Early View

Original research article

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Please cite this article as: McDowell PJ, Stone JH, Zhang Y, *et al.* Glucocorticoid toxicity reduction with Mepolizumab using the glucocorticoid toxicity index. *Eur Respir J* 2021; in press (<https://doi.org/10.1183/13993003.00160-2021>).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Glucocorticoid Toxicity Reduction with Mepolizumab using the Glucocorticoid Toxicity

Index

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Take home message:

Anti-T2 biologics decrease glucocorticoid (GC) requirements in severe eosinophilic asthma, but GC-reduction does not correlate with GC toxicity reduction in individuals. Assessment of GC toxicity reduction is crucial when considering response to biologics.

Abstract:

Reduction in glucocorticoid exposure is the primary benefit of new biologic treatments in severe asthma, but there is currently no evidence that reduction in glucocorticoid exposure corresponds to a proportionate reduction in associated toxicity.

Objectives: To use the validated Glucocorticoid Toxicity Index (GTI) to assess change in glucocorticoid toxicity after 12 months treatment with mepolizumab, and compare toxicity change to glucocorticoid reduction and change in patient reported outcome measures (PROMs).

Methods: A longitudinal, real world prospective cohort of 101 consecutive patients with severe asthma commenced on mepolizumab in a Specialist UK Regional Severe Asthma clinic. GTI toxicity assessment, cumulative glucocorticoid exposure and PROMs were recorded on commencing mepolizumab (V1), and after 12 months treatment (V2).

Results: There was significant reduction in oral glucocorticoid exposure (V1 4280mg prednisolone/year [interquartile range (IQR) 3083,5475] vs V2 2450mg prednisolone/year [1243,3360], $p < 0.001$). Substantial improvements in individual toxicities were observed but did not correlate with oral glucocorticoid reduction. Mean GTI Aggregate Improvement Score (AIS) was -35.7 (SD 57.8) with a wide range in toxicity change at individual patient level (AIS range -165 to +130); 70% (71/101) had a reduction in toxicity (AIS < 0), 3% (3/101) had no change (AIS = 0) and 27% (27/101) an increase in overall toxicity. Sixty-two (62/101) patients met the AIS minimally clinically important difference of ≤ -10 , but AIS did not correlate with glucocorticoid reduction or change in PROMs.

Conclusion: Mepolizumab resulted in substantial oral glucocorticoid reduction but this did not correlate with reduction in oral glucocorticoid toxicity, which varies widely at the

individual patient level. Oral glucocorticoid reduction is not a comprehensive measure of response to mepolizumab.

Key words: Asthma, biological therapy, glucocorticoids.

Introduction

Biological therapies targeting type-2 (T2) inflammatory pathways in severe eosinophilic asthma (SEA) are effective in facilitating a decrease in systemic glucocorticoid (GC) exposure by reducing asthma exacerbations by approximately 50%,[1][2][3][4] and facilitating maintenance oral GC weaning.[5][6][7]

A key anticipated benefit of biologics is GC toxicity reduction given the frequently occurring, multisystem adverse events known to have an increased incidence in individuals with severe asthma exposed to GCs, when compared to matched mild-moderate asthmatics and non-asthmatic controls.[8][9][10][11] Reduction in GC exposure is the pragmatic primary outcome of clinical trials for biologics in SEA, but there is currently no evidence that reduction in GC exposure produces a corresponding reduction in toxicity.

Mepolizumab, an anti-IL5 monoclonal antibody, is used in the treatment of SEA to inhibit the recruitment, activation and longevity of eosinophils in the airways.[1][5][12] In the UK, access to mepolizumab and other biologics in SEA, is governed by the National Institute for Health and Care Excellence(NICE), which advises that the decision of continuing or discontinuing biological therapy is based on the determination of an “adequate response” defined as a “clinically significant reduction in GC-requiring exacerbations” (50% reduction for mepolizumab) or a “clinically significant reduction in continuous oral GCs”. [13][14][15][16] There is no clear guidance on what constitutes a ‘clinically significant reduction’, but accepting the major problem with systemic GC are the well-recognised side effects, toxicity reduction is a central issue which is becoming more widely acknowledged.[17]

Using the Glucocorticoid Toxicity Index (GTI) [18], we have previously shown that quantification of pre-biologic GC toxicity in SEA patients with substantial systemic GC exposure demonstrates

wide variation at the individual patient level.[19] Here, we use the GTI to quantify change in GC-associated toxicity in a SEA patient population treated with mepolizumab over a 12-month period in the course of routine clinical care. We evaluate the relationships between GC toxicity change, variation in cumulative GC dose and asthma outcome measures typically used to define a treatment response to biological therapies.

Methods

Design

This was a prospective, single-centre, observational cohort of GC exposure and GC toxicity change in sequential mepolizumab-treated SEA patients in a Regional Severe Asthma Specialist clinic in the UK. The GTI enabled systematic assessment of GC-toxicity using medical history, medication review, physical examination and routine blood tests. Patients underwent GTI assessment on commencing mepolizumab (V1), and after 12 months treatment (V2). Baseline pre-biologic GC-associated toxicity burden has previously been described in this cohort with a mean toxicity of 177.5 points (73.7) [19].

