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Adherence to Inhaled Corticosteroids and Clinical Outcomes in Mepolizumab Therapy for Severe Asthma

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Keywords:

Asthma, adherence, inhaled corticosteroids, Mepolizumab

Take home message:

Poor adherence to ICS is common in severe asthma patients receiving mepolizumab, and is associated with increased oral corticosteroid exposure and exacerbation risk.

Abstract

Introduction

Inhaled corticosteroids (ICS) achieve disease control in the majority of asthmatics, although adherence to prescribed ICS is often poor. Patients with severe eosinophilic asthma (SEA) 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 SEA patients who completed 1 year of mepolizumab therapy. The ICS Medicines Possession Ratio was calculated (MPR; 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

Of 109 patients commencing mepolizumab, 91 who had completed 12 months of treatment were included in the final analysis. Whilst 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 on mepolizumab (0.82±0.32;p=0.78). Patients with good adherence had greater reductions in OCS dose (median percentage OCS reduction 100(IQR 74-100) vs 60(IQR 27-100);p=0.031) and exacerbations (AER change -2.1±3.1 vs 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 non-adherence is common in SEA patients receiving mepolizumab, and is associated with a lesser reduction in OCS requirements and AER.

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 last twenty 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 GINA 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). Very little is known, however, about what happens to ICS adherence when patients are commenced on biologic therapy, or indeed if ICS adherence actually 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 (NICE) criteria for initiation of mepolizumab: all had confirmed severe asthma requiring ≥5mg prednisolone daily for at least six months, and had a peripheral blood eosinophil count of ≥300 cells/mcL 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 (author GdA) or nurse specialist (authors 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 second (FEV1), and fractional exhaled nitric oxide (FeNO) levels were recorded, along with Asthma Control Questionnaire (ACQ-6) and Asthma Quality of Life Questionnaire (AQLQ) scores (14, 15). An ACQ-6 score of 1.5 or greater 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 (MCID) 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 NHS sources including Summary Care Records, Local Care Records, GP 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 two-year period (16), one year before initiation of a biologic, and one 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, FeNO level, and ACQ-6 and AQLQ scores. The likelihood of successfully stopping maintenance OCS was also compared between the three levels of ICS adherence.

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. 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, gender, FEV1 <65% predicted, baseline AER, smoking history, body mass index (BMI), and pre-mepolizumab peak peripheral blood eosinophil count as

independent variables. A p value of <0.05 was considered statistically significant. All analyses were performed using SPSS v25 (IBM, Chicago USA).

Results

One hundred and nine 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 daily prednisolone dose of 10mg (IQR 10-15)(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 whilst 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).

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 9 (15.4%) of those with prior good ICS adherence having an ICS MPR <0.75 whilst receiving mepolizumab. There was a significant reduction in 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 completely stop OCS (table 3). Outcomes generally were not as good in patients with poor ICS adherence (table 3): non-adherent patients had lesser reductions in OCS dose than those with good adherence (median percentage OCS dose reduction 60(IQR 27-100) *vs* 100 (IQR 74-100); p=0.031), whilst 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, as defined as an inability to reduce OCS or exacerbation frequency by ≥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 benefited from Mepolizumab therapy (46.2% vs 12.8%; p=0.011).

Discussion

In a real world cohort of SEA patients being commenced on biologic therapy, we observed statistically significant and clinically important differences in the effect of mepolizumab on 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 non-adherence, but somewhere between 35% and 59% of patients attending severe asthma clinics seem to be non-adherent to prescribed ICS (10, 11, 17). This appears to be equally true of patients being assessed for potential initition of a biologic agent and patients receiving long-term treatment with omalizumab, at least half of whom were non-adherent 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 two week assessment period in patients receiving long-term omalizumab (18), and the initiation of omalizuamb seems to improve bronchial hyper-responsiveness and exacerbation control in patients with known non-adherence to ICS (19). Our data would suggest that continued ICS adherence remains relevant in patients receiving mepolizumab, and particularly in patients who are having maintenance OCS therapy weaned.

