Mepolizumab and oral corticosteroid stewardship – data from Australian Mepolizumab Registry

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Abstract

Background: Oral corticosteroids (OCS) carry serious health risks. Innovative treatment options are required to reduce excessive exposure and promote OCS stewardship.

Objectives: This study evaluated the trajectories of OCS exposure (prednisolone-equivalent) in severe eosinophilic asthma patients before and after starting mepolizumab and the predictors of becoming OCS free after 6-months of mepolizumab therapy.

Methods: This real-world observational study included 309 patients from the Australian Mepolizumab Registry who were followed-up for one year (n=225).

Results: Patients had a median age of 60 (IQR 50,68) years, and 58% were female. At baseline, 48% used maintenance OCS, 96% had ≥1 OCS burst and 68% had received ≥1gram OCS in the previous year. After commencing mepolizumab, only 55% of those initially on maintenance OCS remained on this treatment by 12-months. Maintenance OCS dose reduced from median 10 (5.0,12.5) mg/day at baseline to 2 (0,7.0) mg/day at 12-months ($p<0.001$). Likewise, proportions of patients receiving OCS bursts in the previous year reduced from 96% at baseline to 50% at 12-months ($p<0.001$). Overall, 137 (48%) patients required OCS (maintenance/burst) after 6-months' mepolizumab therapy. Becoming OCS free was predicted by a lower body mass index (OR 0.925; 95%CI 0.872-0.981), late-onset asthma (1.027; 1.006-1.048), a lower Asthma Control Test score (1.111; 0.011-1.220) and not receiving maintenance OCS therapy at baseline (0.095; 0.040-0.227).

Conclusion: Mepolizumab led to a significant and sustained reduction in OCS dependence in patients with severe eosinophilic asthma. This study supports the OCS-sparing effect of mepolizumab and highlights the pivotal role of mepolizumab in OCS stewardship initiatives.

Highlights box

1. What is already known about this topic?

Although oral corticosteroids (OCS) have been integral part of severe asthma management, they carry serious health risks; and minimisation of patient exposure to them is the key goal of OCS stewardship initiatives.

2. What does this article add to our knowledge?

At baseline, patients in the Australian Mepolizumab Registry represented a high burden OCS cohort with extreme risk of complications. Mepolizumab therapy minimised OCS exposure, confirming the pivotal role of mepolizumab in OCS stewardship initiatives.

3. How does this study impact current management guidelines?

The extremely high OCS burden among this population requires urgent attention. OCS sparing agents such as mepolizumab should be considered to minimise the adverse health impact of OCS and promote OCS stewardship.

Key words

Oral corticosteroid, mepolizumab, severe eosinophilic asthma, OCS stewardship, observational study

Abbreviations

ACQ-5	Asthma Control Questionnaire, 5-item version
ACT	Asthma Control Test
AMR	Australian Mepolizumab Registry
AQLQ(S)	standardised Asthma Quality of Life Questionnaire
BMI	Body Mass Index
FeNO	Fraction of exhaled nitric oxide

FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
IQR	Interquartile range
OCS	Oral corticosteroids
OR	Odds ratio
PBS	Pharmaceutical Benefits Scheme
RCT	Randomised controlled trials
SD	Standard deviation

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Introduction

Severe asthma affects 10.2 – 33.9 million people worldwide and is associated with substantial health and economic burden (1-4). People with severe asthma often require large doses of inhaled and/or systemic corticosteroids to prevent and manage exacerbations, and almost one-third require daily oral corticosteroid (OCS) therapy (3). Although corticosteroids have played a vital role in the management of asthma symptoms over the last 60 years, they have the potential to damage nearly every organ system in the body, and regular or frequent exposure can result in serious and often irreversible health risks. Recent research indicates that the adverse effects associated with OCS begin at a cumulative lifetime dose of just one-gram of prednisolone or equivalent, which is equivalent to four bursts (each 25-50mg/day over a few days) (5). The Asthma and Allergy Foundation of America (AAFA) highlighted the need for raising awareness of OCS overexposure in moderate-to-severe asthma treatment(6). A paradigm shift in treatment approaches to severe asthma is warranted (7, 8).

The concept of OCS stewardship focuses upon optimising a balance between OCS efficacy and safety, and continued promotion of alternative agents that allow minimisation or, ideally, discontinuation of OCS. A key aspect of OCS stewardship is the successful use of newer drug classes that can effectively treat severe asthma, without the adverse effect profile of OCS (8). Monoclonal antibody therapies targeting the Type 2 (T2) inflammation pathway are effective in severe asthma (9). Mepolizumab is a monoclonal anti-interleukin-5 antibody that acts by reducing eosinophil driven airway inflammation (10, 11), and the agent is registered and subsidised in many countries for the treatment of severe eosinophilic asthma.

Previous studies have found that mepolizumab has a significant OCS sparing effect and reduces OCS requirements in addition to reducing the number of acute exacerbations in severe eosinophilic asthma (10, 12-20). However, the magnitude and onset of effect are not consistent in all patients. In some patients, the benefits are observed at an early stage of therapy, others require a longer duration of treatment and a subgroup will require continued OCS to control asthma symptoms and exacerbations. A comprehensive assessment of the trajectories of OCS

exposure after starting mepolizumab therapy in a real-world setting has not been previously performed. This study focused on the potential role of mepolizumab in OCS stewardship, by evaluating baseline demographic and clinical factors associated with OCS exposure; the effect of mepolizumab on OCS exposure at various stages of mepolizumab therapy; and identification of predictors of becoming OCS free after initiating mepolizumab therapy.

Methods

Data were obtained from the Australian Mepolizumab Registry (AMR), an investigator-initiated, observational database of patients with severe eosinophilic asthma undergoing mepolizumab therapy (13). The study was approved by the centres' relevant Human Research Ethics Committee, and all patients provided written informed consent prior to enrolment. Patients providing consent were registered consecutively between January 2017 and April 2019 at 20 specialist clinics. The AMR is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12618001497291).

Patients: Eligible patients needed to meet the criteria set by the Australian Government Pharmaceutical Benefits Scheme (PBS) to initiate subsidised mepolizumab therapy (Table E1), including treatment with daily OCS for at least six weeks OR a cumulative dose of ≥0.5gram prednisolone equivalent in the previous 12 months with some occasional exceptions allowed.

Measures and assessments: Data were collected face-to-face prior to commencement of mepolizumab therapy (baseline) and prospectively at 3-, 6- and 12-months post-commencement. Baseline data collection included patient demographics, medical history including comorbidities commonly associated with corticosteroids, medication use, allergy history and atopic status. Asthma-related data included diagnosis, exacerbation history, asthma control and triggers. Patients completed the five-item Asthma Control Questionnaire (ACQ)-5(21), Asthma Control Test (ACT)(22) and standardised Asthma Quality of Life Questionnaire (AQLQ(S))(23). Spirometry (within one-month prior to starting mepolizumab), fraction of exhaled nitric oxide (FeNO), full blood count and total serum immunoglobulin (Ig)E concentration (within 12 months prior) were recorded. Follow-up data included ACQ-5, ACT, AQLQ(S), frequency and type of acute exacerbations, medication use, adverse effects, and full blood count.