Asthma-specific and quality-of-life patient-reported outcome measures (PROMs) were completed at V1 and V2, including the Mini-Asthma Quality of Life Questionnaire (mini-AQLQ), St. George's Respiratory Questionnaire (SGRQ), Asthma Control Questionnaire 5 (ACQ5), Hospital Anxiety and Depression score (HADS), and EuroQol-5D5L (see online supplement for further information). Asthma nurse specialists evaluated patients every 4 weeks to administer mepolizumab, review medication use and asthma control (symptoms, lung function and exacerbation history). After 3 months of mepolizumab, GC dose was reduced in those receiving maintenance GCs in accordance with clinical protocol (see online supplement).[20][21]

Patients

All patients had SEA as defined by the Global Initiative for Asthma (GINA) guidelines[22] and were eligible to receive mepolizumab (100mg subcutaneously every 4 weeks) according to NICE guidelines (see online Supplement[16]). As part of eligibility criteria, all underwent adherence evaluations to standard of care inhaled treatment using digital monitoring technology,[23] medicines possession ratio, and number of rescue GC courses required. These data were retrieved through electronic healthcare prescribing records.[24]

GTI Scoring

The GTI [18] and its online application (GTI 2.0 app© 2016, 2018. Massachusetts General Hospital. All rights reserved[19]) were developed as a practical tool to systematically measure GC toxicity and assess change over time. The GTI captures the full sweep of GC toxicity and permits the app to apply systematically determined relative weights to each toxicity item. Development and validation of the GTI, including its minimal clinically important difference (MCID), have been reported previously.[18][19] In brief, the Cumulative Worsening Score (CWS) is an additive record of GC-related toxicities experienced by a patient from baseline. The score is always ≥ 0 . A CWS of zero indicates that no new GC toxicities were present at V2. The higher the CWS, the greater the number of new toxicities encountered. The maximum possible CWS is 439. The Aggregate Improvement Score (AIS) records present toxicity, allowing both improvement and worsening. A positive score indicates increased total toxicity, whereas a negative score reflects reduced toxicity. The MCID for the AIS is -10.[19] The minimum AIS possible is -346, the maximum +439.

Statistical analysis:

Numbers and frequencies were reported for categorical variables. Continuous variables were reported as means with standard deviations (SD) or medians with interquartile ranges [IQR], as appropriate considering their distributions. We calculated the differences between V2 and V1, as reported in Table 2. The distributions of these differences are normal. We therefore used paired t-tests to obtain the mean of the differences and their 95% CIs. We used a logistic regression model to examine the association between measures of GC use and the AIS MCID. We also assessed changes of each patient's reported outcome in relation to the AIS MCID using the logistic regression model. This model was adjusted for age and sex. We provide the odds ratio and 95% confidence interval for each point estimate. We created a scatterplot of AIS against percentage reduction in GC exposure and calculated the Spearman correlation coefficient. For the data reported in Table 4, we divided the CWS into two categories, namely: CWS=0 and CWS>0. These categories signify, on one hand, no worsening of glucocorticoid toxicity between V1 and V2 and, on the other, the development of new toxicity between these time points. We then examined the relationships of measures of GC use as well as the patients reported outcomes to CWS worsening using logistic regression, adjusted for age and sex. Statistical analysis was undertaken on SPSS version 25 (IBM, Chicago, IL).

Results

Between April 2017 and November 2019, GTI assessment was undertaken on sequential patients commencing mepolizumab (n=101, Table 1, Table E1) and after 12 months treatment. Clinical disposition after 12 months mepolizumab is shown in figure 1. Of the 83 participants on maintenance prednisolone, 30/83 withdrew prednisolone completely and 32/83 had HPA axis

suppression precluding complete withdrawal, with only 21/83 requiring maintenance prednisolone for asthma control.

The cohort's baseline systemic GC exposure was substantial, consistent with NICE access requirements for biologic therapy eligibility.[16] Eighteen (18/101) participants had ≥ 4 GC rescue courses in the 12 months preceding mepolizumab therapy with the remainder on maintenance prednisolone (Figure 1). In the year before V1, median GC exposure was 4280mg prednisolone/year [3082.5, 5475.0] (median daily dose 11.7 mg prednisolone/day [8.4, 15.0]), reducing to 2450 mg prednisolone/year [1242.5, 3360] (median daily dose 6.7mg prednisolone/day [3.4, 9.2]) on mepolizumab at V2 ($p<0.001$), representing a median 44.5% [34, 64] reduction in cumulative GC exposure. Comparing the 12 months prior to commencing mepolizumab (V1) with the 12 months on mepolizumab treatment (V2), asthma exacerbations declined (5 [2, 7] vs 1 [0, 2], $p<0.001$) with an 88% reduction in Emergency Department visits and 72% reduction in hospital admissions. There was no difference in pre-bronchodilator spirometry or FeNO between V1 and V2 (Table 2, Table E2).

Toxicity change

Change in specific toxicities are displayed in Table 2 and Table E2. Mean BMI declined between V1 and V2 with 38% (38/101) of patients having a reduced BMI, 5% (5/101) an unchanged BMI and 57% (58/101) an increased BMI at V2. The correlation between BMI change and percentage reduction in prednisolone exposure was not significant ($\rho=0.14$, $p=0.18$).

Glycaemic control: On commencing mepolizumab, 13 patients were prescribed anti-diabetic medication with a significant fall in HbA1c seen at V2 (Figure E1). Of the 88/101 patients not known to have diabetes at V1, 64.8% (57/88) had an HbA1c in the normal range, 27.3% (24/88)

had an HbA1c in the high-risk pre-diabetic range and 8% (7/88) in the diabetic range. There was no significant correlation between change in HbA1c and percentage reduction in cumulative GC exposure.

Lipids: Twenty-seven (26.7%) of the cohort received anti-lipid medication at V1 with median LDL concentrations of 2.8 mmol/L [1.6, 3.8] and 2.4 mmol/L [1.5, 3.2] at V2, ($p=0.07$); 24/27 patients had no change in anti-lipid medication, 2/27 had a decrease and 1/27 had an increase in anti-lipid medication from V1-V2. There was no correlation between LDL and percent change in cumulative GC exposure from V1 to V2.

Infection: In the 12 months prior to starting mepolizumab, 18.6% (18/97) of patients had candidiasis (oral or vaginal) or herpes zoster without neuralgia or ophthalmic involvement declining to 5% (5/101) at V2 ($p=0.002$). Herpes zoster with neuralgia or eye involvement was described in 2 patients in the twelve months before V1, but no cases were identified between V1 and V2. In the 12 months prior to initiation of mepolizumab therapy, 18.8% (19/101) patients had at least one hospitalisation for infection. This percentage declined to 7.9% (8/101) at V2, $p=0.04$.