Our finding that patients receiving mepolizumab therapy who are non-adherent 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 either further suppress airway eosinophila 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-5R 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 non-adherence may facilitate targeted interventions to promote medication use. In our cohort, the only identified risk factors for non-adherence to ICS whilst on mepolizumab were prior suboptimal adherence and smoking. However, we did not assess socio-economic 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 non-adherent 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 FeNO levels were numerically better at baseline in patients who had poor ICS adherence, albeit it 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 non-adherence 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 likely overestimates ICS usage (16). The values we used to define adherence cut-offs, though consistent with other studies (11,12,13,17,23,26), were arbitrary. We did not record adherence data regarding medications not directly related to asthma, and hence cannot comment on whether ICS non-adherence 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 FeNO suppression testing (25), electronic remote inhaler usage monitoring (17), or a combination of both (26) 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 non-adherence in severe asthma populations.

Conclusion

This is to our knowledge 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 non-adherent patients. Our data highlight the need for healthcare professionals caring for SEA patients treated with biologic therapies to re-assess and address ICS adherence, particularly in the context of any apparent failure of biologic therapy.

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Table 1. Patient baseline characteristics stratified by ICS adherence whilst on Mepolizumab.

	Overall	Good adherence	Intermediate adherence	Poor adherence	p value
N (%)	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 n(%)	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
Smoker n(%)	3 (3.3)	0	0	3 (18.8)	0.001
Ex-smoker n(%)	25 (27.5)	20 (32.3)	1 (7.7)	4 (25)	0.191
AER (events/year)	2.7 (2.7)	3.2 (2.9)	1.9 (2.3)	1.8 (2.2)	0.1
Median prednisolone dose (mg/day)	10 (10-15)	10 (10-15)	12 (10-15)	10 (10-15)	0.582
FEV1 (L/sec)	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
FeNO (ppb)	56.7 (44.3)	56.8 (42.0)	74 (57)	42.4 (38.9)	0.161
Peak Eosinophil Count ($x10^9/L$)	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 n(%)	20 (22)	8 (12.9)	2 (15.4)	10 (62.5)	<0.001

Data displayed as n(%), mean(SD) or median (IQR) as appropriate. BMI: body mass index; AER: annual exacerbation rate; FEV1: forced expiratory volume in 1 second; FeNO: fractional exhaled nitric oxide; ACQ-6: asthma control questionnaire; AQLQ: asthma quality of life questionnaire

Table 2. Inhaler use changes over 12 months on Mepolizumab

	Baseline	On Mepolizumab	p value
ICS MPR	0.81(0.32)	0.82(0.32)	0.786
ICS number	9.8(3.9)	9.9(3.8)	0.796
SABA number	10.2(12.1)	7.9(9.9)	0.013
SABA daily doses	5.7(6.6)	4.3(5.5)	0.009

MPR: medicines possession ratio; ICS: inhaled corticosteroid; SABA: short acting B-agonist

Table 3. Outcomes in Mepolizumab patients according to adherence

	All Patients	Good ICS Adherence	Intermediate ICS Adherence	Poor ICS Adherence	p value
N	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
FEV1 % 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)	-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 n(%)	73 (80)	54 (87)	10 (77)	9 (57)	0.021
Stopped OCS n(%)	47(52)	37(60)	5(39)	5(31)	0.075
Treatment failure n(%)	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 mean (SD), median (IQR), or n(%) as appropriate. ACQ: asthma control questionnaire; FEV1: forced expiratory volume in 1 second; OCS: oral corticosteroids; AER: annual exacerbation rate. Treatment failure defined as inability to reduce either daily OCS dose or annual exacerbation rate by ≥50% after 12 months of Mepolizumab therapy.

Table 4. Predictors of likelihood of stopping maintenance 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%	2.21	0.73-6.72	0.16
Baseline AER >4	0.99	0.70-1.40	0.94
Non-smoker	2.31	0.77-6.97	0.13
Peak Eosinophils	0.83	0.28-2.46	0.74
BMI >30	1.69	0.56-5.06	0.35

ICS: inhaled corticosteroids; FEV1: forced expiratory volume in 1 second; OCS: maintenance oral corticosteroids; AER: annual exacerbation rate; BMI: body mass index

Figure 1. Changes in annual exacerbation rate on mepolizumab stratified by ICS adherence. ANOVA p=0.004; ★ p=0.065; ★★ p=0.011