Outcome measures: Exposure to OCS (prednisolone equivalent) was evaluated before and after starting mepolizumab therapy. Both long-term exposure (referred to as maintenance OCS) and short-term exposure (referred to as OCS burst) were recorded at baseline and at each follow-up visit. The overall OCS exposure included both maintenance OCS and OCS bursts.

At baseline, patients were categorised into two groups based on their magnitude of cumulative exposure to OCS (prednisolone equivalent) in the previous year; 1) <1gram and 2) ≥1gram (24). The registry recorded the number of OCS bursts in the previous year; based on previous studies, each OCS burst was assumed as 250mg exposure, and four OCS bursts were considered as one-gram exposure (5).

Patients were also categorised in two groups based on their exposure to OCS between six months and 12 months follow-up whilst receiving mepolizumab treatment; 1) No exposure to OCS (OCS free) and 2) exposed to OCS (i.e., on maintenance OCS at 6- or 12-month follow-up, or OCS bursts after 6-month follow-up).

Statistical analysis: Statistical analyses were performed using Stata14.2 (StataCorp, College Station, TX, USA); results are reported as mean ± standard deviation (SD) for normally distributed data and median (interquartile range [IQR]) for non-normally distributed data. Comparisons were performed using Chi-squared or Fisher's exact test for categorical data and Student's t-test or Wilcoxon rank-sum test for continuous data. Survival analysis was used to assess the time to first OCS burst and time to cease maintenance OCS therapy. Univariate analysis was used initially to evaluate the predictors of becoming OCS free after six months of mepolizumab treatment. The variables with a p-value ≤0.2 in the univariate analysis were entered in the multivariate model. A backwards selection of the variables was used, with an exclusion criterion of a p-value >0.2. The removal of variables was completed one at a time. The revised model was compared to the previous level using the Likelihood ratio test, checking for an improvement in fit. The same number of participants were used in the model each time, allowing for valid comparison to the full model via the likelihood ratio test. The goodness of fit of the final model was confirmed by the Hosmer-Lemeshow test. Results were considered statistically significant when $p<0.05$.

Results

At the time of data extraction (September 2019), 309 patients were enrolled in the registry and had commenced mepolizumab. Of those 299 had completed the 3-month, 284 had completed the 6-month and 225 had completed the 12-month follow-up visits. Patients awaiting follow-up completion were seven at six-months and 49 at 12-months. There were two deceased patients and seven who withdrew consent. The remaining missed follow-ups at various stages. One patient who missed 6-month follow-up completed the 12-month follow-up.

Patients had a median age of 60 years (IQR 50, 68) and 58% were females. All patients were using an inhaled corticosteroid at baseline with a median chlorofluorocarbon-beclometasone dipropionate equivalent dose of 2000 (IQR 1000, 2000) mcg/day at baseline. Almost all (99%) were on long-acting beta agonist (LABA) and 53% were on long-acting muscarinic antagonist (LAMA). At baseline, 48% were using maintenance OCS therapy, 96% had required at least one OCS burst in the previous year and 68% had received ≥1gram prednisolone or equivalent in the previous year. The distribution of maintenance OCS dose at baseline is provide in figure E1.

Patients' baseline characteristics are presented in Table 1. Patients who had received ≥1gram OCS were less likely to be atopic, had shorter duration of asthma, higher exposure to dusty occupations, more morning symptoms and more frequent reliever use, and their asthma-related quality of life was poorer. They had required a median of 4 (IQR 3,7) vs 2 (IQR 1,3) OCS courses in the previous year and 63% were taking daily maintenance OCS (12% in <1gram exposure category) at baseline. The median peripheral blood eosinophil count was similar in both groups, 530 (IQR 400, 830) vs 600 (IQR 400, 830), p=0.65.

There were no significant associations between the comorbidities assessed at baseline and the exposure categories (Table E2).

Effect of mepolizumab on OCS exposure

Significant and sustained reductions in OCS exposure were observed after commencing mepolizumab therapy (Figure 1). The proportion of patients receiving maintenance OCS therapy reduced gradually at each follow-up visit and reached almost half by 12-month follow-up (Figure 1a). Likewise, the proportions of patients experiencing OCS bursts in the previous year were reduced from 96% at baseline to 50% at 12-month follow-up ($p<0.001$) (Figure 1b). Similarly, the proportions of patients receiving any OCS (maintenance and/or burst) in the previous year were reduced from 97% at baseline to 67% at 12- month follow-up ($p<0.001$) (Figure 1b). The proportions of patients who reported the need for OCS bursts at each visit are also provided in Figure 1c.

Pattern of maintenance OCS dose reduction: There were 144 patients using maintenance OCS therapy at baseline. Following mepolizumab commencement, the daily dose reduced from a median (IQR) of 10 (5.0, 12.5) mg/day at baseline to 2 (0, 7.0) mg/day at 12-month follow-up ($p<0.001$). The magnitude of dose reduction by 12-month follow-up is presented in Table 2. Compared to baseline, the maintenance OCS dose reduced 21% by 3-month, 42% by 6-month and 60% by 12-month follow-ups. The rate of OCS bursts over the 12 months period was similar among those who had stopped/reduced maintenance OCS compared to their counterparts. In this cohort (N=144), 5 patients required an increase in maintenance dose after starting mepolizumab.

Among those who were not taking maintenance OCS therapy at baseline, none started it after commencing mepolizumab.

Survival analyses

Time to cease maintenance OCS therapy: Almost half the patients ceased maintenance OCS therapy (Figure 2a). Among those who ceased, almost half ceased within six months after starting mepolizumab therapy (Figure 2b). The time to ceasing maintenance OCS was similar in those who were under and over median OCS dose of 10 mg/day at baseline ($P>0.05$) (Figure 2c).

Time to first OCS burst: More than half of all patients required at least one OCS burst and 25% used the first OCS burst within four months and 50% in 10 months (Figure 3a). Among those who had at least one OCS burst, the first OCS burst occurred within four months in 50% of cases (Figure 3b). The time to first OCS burst was similar among those who were on maintenance OCS at baseline and those who were not (P>0.05) (Figure 3c).

OCS exposure after six months' treatment with mepolizumab

A total of 285 patients who had at least six months data of mepolizumab therapy (i.e., completed either six- or 12-months follow-up visit) were included in this analysis. There were 137 (48%) patients who required OCS (either maintenance or burst) after six months of mepolizumab treatment. Those who required OCS therapy were more likely to be obese (57% vs 36%, p<0.001) and had a lower (worse) median (IQR) ACT score (10 [8, 14] vs 13 [9,16], p=0.002) and lower (worse) mean±SD AQLQ score (3.45±1.09 vs 4.09±1.16, p<0.001) at baseline. A greater proportion of these patients were prescribed maintenance OCS therapy at baseline (73% vs 19%, p<0.001) compared to those who became OCS free after six months of mepolizumab. Smoking history was not associated with ongoing OCS use (Table E3). Those who required OCS after six months' mepolizumab therapy also reported a higher rate of comorbidities such as gastro-oesophageal reflux disease, obstructive sleep apnoea, vocal cord dysfunction, anxiety and depression, and endocrine and metabolic disease at baseline (Table E4).