Skin: A significant reduction in skin toxicity was apparent at V2. Acneiform rash was reported by 6/101 patients at V1 and 2/101 at V2 ($p=0.046$); easy bruising by 68/101 patients at V1 and 54/101 at V2 ($p=0.003$); and striae by 35/101 at V1 and 20/101 at V2 ($p=0.003$). Of the 58 female patients in this cohort, 25 (43.1%) had hirsutism at V1 but only 9 (15.5%) at V2 ($p<0.001$).

Neuropsychiatric: The most common toxicity at mepolizumab initiation was neuropsychiatric disturbance. Depressive symptoms were highly prevalent at baseline and continued to be an important issue through to V2 (Table E3). At V2, 45/101 (44.6%) patients reported fewer depressive symptoms and only 5/101 (5%) reported increased symptoms.

Mood disturbance of irritability or mood elevation improved at V2, with 43/101 (42.6%) patients reporting mood improvement and only 8/101 (7.9%) reporting worsening mood disturbance. Two patients had experienced previous psychotic episodes whilst receiving high dose GCs at V1, there were no episodes described at V2.

The majority of patients (56/101, 55%) reported some degree of insomnia at initiation of mepolizumab. At V2, 30.7% (31/101) had improved insomnia and 8.9% (9/101) had worsened insomnia symptom. (See Table E4 for further detail on neuropsychiatric change).

Patient-reported outcomes

Changes in PROMs are shown in Table 2 and Table E5. For ACQ5, 59% (58 of 98 paired questionnaires) of patients met or exceeded the ACQ5 MCID (≥ 0.5), and 60% (58/96) and 71% (68/96) met the MCID for the mini-AQLQ and St George's respiratory questionnaire respectively. At V2, patients reported improvement in their overall health status measured with ED5L5D Health scale.

Overall anxiety and depression scores improved at V2 (Table 2), 10% fewer patients were in the severe HADs category for anxiety (score ≥ 11) and 9% more were in the normal range. There was an 11% decrease in the number of patients in the HADs severe depression category (score ≥ 11), a 4% increase in the moderate category, and an 8% increase in the number of patients in the normal range. The GTI depression score correlated well with the HADs depression scores at V1 ($\rho=0.6$, $p<0.001$) and V2 ($\rho=0.53$, $p<0.001$), (Table E6).

There was a weak correlation between percentage prednisolone reduction and change in mini-AQLQ ($\rho=-0.25$ $p=0.015$), however, no correlation with change in ACQ5, SGRQ, HADs depression or HADs anxiety scores.

Quantifying change in toxicity over time

The mean AIS for this cohort was -35.7 (SD 57.8). The degree of toxicity change varied widely at the individual patient level (AIS range -165 to +130, Figure 2). A reduction in toxicity (AIS <0) was seen in 70% (71/101) of the cohort, while 3% (3/101) had no change (AIS = 0) and 27% (27/101) an increase (AIS ≥1). AIS did not correlate with baseline GC-associated toxicity score or change in PROMs (Figure E2). Toxicity change (AIS) did not have a significant linear correlation with oral GC reduction from V1 to V2 when measured as percentage reduction in GC, cumulative reduction in GC (mg) or reduction in GC rescue courses (Figure E3).

Of the 101 patients, 62 patients met the AIS MCID of ≤-10 (mean AIS -71.4 (37.2), range -165 to -10, Figure 2) and 39 patients did not (mean AIS 21.1 (34.3), range -9 to +130). Participants who met the MCID had fewer GC rescue courses for exacerbations at V2 (1 rescue course [0, 2] versus 2 rescue courses [0, 3], OR 0.73 (95% CI 0.55,0.98), p=0.04) and a greater percentage reduction in prednisolone exposure from V1 to V2 (48.6% [34.8, 70.0] versus 40.8% [26.1, 57.2], OR 0.80 (95% CI 0.66,0.96), p=0.02). However, the proportion of patients receiving maintenance GC and daily dose did not differ in those who met the MCID and those who did not (Table 3). Baseline GC-associated toxicity on commencing mepolizumab and change in PROMs did not differ in those who met the AIS MCID and those who did not (Table 3).

Defining a ≥50% reduction in annual GC exposure from V1 to V2 as a clinically significant reduction, 32% (32/101) of patients did not meet this response threshold yet had a clinically meaningful reduction in GC-associated toxicity (AIS ≤-10), Figure 3, quadrant C. In addition, 12% (12/101) of patients who met this threshold of GC reduction did not reach the MCID for GC toxicity reduction (Figure 3, quadrant B).

Of the 101 patients in the cohort, 38% (38/101) had a CWS of zero, indicating no new GC toxicity at V2. The remaining 62% (63/101) had a positive CWS, with individual scores ranging from 1 to 167 (Figure 4). Neither baseline GC-associated toxicity nor oral GC reduction from V1 to V2 correlated with the occurrence of new toxicities as measured by the CWS (Figure E4).

When comparing the 38 patients with no new toxicities (CWS 0) and the 63 patients with new toxicities (CWS ≥ 1), there was no difference in the proportion of patients on maintenance prednisolone at V1 or V2 and no difference in GC reduction between the two groups (Table 4). Although there was no difference in the number of GC rescue courses for asthma exacerbations at V1, fewer exacerbations occurred in the group with no new toxicities at V2 (Table 4). Both groups, CWS of zero and CWS ≥ 1 , reported improvement in asthma symptoms and reported QOL, with no difference between the groups.

Duration of asthma was associated with risk of CWS worsening (odds ratio=1.03, 95% CI: 1.00-1.06); however, no other demographic, anthropometric or baseline clinical factors were associated with the risk of CWS worsening. No associations were observed between these factors and AIS.

