, significant numbers of patients adjusted their ICS use of their own volition over the course of 12 months of biologic therapy.

Previous studies have provided mixed data regarding the effect of suboptimal ICS use in difficult and severe asthma populations. Among patients attending a severe asthma clinic, suboptimal adherence was associated with a reduced FEV₁ and increased airway inflammation, and an increased likelihood of a prior need for mechanical ventilation [12]. Conversely, adherence levels did not appear to lead to differences in lung function or symptom scores over a 2-week assessment period in patients receiving long-term omalizumab [18], and the initiation of omalizumab seems to improve bronchial hyperresponsiveness and exacerbation control in patients with known nonadherence to ICS [19]. Our data suggest that continued ICS adherence remains relevant in patients receiving mepolizumab, and particularly in patients who are having maintenance OCS therapy weaned.

TABLE 4 Predictors of likelihood of stopping maintenance oral corticosteroids (OCS) on mepolizumab

	OR (95% CI)	p-value
OCS baseline dose	0.86 (0.76–0.95)	0.003
Good ICS adherence	3.19 (1.02–9.94)	0.045
Female	0.87 (0.30–2.46)	0.79
FEV₁ <65% predicted	2.21 (0.73–6.72)	0.16
Baseline AER >4	0.99 (0.70–1.40)	0.94
Nonsmoker	2.31 (0.77–6.97)	0.13
Peak eosinophils	0.83 (0.28–2.46)	0.74
BMI >30 kg·m⁻²	1.69 (0.56–5.06)	0.35

ICS: inhaled corticosteroids; FEV₁: forced expiratory volume in 1 s; AER: annual exacerbation rate; BMI: body mass index.

Our finding that patients receiving mepolizumab therapy who are nonadherent to ICS have worse clinical outcomes offers potential insights into the immunology of severe asthma. Although inhibiting IL-5 activity with mepolizumab reduces eosinophilic inflammation, it is recognised that this suppression is incomplete, with almost 50% of airway eosinophilia persisting [20]. In addition, other important aspects of steroid-responsive type 2 inflammation which are not inhibited by mepolizumab, including IL-4 and IL-13 activity, may be driving some of the morbidity in these patients [4]. As such, many severe asthma patients may require concomitant ICS therapy to further suppress either airway eosinophilia or other aspects of type 2 inflammation. In the case of the former, it is conceivable that ICS withdrawal may be better tolerated if other eosinophil targeting strategies that lead to a more complete eosinophil depletion are used, for example the weight-based serum-neutralising antibody reslizumab or the IL-5 receptor antibody benralizumab [21, 22]. Alternatively, poor ICS adherence in these patients may simply reflect a lifestyle or approach to asthma self-management that is less conducive to achieving good disease control.

Identifying characteristics that predict nonadherence may facilitate targeted interventions to promote medication use. In our cohort, the only identified risk factors for nonadherence to ICS while on mepolizumab were prior suboptimal adherence and smoking. However, we did not assess socioeconomic status or patients' beliefs regarding medication safety and efficacy, factors which do appear to be associated with lower adherence rates in asthma patients [23, 24]. It is possible that a number of nonadherent patients were not using their ICS because they felt reasonably well on maintenance OCS; it is notable that ACQ and AQLQ scores, lung function and F_{ENO} levels were numerically better at baseline in patients who had poor ICS adherence, albeit not to a statistically significant degree.

Our study has a number of important limitations. First, it is a retrospective study, and although all clinical data were recorded prospectively, it is consequently vulnerable to the associated biases. Second, we assessed only OCS-dependent patients being started on mepolizumab. We chose to evaluate these patients because we anticipated that the withdrawal of OCS would allow any effects of nonadherence to ICS to come to the fore. Third, we used MPR as our measure of adherence. This is a function of prescriptions issued and does not directly measure medication use, and hence probably overestimates ICS usage [16]. The values we used to define adherence cut-offs, though consistent with other studies [11–13, 17, 23, 25], were arbitrary. We did not record adherence data regarding medications not directly related to asthma, and hence cannot comment on whether ICS nonadherence represented a specific or general trend in adherence patterns. Using the MPR to assess adherence gives an annualised estimate of inhaler use, but does not facilitate assessment of dynamic day-to-day or week-to-week changes in adherence, potentially important data in evaluating how biologic therapy may influence ICS use over time. Future studies using alternate techniques such as F_{ENO} suppression testing [26], electronic remote inhaler usage monitoring [17] or a combination of both [25] will facilitate a clearer understanding of how ICS adherence might influence clinical decision-making and clinical outcomes in patients receiving biologic therapy [27], while qualitative interview studies may better elucidate patient factors contributing to nonadherence in severe asthma populations.

Conclusion

To our knowledge, this is the first report of the impact of poor adherence to ICS on the clinical effectiveness of mepolizumab. In a large, real-world cohort of patients requiring maintenance OCS in addition to mepolizumab for severe eosinophilic asthma, we observed significant rates of poor adherence to prescribed ICS. This was associated with worse clinical outcomes, including a higher asthma exacerbation rate and a lesser reduction in maintenance OCS requirement in nonadherent patients. Our data highlight the need for healthcare professionals caring for severe eosinophilic asthma patients treated with biologic therapies to re-assess and address ICS adherence, particularly in the context of any apparent failure of biologic therapy.

Conflict of interest: G. d'Ancona reports personal fees from GSK, during the conduct of the study; grants and personal fees from AstraZeneca, personal fees from Napp Pharmaceuticals, Chiesi Pharmaceuticals, Boehringer Ingelheim and Teva Pharmaceuticals, outside the submitted work. J. Kavanagh has nothing to disclose. C. Roxas has nothing to disclose. L. Green has nothing to disclose. M. Fernandes has nothing to disclose. L. Thomson has nothing to disclose. J. Dhariwal has nothing to disclose. A.M. Nanzer has nothing to disclose. D.J. Jackson reports grants and personal fees from AstraZeneca, outside the submitted work. B.D. Kent reports personal fees from GSK, during the conduct of the study; personal fees from AstraZeneca, Napp Pharmaceuticals and Chiesi Pharmaceuticals, non-financial support from Boehringer Ingelheim and Teva Pharmaceuticals, outside the submitted work.

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