Asthma symptoms were well controlled among those who became OCS free after six months of mepolizumab therapy, median (IQR) ACQ-5 at 6-month was 1.0 (0.6, 1.8). Those who still required OCS had a higher severity of airway obstruction and lower ACT and AQLQ scores at 6-month follow-up (Table E5).

Those who required maintenance OCS therapy at 12 months had a lower level of asthma symptom control (median ACQ-5 1.8 [1.0,2.4] vs 1.1 [0.5,2.0], p=0.009; median ACT 16 [13,20] vs 19 [14,23], p=0.037) and median blood eosinophil count (50 cells/uL [10.0,100.0] vs 100 [60.0,100.0], p=0.007) at 12 months.

Predictors of becoming OCS free after receiving mepolizumab therapy for six months

Following the univariate analysis, nine variables (age, gender, BMI, age: asthma symptoms onset, ACT score, post-bronchodilator % predicted FVC, number of comorbidities, baseline OCS use and number of asthma medications) were entered in the multivariable model. Of those, five variables (BMI, age: asthma symptoms onset, ACT score, corticosteroid exposure at baseline and number of asthma medications) were retained in the model. The odds of becoming OCS free after six months' treatment with mepolizumab decreased by 7.5% for each BMI unit increase, increased by 2.7% for each year late-onset of asthma symptoms and increased by 11.1% for each unit increase in ACT score. The likelihood of being OCS free is reduced by 90.5% for participants who were on maintenance OCS at baseline compared to those who were not (Table 3). Hosmer-Lemeshow test indicated a good model fit and there was no collinearity in the final model. The model predicted 81% of the patients' OCS exposure.

Discussion

This real-world study comprehensively evaluated the trajectories of OCS exposure before and after starting mepolizumab therapy. It focused mainly on OCS exposure and its timing of change from treatment commencement, within a 12-month observation period. At baseline, OCS exposure was very high with most patients experiencing at least one OCS burst in the previous year, and half receiving maintenance OCS therapy. Additionally, two-thirds had received ≥1gram of OCS in just one year. A significant and sustained reduction in OCS exposure (both maintenance and OCS burst) was observed after commencing mepolizumab. The effect was observed by the first follow-up visit, i.e., three months after treatment commencement. Although the majority became OCS free after six months of mepolizumab therapy, a significant proportion still required some OCS. This study extends our knowledge about the effects of mepolizumab on OCS exposure and emphasises the importance of mepolizumab (and other biological therapies) in the development and implementation of OCS stewardship initiatives to minimise the OCS burden among people with severe asthma.

The magnitude of OCS exposure at baseline was extremely high in our cohort compared to the background community rates. In a recent PBS data evaluation of asthma patients who were receiving high doses of inhaled corticosteroid and long-acting beta-agonist, only 9.8% received ≥1gram prednisolone in the previous year compared to 68% in the current cohort (25). It is also important to note that the 1gram toxicity criterion proposed by Price et al (5) was based on adverse effects observed during a median 6-7 years' follow-up, whereas we found that the majority of our patients crossed that limit within a year. This is a remarkably high burden of OCS, representing an extreme risk of complications within this population which requires urgent attention and highlights the importance of OCS stewardship initiatives. However, the high OCS exposure in the current cohort would likely have been influenced by the fact that, with very few exceptions, to be eligible for mepolizumab prescription, the PBS required either ≥500mg OCS exposure in the previous year or maintenance OCS for the prior six weeks,. This PBS criterion may exclude many patients with uncontrolled asthma who experience 2-3 OCS bursts each year and may conflict with the goals of OCS stewardship initiatives which may require careful

consideration. Relaxing the criteria for access to mepolizumab in Australia with a lower total dose of OCS might help these patients.

The number of people receiving maintenance OCS therapy gradually reduced at each follow-up visit after starting mepolizumab therapy and reached almost half by 12-month follow-up. This effect was much greater than that observed in previously reported randomised controlled trials (RCTs) of mepolizumab, but comparable to other observational studies. For example, the SIRIUS RCT reported that 14% patients successfully discontinued maintenance OCS at six months (12) whereas in previous observational studies it ranged from 27% to 57% at six months (26-30) and 34% to 66% at 12 months (20, 27-29, 31, 32). We also assessed the rate of OCS bursts among those who had ceased or reduced maintenance OCS compared to their counterparts, and found that there was no significant difference. Moreover, asthma symptoms were well controlled among those who became OCS free after six months of mepolizumab therapy. These findings indicate that the de-escalation of maintenance OCS did not lead to worsening of symptoms or additional exacerbations, suggesting that the effect observed is a true effect. This supports the OCS sparing effect of mepolizumab and its pivotal role in OCS stewardship programmes.

This study also evaluated the use of OCS bursts during the study period, a practice that has not been analysed in previous studies. In this study more than half of patients experienced at least one OCS burst after starting mepolizumab therapy. Among those who had at least one OCS burst, 50% experienced the first OCS burst within four months and this was independent of the baseline OCS dose.

Another important question relates to the duration needed to observe an effect on OCS reduction after commencing mepolizumab therapy. We observed an effect from the first follow-up visit at 3 months, which is comparable to previous studies that reported an effect from one to three months(14, 29). Among those who had ceased maintenance OCS, half did so within six months of commencing mepolizumab. The time to cease maintenance OCS was not affected by baseline OCS dose.

Although there was a significant reduction in OCS exposure, 48% of patients continued to use OCS even after six months of mepolizumab treatment. However, previous longer term studies reported a further reduction in maintenance OCS exposure after 12 months' treatment (29). Hence the observed effect in this study might not reflect the complete effect of mepolizumab and to observe the full effect a longer follow-up duration might be required. In addition, the renewal assessment for PBS subsidised mepolizumab in Australia occurs after 26-30 weeks of therapy. Hence, a clinician might be reluctant to down-titrate the OCS dose too quickly because if symptoms worsened, the patient may not have met the criteria for continuation of mepolizumab. Moreover, there was no systematic protocol for steroid reduction and this was undertaken on an ad hoc basis. The independent predictors of becoming OCS free included BMI, age of asthma symptoms onset, ACT score and the maintenance OCS use status at baseline. Of those, only BMI is a modifiable risk factor emphasising the importance of exercise and weight reduction in the management of severe asthma. It might also be possible that obese severe asthma patients require more mepolizumab based on their body weight, although it was not supported by a recent meta-analysis (33). Graff et al recently reported that a late-onset of asthma is a risk factor for chronic OCS use in severe asthma patients although this study was not focused on patients receiving mepolizumab (34). We found that the chance becoming OCS free was higher for patients with a late-onset of asthma symptoms. We also found that smoking history was not associated with the ongoing OCS use indicating that mepolizumab is equally effective in both never smokers and ex-smokers (35).

The strengths of this study include the sample size of >300 patients, nation-wide recruitment (20 sites across Australia), regular follow-up over 12 months, careful evaluation of patients, and the observational design which is free from limitations of the RCT such as strict inclusion criteria. However, the absence of a control group and blinding make observational studies susceptible to bias and confounding factors. The use of self-reported outcome data (OCS exposure) in this study might be subject to recall bias. The design of our study did not allow us to determine the contribution of other conditions (e.g., adrenal insufficiency and chronic rhinosinusitis) to an inability to completely cease maintenance OCS. A combination of physician diagnosed and

425 patient reported comorbidities were considered and reported in this study. Although the role of
426 small airway dysfunction in asthma has been increasingly recognised in recent years (36-38),
427 and Australian data exist indicating the mepolizumab improve small airway function (39), the
428 AMR registry did not collect data measuring small airway function or the effect of treatment on
429 this outcome. Hence we were not able to assess its impact on OCS use.