Discussion

Previous studies have provided evidence for an increase in adverse events on exposure to oral glucocorticoids, and in asthma, have provided evidence for an increase in GC-associated adverse events in oral GC-exposed severe asthmatics when compared to matched-controls (both mild/mod asthmatics, and non-asthmatic individuals)[8][9][10][11]. Here, we prospectively evaluated GC reduction with 12 months mepolizumab in a real-world SEA cohort, and related

this to changes in GC toxicity and PROMs. The SEA cohort themselves acted as a control, with the comparison of baseline pre-biologics toxicity assessment, to toxicity assessment after 12 months treatment with a GC-sparing medication. There was substantial reduction in GC requirement, with the majority of patients having significant GC-related toxicity reduction and PROM improvement, however the relationship between GC reduction and toxicity change was not linear.

Prior to initiation of mepolizumab, this cohort received substantial asthma treatment (Table 1), yet continued to have evidence of T2 cytokine driven disease. In keeping with clinical trials,[1][12] this real-world cohort had mepolizumab-enabled reduction of asthma exacerbations, hospitalisations, ED visits and a 44.5% reduction in 12-month cumulative GC exposure.

Whilst this considerable reduction in GC led to a statistically significant reduction in BMI, systolic BP, lipid profile and HbA1C, the overall changes were small and the clinical significance may seem questionable. However, it is recognised that elevation of these markers of vascular and metabolic dysfunction represents a cumulative continuum of risk,[25][26][27] therefore even small reductions may be beneficial. In addition, GC exposure is not the only influence on these measures, with calorie intake, exercise and daily activity reflecting complex behavioural and social habits emerging over years of having severe asthma and substantial GC exposure. These factors may be more challenging to modify, and biologic-induced GC reduction may need coupled with exercise programmes and dietary education to modify behaviour and facilitate reduction of metabolic risk. Medications to manage risk factors play a role, though importantly, GTI scoring takes medication changes into consideration when calculating toxicity change.

Improvement in mood disturbance was common, with double the number of patients reporting no depressive symptoms at V2, and a halving of those reporting severe depressive symptoms. Significant improvement in mood disturbance/mania and insomnia were also apparent. The aetiology of improved mood is multifactorial; reduction in GC and improvements in disease control (ACQ5, SGRQ, mini-AQLQ) occur alongside improvement in overall health (EuroQol5D5L Health scale) and reduction of total toxicity burden in the majority of patients.

Across the three respiratory PROMs, 60-70% of patients had improvement in symptoms that met the PROM MCID; there was a mean improvement in perceived overall health (ED5D5L health scale). The improvement in PROMs correlated neither strongly nor significantly with reduction in GC exposure or AIS toxicity change.

The wide distribution in AIS reflects varied toxicity change at the individual patient level after introduction of mepolizumab. Although the majority of patients had a significant reduction in toxicities, 30% had no change or worsening overall toxicity which may not be surprising given that the median daily prednisolone dose at V2 was 6.7mg/day [3.4,9.2], a dose at which GC toxicity may continue to occur in some patients.

Whilst these data demonstrate substantial reduction in GC exposure, reduction of total toxicity burden and improvement in PROMS in the majority of mepolizumab-treated patients, the relationships between these three outcome measures are complex. Those who met the AIS MCID had fewer GC rescue courses and a greater percentage GC reduction at V2 than those who did not, but reduction in GC dose did not correlate linearly with AIS. In fact, defining a 50% reduction in GC exposure as an adequate GC-sparing response to mepolizumab resulted in one third of this cohort being defined as “non-responders”, despite demonstration of a substantial improvement in GC toxicity. Figure E5 further illustrates the point that not all patients will derive

the same degree of toxicity reduction benefit from a given reduction in oral glucocorticoid treatment. Furthermore, a greater reduction in GC did not equate to a reduced incidence of new GC-toxicities when on mepolizumab.

Strengths of these data include the size of the severe asthma cohort, prospective data collection, and toxicity assessment using a standardized, validated instrument applied according to a specific protocol. Although components scored within the GTI were included as they are likely to exhibit change over the course of a reasonable period of clinical observation (e.g. between 3 months and 3 years), as is demonstrated in this manuscript with many GC-associated toxicities improving, one potential limitation is the possibility that a time-lag from GC reduction to toxicity improvement may exist with some toxicities, and in fact, once present, some toxicities may not be reversible. We hope to address this with further longitudinal assessment of toxicity change using the GTI, and anticipate that many of those patients with HPA axis suppression will have adrenal recovery and be able to withdraw prednisolone completely.

In summary, observation of toxicity in this GC-dependent cohort commencing a GC-sparing therapy shows a significant reduction in GC exposure, reduction in GC-toxicity and improvement in PROMS in the majority of patients. Toxicity change varies widely at the individual patient level and GC reduction is not a simple substitute for measuring toxicity change. As the purpose of GC-sparing agents is to reduce toxicities resulting from the GC, caution should be applied when solely using GC reduction as a measure of response to mepolizumab.

Acknowledgements:

We would like to acknowledge the support of Martha Stone in the development of the GTI 2.0 app.

Funding: This work was unfunded.

Author's contributions:

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship. LGH, PJM and JHS contributed to the design of the work, PJM, KH, LD, RJJ, CAB and LGH contributed to acquisition of the data. LGH, PJM, JHS and YZ analysed the data and undertook interpretation of the data. All authors contributed to the review and editing of the manuscript, approved the final draft of the manuscript for submission and agree to be accountable for all aspects of the work.

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Table 1. Clinical and demographic features of patients with severe eosinophilic asthma on commencing mepolizumab (V1).