430 In conclusion, this study confirms the steroid-sparing effect of mepolizumab in a real-world
431 population of patients with severe asthma and demonstrates its role in reducing OCS use and
432 hence supporting OCS stewardship programmes. Response to therapy began within three
433 months, and treatment effect was sustained over time.

Figure legends

Figure 1: OCS exposure before and after starting mepolizumab; a) maintenance OCS use (baseline n=144, 3-month n=141, 6-month n=128, and 12-month n=101); b) proportions of patients who experienced OCS burst and overall OCS exposure (either burst or maintenance) 12-months before and after starting mepolizumab; c) proportions of patients reporting OCS burst at each visit (baseline: over the previous 12-months; 3-and 6-month: previous 3-months; 12-months: previous 6-months).

Figure 2: Survival analysis, a) time to cease maintenance OCS including all those who were on maintenance OCS at baseline (n=144), b) time to cease maintenance OCS including only those who had ceased, c) time to cease mainentance OCS by OCS dose at baseline (under and over median OCS dose).

Figure 3: Survival analysis, a) time to 1st OCS burst including all patients (n=309), b) time to 1st OCS burst including only those who had an OCS burst, c) time to 1st OCS burst by maintenance OCS usage status at baseline (on maintenance OCS and not on maintenance OCS).

449 **Table 1: Baseline characteristics by OCS exposure over 12 months prior to enrolment**

450 **(<1gram and ≥1gram)**

	Total (N=300)*	**<1gram exposure (N=90)**	**≥1gram exposure (N=210)**	**p-value**
Age (N=299)	59.58 (49.8, 68.2)	59.58 (52.8, 68.8)	59.59 (49.2, 68.2)	0.50
Gender (Male) (n=300)	126 (42.0%)	32 (35.6%)	94 (44.8%)	0.14
Race (n=279)				
Caucasian	245 (87.8%)	72 (87.8%)	173 (87.8%)	
Asian	20 (7.2%)	6 (7.3%)	14 (7.1%)	
Other	14 (5.0%)	4 (4.9%)	10 (5.1%)	1.00
Body Mass Index (BMI), kg/m^2 (n=288)	29.52 (25.26, 34.42)	28.80 (23.95, 34.11)	29.61 (26.89, 34.63)	0.11
Obese (BMI≥30 kg/m^2) (n=288)	133 (46.2%)	40 (46.0%)	93 (46.3%)	0.96
Smoking (n=295)				
Never	182 (61.7%)	58 (65.2%)	124 (60.2%)	
Current	1 (0.3%)	0 (0.0%)	1 (0.5%)	
Ex-smoker	112 (38.0%)	31 (34.8%)	81 (39.3%)	0.66
Pack Years (ex-/current-smoker) (n=107)	15.00 (4.00, 29.00)	17.50 (7.50, 31.50)	14.00 (4.00, 27.00)	0.53
Atopy$^{\#}$ (n=213)	151 (70.9%)	46 (85.2%)	105 (66.0%)	**0.007**
Asthma duration, years	27.52 (13.47,	33.49 (18.79,	26.35 (12.43,	**0.010**

(n=265)	46.08)	50.61)	42.76)	
Previous exposure to dusty occupation (n=273)	106 (38.8%)	24 (28.9%)	82 (43.2%)	**0.026**
Exacerbation history (past year)				
Number of patients requiring OCS burst/s (n=300)	292 (97.3%)	89 (98.9%)	203 (96.7%)	0.44
Number of OCS bursts (n=288)	3.00 (2.00, 6.00)	2.00 (1.00, 3.00)	4.00 (3.00, 7.00)	**<0.001**
Number requiring hospital admissions (n=300)	79 (26.3%)	20 (22.2%)	59 (28.1%)	0.29
Number of admissions (n=79)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 3.00)	0.19
Intensive care unit admissions (n=300)	52 (17.3%)	10 (11.1%)	42 (20.0%)	0.062
Number of Intensive care unit admissions (n=52)	1.00 (1.00, 2.50)	1.00 (1.00, 2.00)	1.00 (1.00, 3.00)	0.82
Unscheduled doctor/GP visit (n=300)	81 (27.0%)	18 (20.0%)	63 (30.0%)	0.074
Number of doctor/GP visit (n=80)	4.00 (2.00, 6.00)	2.00 (1.00, 3.00)	5.00 (3.00, 6.00)	**<0.001**
Lung function at baseline				
Pre-bronchodilator % Predicted FEV1 (n=226)	57.01 (17.85)	58.01 (16.54)	56.61 (18.38)	0.60
Pre-bronchodilator % predicted FVC (n=225)	78.48 (16.84)	79.11 (16.85)	78.23 (16.88)	0.72
FEV1/FVC (pre B2) (n=225)	0.57 (0.13)	0.58 (0.12)	0.57 (0.14)	0.86
Post-bronchodilator % Predicted FEV1 (n=206)	62.76 (19.03)	63.59 (17.42)	62.44 (19.68)	0.70

Post-bronchodilator % predicted FVC (n=206)	83.56 (16.61)	83.49 (15.50)	83.58 (17.07)	0.97
FEV1/FVC (post B2) (n=206)	0.59 (0.14)	0.59 (0.12)	0.59 (0.15)	0.84
Asthma symptom control and quality of life				
ACQ-5 (n=297)	3.40 (3.00, 4.20)	3.40 (2.80, 4.20)	3.40 (3.00, 4.20)	0.41
ACT (n=227)	11.00 (9.00, 15.00)	14.00 (10.00, 17.00)	10.00 (8.00, 14.00)	**<0.001**
AQLQ(S) (n=215)	3.80±1.16	4.20±1.17	3.64±1.13	**0.001**
Asthma symptoms (past week)				
Number of nights woken due to asthma (n=217)	3.00 (1.00, 7.00)	2.00 (0.00, 5.00)	3.00 (1.00, 7.00)	0.067
Number of mornings woken with asthma (n=217)	6.00 (3.00, 7.00)	4.00 (2.00, 7.00)	7.00 (3.00, 7.00)	**0.009**
Number of days with activity limitation (n=216)	7.00 (3.00, 7.00)	7.00 (3.00, 7.00)	7.00 (3.00, 7.00)	0.81
Number of days reliever used (n=214)	7.00 (4.00, 7.00)	7.00 (3.00, 7.00)	7.00 (6.00, 7.00)	**0.010**
Biomarkers				
Peripheral blood eosinophil count (cells/μL) (n=294)	590.00 (400.00, 830.00)	530.00 (400.00, 830.00)	600.00 (400.00, 830.00)	0.65
Eosinophils >600μl (n=300)	126 (42.0%)	38 (42.2%)	88 (41.9%)	0.96
IgE (IU/mL) (n=196)	141.50 (54.00, 461.50)	225.00 (42.00, 1051.00)	131.00 (58.00, 360.00)	0.17
FeNO (ppb) (n=145)	35.00 (20.00, 61.00)	36.00 (18.50, 61.00)	34.00 (20.00, 60.85)	0.97
Baseline respiratory medications				
Number of respiratory	4.00 (3.00,	3.00 (3.00,	4.00 (3.00,	**0.002**

medications (n=300)	5.00)	4.00)	5.00)	
Maintenance OCS (n=300)	143 (47.7%)	11 (12.2%)	132 (62.9%)	**<0.001**
OCS dose, prednisolone equivalent (mg/day) (n=143)	10.00 (5.00, 12.50)	5.00 (5.00, 10.00)	10.00 (5.00, 12.50)	0.14
Previous treatments				
Omalizumab (Xolair) (n=299)	47 (15.7%)	7 (7.8%)	40 (19.1%)	**0.015**
Anti-IL-5 drug (n=291)	9 (3.1%)	2 (2.3%)	7 (3.4%)	1.00
Bronchial Thermoplasty (n=286)	13 (4.5%)	1 (1.2%)	12 (5.9%)	0.12

OCS: oral corticosteroids; GP: general practitioner; FEV1: forced expiratory volume; FVC: forced vital capacity; ACQ: Asthma Control Questionnaire, 5-item version; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; FeNO: fraction of exhaled nitric oxide; IgE: immunoglobulin E. Data reported as mean±SD or median (IQR) or n(%). * The OCS exposure data was missing for 9 participants at the baseline and hence not included in this table. [#]Atopy positive classified by positive skin prick test or radioallergosorbent test/ImmunoCAP and/or previous omalizumab treatment.

458 **Table 2: Magnitude of maintenance OCS dose reduction by 12 months follow-up**

	No. of patients
90-100% reduction	47 (36.7%)
75-<90% reduction	04 (3.1%)
50-<75% reduction	15 (11.7%)
25- <50% reduction	09 (7.0%)
0-<25% reduction	53 (41.4%)
Total	**128 (100%)***

459 *5 increased dose and 11 missing

460 **Table 3: Predictors of becoming OCS free after six months mepolizumab therapy**

	Odds Ratio	**P value**	**95% confidence interval**	
Body Mass Index	0.925	**0.009***	0.872	0.981
Age: asthma symptoms onset	1.027	**0.010***	1.006	1.048
Asthma control test	1.111	**0.028***	1.011	1.220
Baseline maintenance OCS use	0.095	**<0.001***	0.040	0.227
Number of respiratory medications	0.789	0.142	0.574	1.083

461 *significant

462

463

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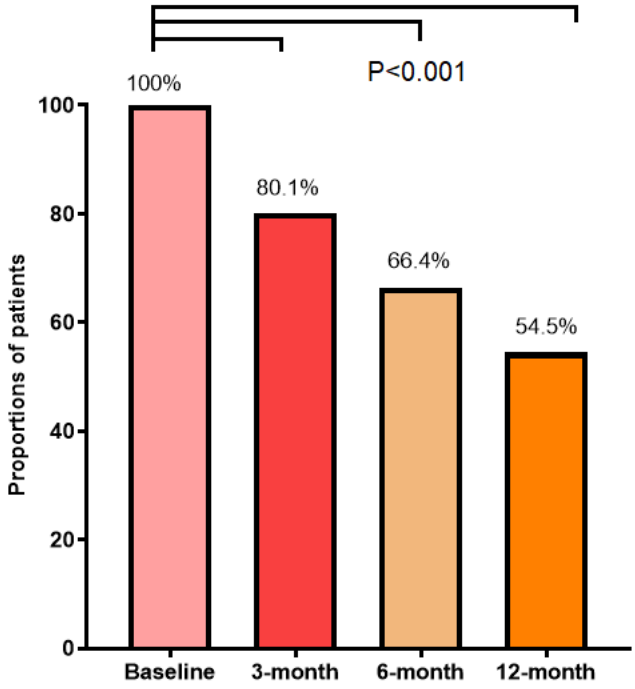
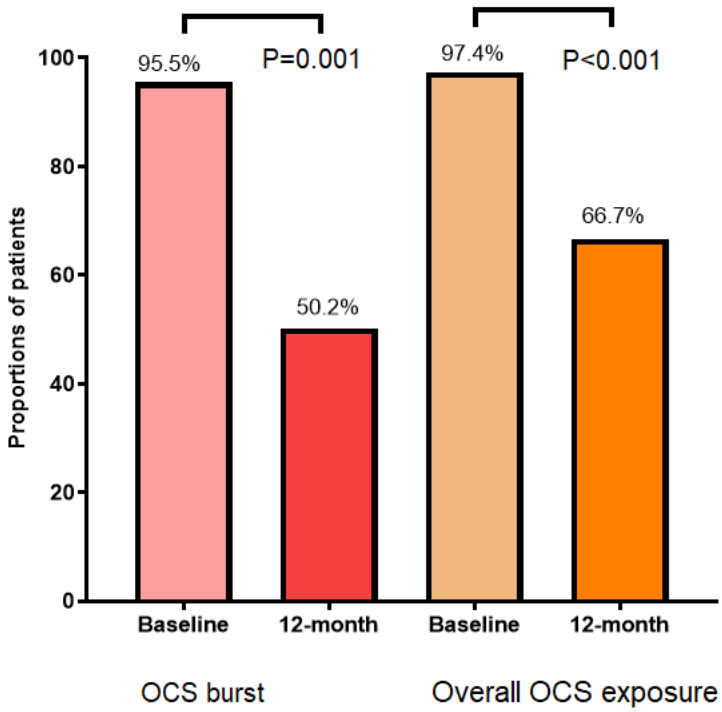
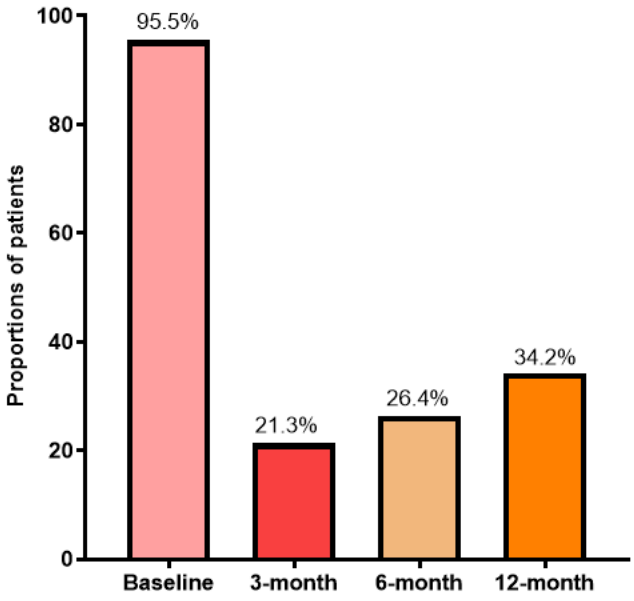

P<0.001
100%
80.1%
66.4%
54.5%
Proportions of patients
100
80
60
40
20
0
Baseline
3-month
6-month
12-month