Number of patients 101	
Age (years)	54.4 (11.9)
Female	58 (57.4%)
Smoking status	
Never smoker	60 (61.9%)
Ex-smoker	35 (36.1%)
Current smoker	2 (2.1%)
BMI (kg/m ²)	30.5 (5.8)
Age at onset of asthma (years)	30 [14, 40]
Atopic disease	47 (48.5%)
GC rescue courses / 12 months	5 [2, 7]
Cumulative prednisolone dose (mg) / 12 months	4280 [3085, 5475]
ED visits / 12 months	120/39 patients
Hospital admissions / 12 months	60/29 patients
Ever been ventilated	14 (13.9%)
FEV1 % Predicted*	68.9 (19.0)
FEV1/FVC %	61.9 (14.6)
FENO (ppb)	35 [20.3, 56.8]
Blood Eosinophil (cells/ μ L)	280 [100, 600]
Highest Blood Eosinophils (cells/ μ L) in medical record	860 [600, 1300]
IgE (kU/L)	117.5 [42.3, 351.3]
Bone density T score (Hip)	-0.40 (1.1)
Bone density T score (Spine)	-0.72 (1.1)
Daily prednisolone	83 (82.2%)
Daily prednisolone dose (mg) (n=83)	10 [10,15]
ICS Daily dose (BDP μ g equivalent)	2000 [2000, 2000]
Long acting Beta agonist	101 (100%)
Long acting muscarinic antagonist	35 (36.5%)
Leukotriene receptor antagonists	51 (51%)
Theophylline	38 (38.4%)
Nebulised bronchodilators	33 (34.4%)
Maintenance macrolide	7 (7%)
ACQ5	2.6 (1.3)
Mini-AQLQ	3.6 (1.4)
SGRQ	55.8 (20.9)
Euro-QoL 5D5L Index	0.63 [0.4, 0.8]
Euro-QoL 5D5L Health Scale	65 [50, 75]
HADS Depression	6 [3, 11]
HADS Anxiety	8 [5, 14]

*Using GLI 2012 predictive values. Data are presented as mean (SD), median [IQR] and count (%). Further descriptive statistics for these variables can be found in Table E1.

Table 2. Clinical and patient reported outcomes at baseline (V1) and after 12 months mepolizumab treatment (V2).

	V1	V2	Toxicity change at V2 (95% CI)	P
Clinical Outcomes				
Total ED attendances last 12 months in number of patients	120 in 39	15 in 10	-1.05 (-1.55, -0.55)	<0.001
Hospital admissions last 12 months	60/29 patients	17/11 patients	-0.42 (-0.71, -0.14)	0.004
FEV1 % Predicted	68.9 (19.0)	70.1 (21.7)	1.16 (-1.69, 4.01)	0.42
FVC % Predicted	85.9 (16.0)	86.5 (17.4)	0.79 (-1.66, 3.25)	0.52
FEV1/FVC	61.9 (14.6)	62.1 (16.9)	0.23 (-2.51, 2.97)	0.87
FENO (ppb)	35 [20, 57]	38 [24, 68]	0.01 (-9.56, 9.58)	0.99
Blood Eosinophils cells/ μ L	280 [100, 600]	60 [40, 100]	-280 (-340, -210)	<0.001
BMI	30.5 (5.8)	29.9 (5.5)	-0.66 (-0.27, -1.06)	0.002
BP Systolic (mmHg)	130.3 (16.1)	129.3 (18.0)	-0.96 (-3.58, 1.66)	0.003
LDL (mmol/L)	2.8 (0.9)	2.6 (0.9)	-0.14 (-0.25, -0.02)	0.02
Total Cholesterol (mmol/L)	5.3 (1.1)	5.0 (1.1)	-0.31 (-0.45, -0.17)	0.006
HbA1c (mmol/mol)	41 [37,46]	39 [35,43]	-2.68 (-3.75, -1.62)	<0.001
Mini AQLQ Overall	3.6 (1.4)	4.5 (1.6)	0.88 (0.61, 1.16)	<0.01
SGRQ Overall	55.8 (20.9)	43.4 (23.2)	-12.81 (-16.50, -9.12)	<0.01
ACQ 5total	2.6 (1.3)	1.7 (1.2)	-0.89 (-1.15, -0.63)	<0.01
HADS: Anxiety	8 [5, 13.5]	7 [4,11]	-1.02 (-1.68, -0.36)	<0.01
HADS: Depression	6 [3,11]	5 [2,10]	-1.04 (-1.76, -0.32)	<0.01
ED5L5D Index value	0.63 [0.4, 0.8]	0.71 [0.4, 0.9]	0.05 (0.003, 0.10)	0.04
ED5L5D Health scale	65 [50, 75]	75 [56, 85]	9.68 (5.87, 13.50)	<0.01

Mini-AQLQ and ACQ5: MCID 0.5 , SGRQ MCID: 4 units, HADS: 0-7=normal, 8-10 mildly disturbed, >11 psychiatric impairment. Data are presented as mean (SD), median [IQR] and count. Further descriptive statistics for these variables can be found in Table E2.

Table 3. Associations of oral glucocorticoid use and patient reported outcomes with achieving AIS MCID (≤ -10).