Proportions of patients
100
80
60
40
20
0
95.5%
P=0.001
50.2%
97.4%
P<0.001
66.7%
Baseline
12-month
Baseline
12-month
OCS burst
Overall OCS exposure


100
80
60
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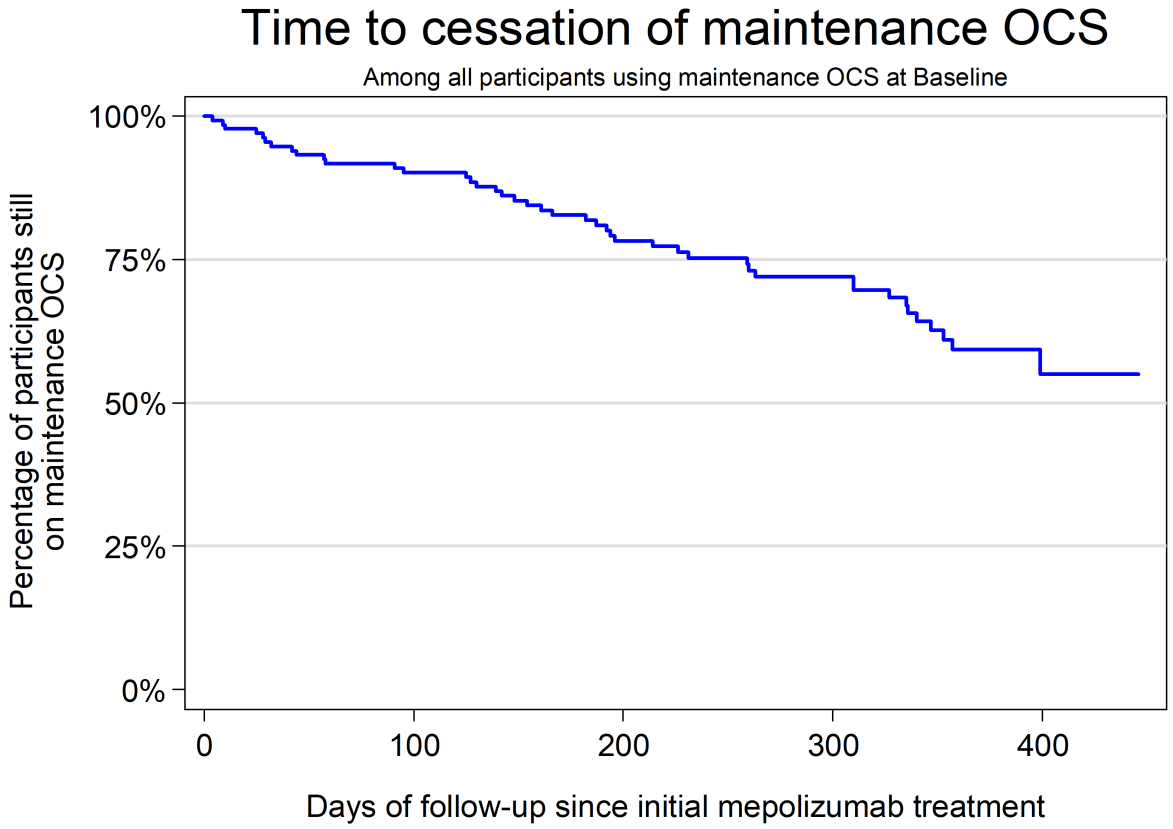
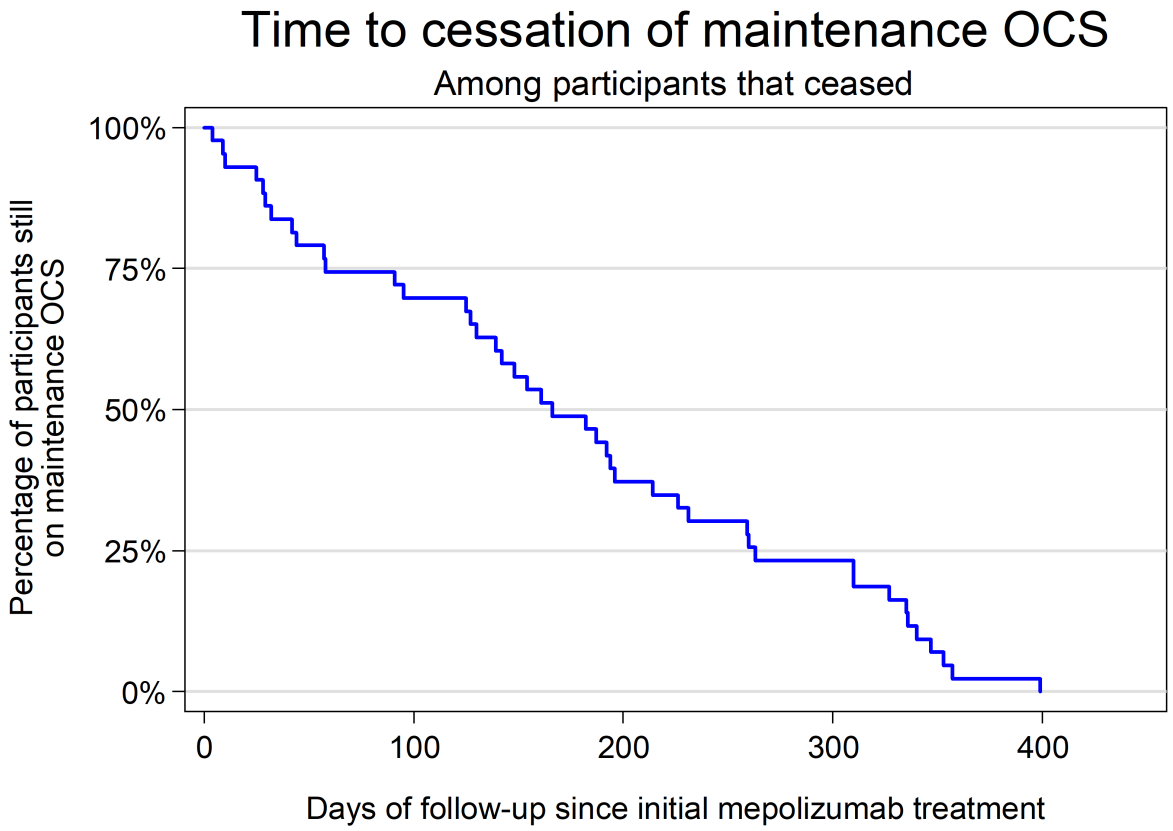
0
Proportions of patients
95.5%
21.3%
26.4%
34.2%
Baseline
3-month
6-month
12-month


Time to cessation of maintenance OCS
Among all participants using maintenance OCS at Baseline
Percentage of participants still on maintenance OCS
100%
75%
50%
25%
0%
0
100
200
300
400
Days of follow-up since initial mepolizumab treatment