	AIS ≤ -10 (n=62)	AIS ≥ -9 (n=39)	Change across AIS MCID Crude OR (95% CI)	Change across AIS MCID Age- sex adj. OR (95%CI)
Glucocorticoid use across AIS MCID				
Median daily prednisolone (mg) V1	11.2 [8.4, 15.0]	12.3 [8.7, 14.6]	0.99 (0.94-1.04)	0.99 (0.94-1.04)
Median daily prednisolone (mg) V2	6.5 [2.2, 8.5]	7.8 [4.0, 9.4]	0.96 (0.91-1.03)	0.96 (0.91-1.03)
Receiving maintenance Prednisolone V1	49 (79.0%)	34 (87.2%)	0.55 (0.18, 1.70)	0.58 (0.18-1.80)
Receiving maintenance Prednisolone V2	27 (43.5%)	25 (64.1%)	0.45 (0.20, 1.02)	0.40 (0.17, 0.96)
Number of GC rescue courses V1	5 [2,7]	5 [3, 8]	0.96 (0.85, 1.08)	0.96 (0.85, 1.08)
Number of GC rescue courses V2	1 [0,2]	2 [0,3]	0.73 (0.55, 0.98)	0.70 (0.52, 0.94)
Decrease Annual prednisolone (mg)	-1925 [-1400, -2888]	-1727.5 [-2527, -1200]	0.98 (0.94, 1.02)	0.98 (0.94, 1.01)
% decrease Annual prednisolone	48.6 [34.8, 70.0]	40.8 [26.1, 57.2]	0.80 (0.66, 0.96)	0.80 (0.66, 0.97)
Baseline GC-associated toxicity score	165.5 [124, 211]	164 [129, 229]	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Change in patient reported outcomes across AIS MCID				
Mini-AQLQ	0.82 [-0.7, 1.6]	0.94 [0.03, -1.7]	0.91(0.67, 1.23)	0.93 (0.68, 1.28)
SGRQ	-13.3 [-23.4, -4.6]	-9.9 [-15.8, 4.6]	0.99 (0.97, 1.01)	0.99 (0.96, 1.01)
ACQ5	-0.6 [-1.4, 0.0]	-0.8 [-2.2, 0.0]	1.26 (0.91, 1.75)	1.29 (0.92, 1.81)
HADs Anxiety	-1.0 [-3.0, 0.8]	-1.0 [-2.0, 1.5]	0.94 (0.83, 1.07)	0.95 (0.83, 1.08)
HADs Depression	-1.0 [-3.0, 1.0]	-1 [-2.0, 0.3]	0.95 (0.85, 1.07)	0.94 (0.84, 1.06)
EQ5L5D Index Value	0.0 [-0.08, 0.1]	0.02 [-0.06, 0.1]	1.29 (0.24, 6.86)	1.43 (0.26, 7.99)
EQ5L5D Health scale	5 [-1, 16.3]	12 [-4, 24]	1.00 (0.97, 1.02)	1.00 (0.97, 1.02)

Table 4 Associations of oral corticosteroid use and patient reported outcomes with the risk of developing new GC-toxicities (CWS ≥1)

	CWS 0 n=38	CWS ≥1 n=63	Change across CWS 0 and ≥1 Crude OR (95% CI)	Change across CWS 0 and ≥1 Age- sex adj. OR (95%CI)
Glucocorticoid use across CWS of 0 and CWS ≥1.				
Median daily prednisolone (mg) V1	11.2 [9.0, 16.7]	11.7 [8.1,14.6]	0.99 (0.95, 1.04)	1.00 (0.95, 1.05)
Median daily prednisolone (mg) V2	6.71 [3.83, 9.88]	6.71 [3.07,9.06]	1.00 (0.94, 1.06)	1.00 (0.94, 1.06)
Receiving maintenance Prednisolone V1	32 (84.2%)	51 (81.0%)	0.80 (0.27, 2.34)	0.77 (0.26, 2.29)
Receiving maintenance Prednisolone V2	20 (52.6%)	32 (50.8%)	0.45 (0.20, 1.02)	0.40 (0.17, 0.96)
Number of GC rescue courses V1	5.0 [2.0, 6.0]	5.0 [2.5, 7.0]	1.04 (0.92, 1.18)	1.05 (0.93, 1.19)
Number of GC rescue courses V2	1.0 [0.0, 2.0]	2.0 [0, 2]	1.42 (1.03, 1.95)	1.44 (1.04, 2.01)
Decrease Annual prednisolone (mg)(V2-V1)	-1881 [-2806,-1374]	-1760 [-2723,-1393]	1.01 (0.98, 1.05)	1.01 (0.97, 1.05)
% decrease Annual prednisolone	-42.0 [-62.9, -34.2]	-44.6 [-66.7, -32.2]	1.01 (0.85, 1.20)	1.01 (0.85, 1.29)
Baseline GC-associated toxicity score	168 [124, 190]	165 [129, 235]	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Change in PROMs across CWS of 0 and CWS ≥1.				
Mini-AQLQ	0.77 [0.1, 1.5]	1.0 [-0.1, 1.8]	1.01 (0.75, 1.38)	1.03 (0.75, 1.41)
SGRQ	-14.0 [-21.0, -5.3]	-11.2 [-20.9, 2.9]	1.01 (0.99, 1.03)	1.01 (0.98, 1.03)
ACQ5	-0.6 [-1.8, -0.2]	-0.6 [-1.8,0.0]	1.04 (0.76, 1.43)	1.02 (0.74, 1.41)
HADS anxiety	-1.0 [-2.5, 1.0]	-1.0 [-3.0, 0.5]	0.97 (0.85, 1.10)	0.96 (0.84, 1.09)
HADS depression	-1.0 [-3.0,1.0]	-1.0 [-3.0,1.0]	1.03 (0.91, 1.15)	1.02 (0.90, 1.14)
ED5L5D Index value	0.0 [-0.05, 0.2]	0.0 [-0.07, 0.1]	0.44 (0.08, 2.32)	0.51 (0.09, 2.77)
ED5L5D Health Scale	7.5 [-5.0, 20.0]	10 [0, 20]	1.01 (0.98, 1.03)	1.01 (0.99, 1.04)

Figure 1. Clinical outcome of cohort and oral glucocorticoid exposure (n=101) from baseline (V1) and after 12 months mepolizumab (V2).

Figure 2. Distribution of aggregate improvement score across the cohort (n=101): (70% (71/101) of patients had an AIS of less than zero, 3% (3/101) an AIS of zero and 27% (27/101) an AIS of greater than zero).

Figure 3. AIS and reduction in annual prednisolone. Quadrant A: less than 50% reduction in prednisolone and AIS >-10. Quadrant B: Greater than 50% reduction in prednisolone and AIS >-10. Quadrant C: less than 50% reduction in prednisolone and AIS ≤-10. Quadrant D: Greater than 50% reduction in prednisolone and AIS ≤-10

Figure 4. Distribution of Cumulative worsening scores across the cohort (n=101). The median CWS was 18 [0, 30], range 0-167.

Glucocorticoid Toxicity Reduction with Mepolizumab using the Glucocorticoid Toxicity Index

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Online Supplement

Supplementary statistical analysis:

Statistical analysis of the data was undertaken on SPSS version 25 (IBM, Chicago, IL). Categorical variables are summarized using counts and percentages. The association between baseline GC toxicity and AIS was examined using linear regression models, mean AIS for each quartile of baseline GC toxicity was compared both unadjusted and adjusted for age and sex. Pearson and Spearman's correlation coefficients were calculated for parametric and non-parametric data, respectively. The threshold for statistical significance throughout was a p value of less than 0.05.

Development of the GTI

The original version of the GTI (GTI 1.0) underwent preliminary validation by a multi-specialty group of nineteen physician experts^(E1). These experts represented ten medical subspecialties: pulmonary medicine, rheumatology, paediatric rheumatology, nephrology, neurology, ophthalmology, dermatology, infectious disease, maternal-fetal medicine and psychiatry. The investigator group, which included 10 researchers from the United States and 9 from Europe, Canada, or Australia, employed group consensus methods and multi-criteria decision analysis^(E2).

A full explanation of how the items required to give a complete quantification of GC-related toxicity were determined is outlined in reference E1. In brief, items to be included in the GTI scoring were determined on the following principles: 1) they occur commonly in GC-exposed patients ($\geq 5\%$ of such patients); 2) they are independent of other items in the GTI; 3) they are more likely to result from GC-exposure than from the underlying disease; 4) they are likely to change over a short period of time (i.e., to either improve or worsen over a period of at least three months); 5) they can be measured simply and non-invasively. A small number of the measured variables may be outside the usual clinical measurements for a given disease, but these are easy to collect and important for assessing GC toxicity as part of routine care. For example, HbA1C is not usually measured in severe asthma clinic, but is required to measure total toxicity in severe asthma patients treated with GC. This is a reasonable test to consider as standard care of a patient on chronic GC.

The GTI assigns relative weights that have been determined systematically to each toxicity item in the Composite Index. These weights were developed through multi-criteria decision analysis (MCDA)^(E2) using pair-wise “forced-choice” methods within the 1000 Minds platform, all possible combinations of Composite Index items were ranked in order of toxicity severity. A point system reflecting the relative weight of each item in terms of toxicity was thereby derived.

Scoring the GTI

The fundamental principle with regard to the scoring approach is that an improvement in GC toxicity is given the same absolute weight as a worsening of GC toxicity of the same (but opposite) magnitude. GTI 2.0 uses the same positive weights derived in the initial GTI validation study and is the version now used in multi-center clinical trials. This approach generated two scores from the Composite Index data called: 1) the Aggregate Improvement Score (AIS); and, 2) the Cumulative Worsening Score (CWS). These scores and their rationales, outlined briefly below.

Aggregate Improvement Score (AIS) - In a disease such as GC-dependent asthma in which patients often have some baseline GC toxicity when starting a new treatment, the AIS is important in establishing that the new therapy is effective at diminishing any GC toxicity over time. With the AIS, toxicities are removed if they improve or resolve completely over longitudinal follow-up. Toxicities can also be added to the AIS over time if new or worsened GC toxicities occur. With the AIS, improvement in GC toxicity has the same absolute value as does worsening to the same degree in the opposite direction.

As an example, an increase in the body mass index (BMI) more than 5 BMI units to a BMI of greater than 25 is associated with an increase in the GTI score of +36 points. Conversely, a decrease in BMI of more than 5 BMI units towards a normal BMI is associated with an improvement in the score of -36 points. Thus, improvements in GC toxicity occurring over longitudinal follow-up are indicated by negative AIS values. If a new treatment agent facilitates reduced GC toxicity over time, the AIS will decrease over time.

Cumulative Worsening Score (CWS) - On the other hand, documentation of cumulative GC toxicity that occurs over the course of the trial or introduction of a new treatment is important, even if some toxicities are transient. The CWS is designed to assess the summative GC toxicity, regardless of whether the toxicity has lasting effects or resolves with time. New toxicities that occur are added to the CWS total, but toxicities that

resolve on follow-up are not removed. The CWS serves as a lasting record of any GC toxicity that has occurred, and can only increase or remain the same over time. Further information on the individual items scored in the GTI can be found in the supplement to reference E3.

Patient-Reported Outcome Measures in Severe Prednisolone-dependent Asthma

Patient-reported outcome measures (PROMs) in this study addressed change in quality-of-life and asthma severity.

Quality of life. The EuroQoL-5L5D Health scale is a visual analogue scale with which patients report their overall health,^(E4) 100 is the best health possible and 0 reflects the worst overall health. The EuroQoL-5L5D Index value reflects impairment of activities of daily living, the closer the score is to 1, the less the impairment of daily living. The change in Index Value following an intervention allows evaluation of the health economics of the intervention through calculation of quality-adjusted life years.

The impact of asthma on quality of life was measured by mini-Asthma Quality of Life Questionnaire (mini-AQLQ) and St. George's Respiratory Questionnaire (SGRQ).^{(E5)(E6)} The mini-AQLQ consists of 15 questions scored on a scale of between 0 and 7, a lower score reflects greater impairment with MCID being met when the mini-AQLQ improves by 0.5 or more. The SGRQ assesses the impact of disease over the preceding 12 months, the higher the score the greater impact disease has on quality of life. The MCID is a score reduction of 4 units.