Time to cessation of maintenance OCS
Among participants that ceased
Percentage of participants still on maintenance OCS
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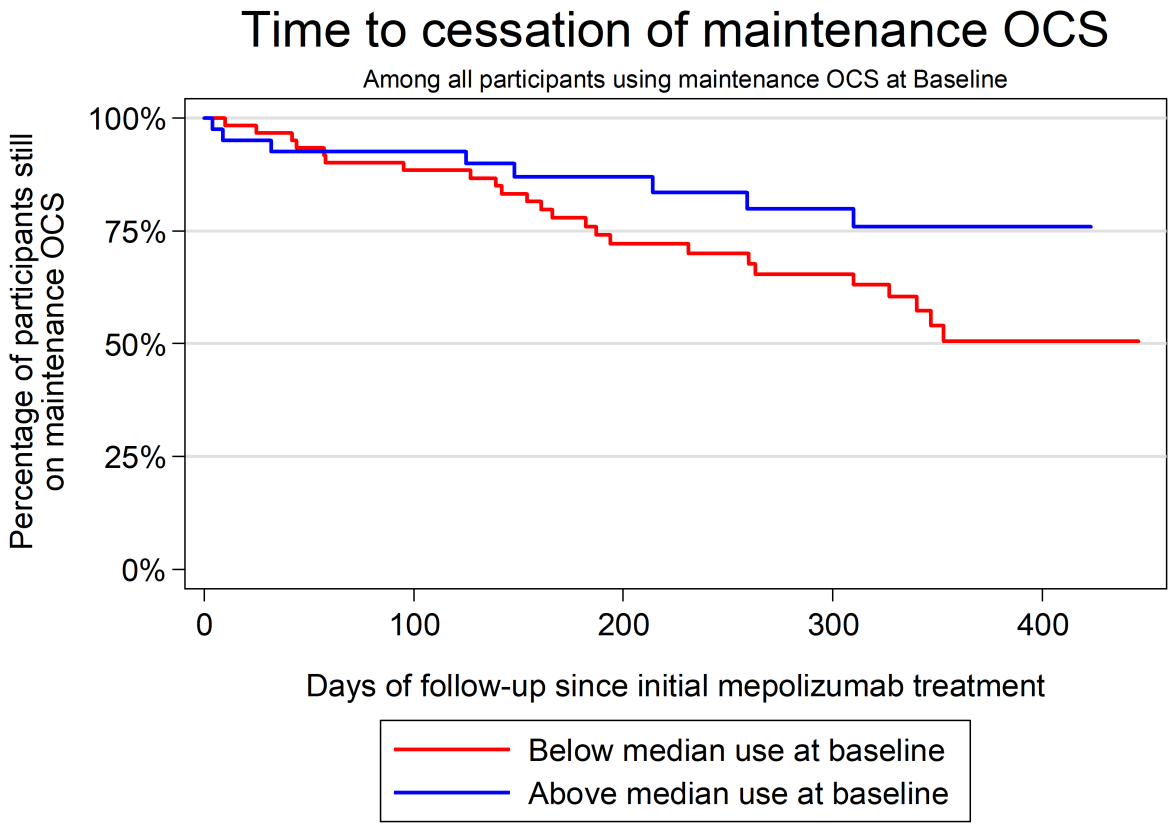
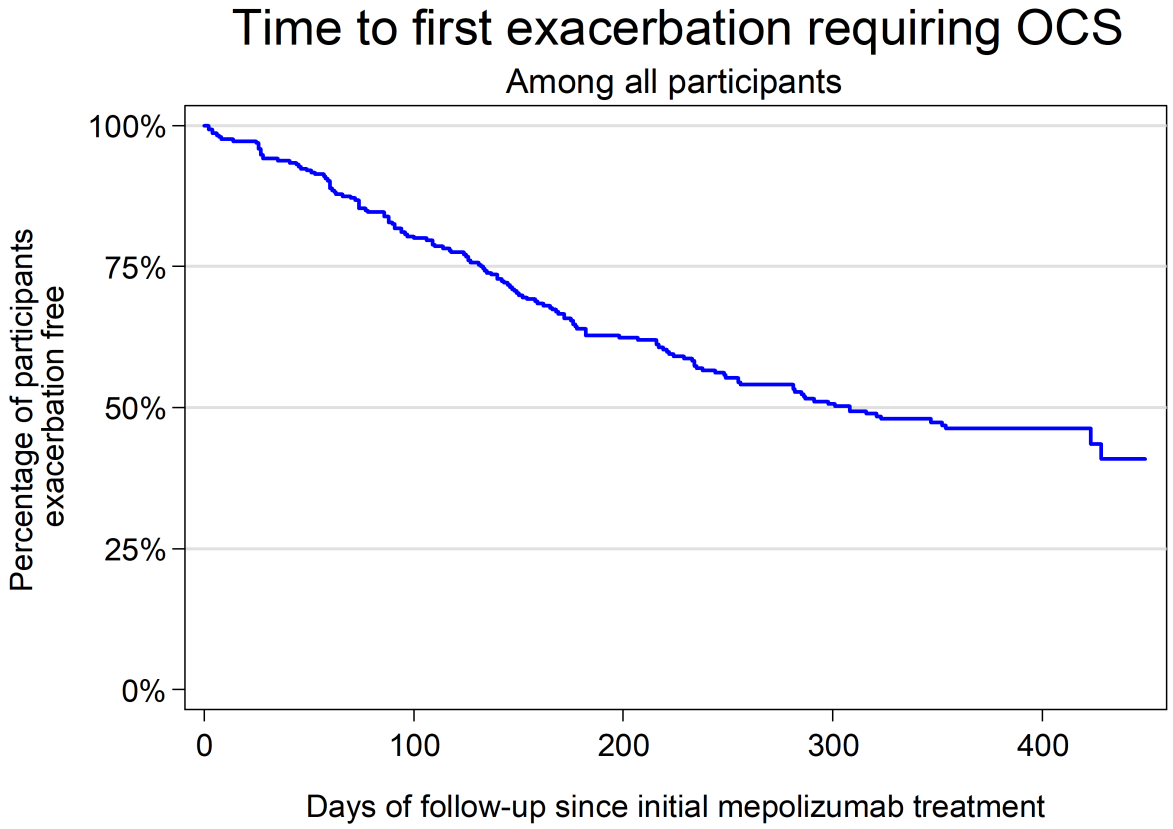
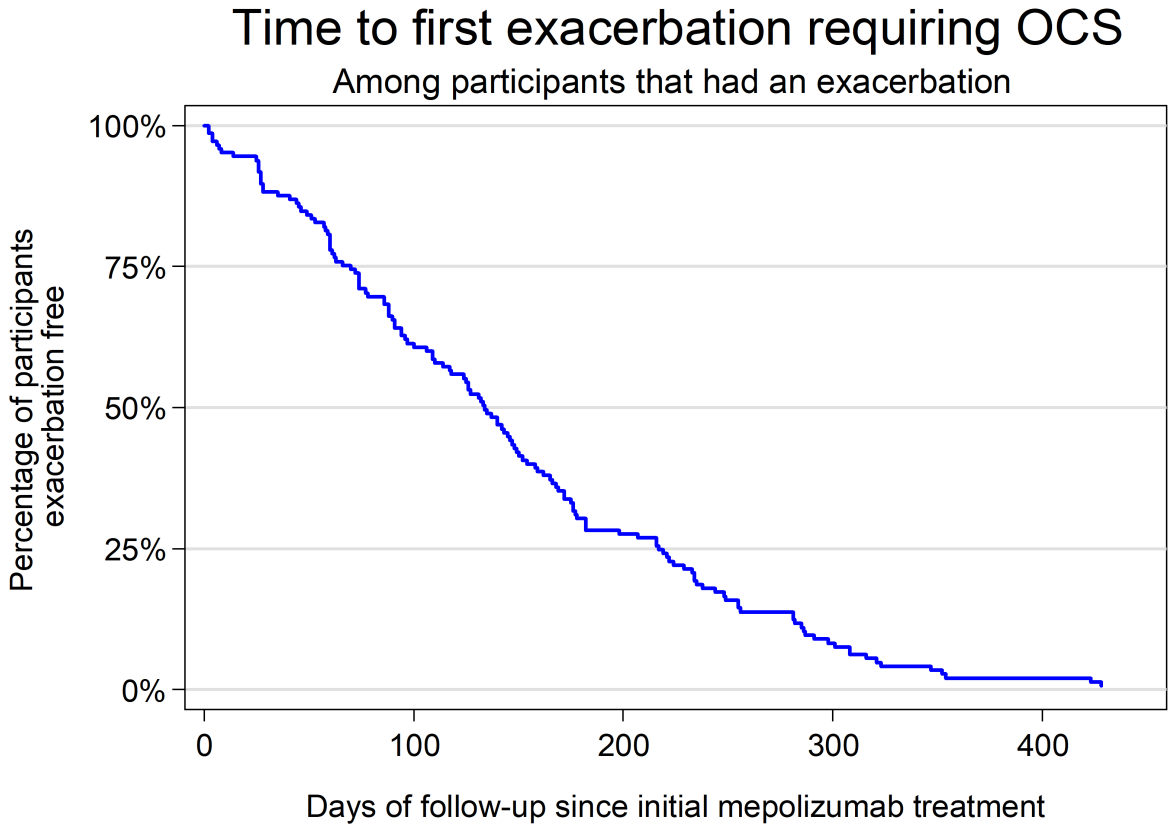
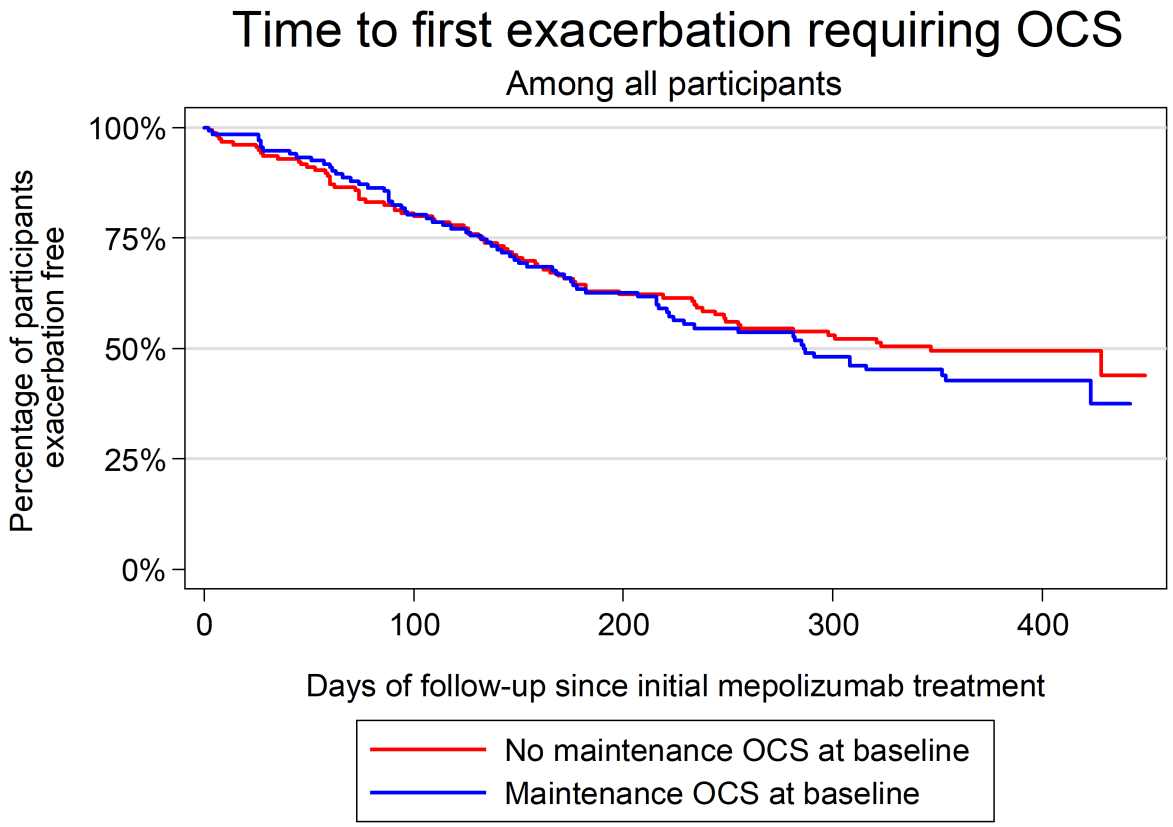
75%
50%
25%
0%
0
100
200
300
400
Days of follow-up since initial mepolizumab treatment


Time to cessation of maintenance OCS
Among all participants using maintenance OCS at Baseline
Percentage of participants still on maintenance OCS
100%
75%
50%
25%
0%
0
100
200
300
400
Days of follow-up since initial mepolizumab treatment
Below median use at baseline
Above median use at baseline


Time to first exacerbation requiring OCS
Among all participants
Percentage of participants exacerbation free
100%
75%
50%
25%
0%
0
100
200
300
400
Days of follow-up since initial mepolizumab treatment


Time to first exacerbation requiring OCS
Among participants that had an exacerbation
Percentage of participants exacerbation free
100%
75%
50%
25%
0%
0
100
200
300
400
Days of follow-up since initial mepolizumab treatment


Time to first exacerbation requiring OCS
Among all participants
Percentage of participants exacerbation free
100%
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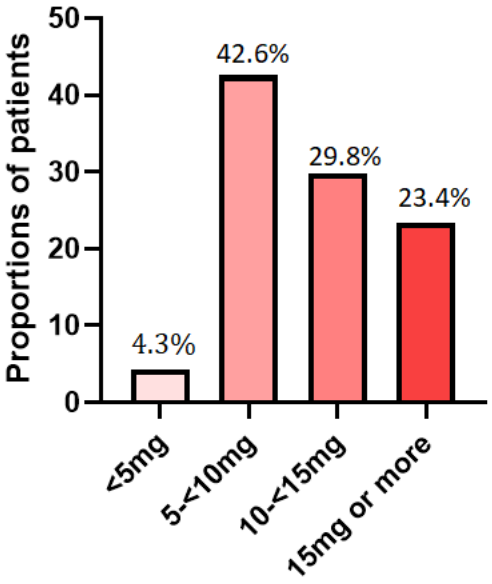
300
400
Days of follow-up since initial mepolizumab treatment
No maintenance OCS at baseline
Maintenance OCS at baseline


Proportions of patients
50
40
30
20
10
0
42.6%
29.8%
23.4%
4.3%
<5mg
5-<10mg
10-<15mg
15mg or more