Asthma control. Asthma control was assessed by the five item asthma control questionnaire.^(E7) An ACQ5 score of 0.75 reflects adequate asthma control, whereas a score of 1.5 or over signals inadequate asthma control. The MCID is a reduction in ACQ5 score of 0.5 or greater.^(E8)

Anxiety and Depression. The Hospital Anxiety and Depression score (HADS) is a validated tool with outputs that quantify anxiety and depression. A score of 0-7 is defined as normal, 8-10 indicates mild anxiety and depression, 11 or more suggests requirement for psychiatric assessment.^{(E9)(E10)}

Oral GC weaning on commencing mepolizumab

After 12 weeks on mepolizumab, participants receiving maintenance oral glucocorticoids (GC) for asthma control began a process of GC weaning in a step-wise manner. Weaning was based on clinical response (symptoms and exacerbation history) until a dose of 5mg prednisolone/day, at which time hypothalamic-pituitary-adrenal (HPA) axis function was checked using 9am cortisol and short Synacthen testing given the high prevalence of HPA axis suppression in those treated with oral GCs. Further weaning was based on adequate HPA axis function, until complete GC withdrawal.

Table E1. Additional descriptive statistics for the clinical and demographic features of patients with severe eosinophilic asthma on commencing mepolizumab (V1).

	n	Minimum	Maximum	Mean	Std. Deviation	Median	Percentiles	
							25	75
Age (years)	101	18.0	76.0	54.4	11.9	55.0	47.0	63.0
BMI (kg/m ²)	101	18.4	48.1	30.5	5.8	30.1	26.4	35.0
Age at onset of asthma (years)	95	2	70	28.7	17.4	30	14	40
GC rescue courses / 12 months	101	0	14	5.0	3.3	5	2	7
Cumulative prednisolone dose (mg) / 12 months	101	1400	22460	4773.4	3043.2	4280	3085	5475
ED visits / 12 months	100	0	14	1.2	2.5	0	0	1
Hospital admissions / 12 months	100	0	10	0.6	1.4	0	0	1
FEV1 % Predicted	100	36.3	110.7	68.9	19.0	68.1	54.2	84.6
FVC % Predicted	98	48.4	120.1	85.9	16.0	84.7	74.8	96.9
FENO (ppb)	100	16	281	49.1	47.7	35	20.3	56.8
Blood Eosinophil (cells/ μ L)	101	0	1850	360.0	320	280	100	600
Highest Blood Eosinophils (cells/ μ L) in medical record	101	0	16660	1190	1680	860	600	1300
IgE (kU/L)	100	2.0	10899.0	416.5	1174.1	117.5	42.3	351.3
Bone density T score (Hip)	94	-3.00	3.30	-0.40	1.1	-0.30	-1.13	0.30
Bone density T score (Spine)	94	-3.70	2.70	-0.72	1.1	-0.80	-1.43	0.03
Mean Daily prednisolone dose/12 month period (mg)	101	3.8	61.5	13.1	8.3	11.7	8.4	15.0
ICS Daily dose (BDP μ g equivalent)	100	800	4000	1883.6	462.3	2000	2000	2000
ACQ5	101	0.0	5.8	2.6	1.3	2.6	1.8	3.5
Mini-AQLQ	100	1.0	6.7	3.6	1.4	3.6	2.5	4.8
SGRQ	99	7.2	94.7	55.8	20.9	57.5	40.0	70.4
Euro-QoL 5D5L Index	99	-0.47	1.00	0.60	0.31	0.63	0.41	0.8
Euro-QoL 5D5L Health Scale	96	15	100	62.4	19.3	65	50	75
HADS Depression	101	0	19	6.9	4.7	6	3	11
HADS Anxiety	101	0	20	8.8	5.3	8	5	14

Table E2. Additional descriptive statistics for the difference in clinical and patient reported outcomes from baseline (V1) to 12 months mepolizumab treatment (V2).

	N	Minimum	Maximum	Mean	Std. Deviation	Median	Percentiles	
	Valid						25	75
Total ED attendances last 12 months in number of patients	100	-14	3	-1.05	2.52	0	-1	0
Hospital admissions last 12 months	99	-10	2	-0.42	1.42	0	0	0
FEV1 % Predicted	100	-33.3	46.0	1.16	14.37	1.6	-6.5	9.3
FVC % Predicted	96	-25.1	41.1	0.79	12.11	1.0	-6.6	7.4
FENO (ppb)	99	-137	273	0.01	46.37	3	-12	18
Blood Eosinophils cells/ μ L	101	-1790	550	-280.00	320.00	-210	-490	-40
BMI	100	-8.2	4.4	-0.66	1.99	-0.6	-1.8	0.7
BP Systolic (mmHg)	100	-53	37	-0.96	13.21	-2	-9	8
LDL (mmol/L)	100	-1.9	1.6	-0.14	0.58	-0.1	-0.4	0.2
Total Cholesterol (mmol/L)	100	-2.6	1.4	-0.31	0.70	-0.2	-0.7	0.1
HbA1c (mmol/mol)	101	-33	6	-2.68	5.38	-2	-5	1
Mini AQLQ Overall	96	-2.4	4.8	0.88	1.35	0.9	0.0	1.6
SGRQ Overall	96	-68.2	25.7	-12.81	18.21	-12.0	-21.0	-0.4
ACQ 5total	98	-5.0	4.0	-0.89	1.29	-0.6	-1.8	0.0
HADS: Anxiety	97	-10	8	-1.02	3.27	-1	-3	1
HADS: Depression	98	-11	9	-1.04	3.59	-1	-3	1
ED5L5D Index value	96	-0.57	1.14	0.05	0.25	0.00	-0.07	0.16
ED5L5D Health scale	91	-55	65	9.68	18.32	10	-3	20

Table E3. Neuropsychiatric scores as assessed by the GTI at baseline (V1) and after 12 months mepolizumab treatment (V2).

	Depression	
	V1 (%)	V2 (%)
None	34 (33.7)	66 (65.3)
Mild	15 (14.9)	9 (8.9)
Moderate	11 (10.9)	7 (6.9)
Severe	41 (40.6)	19 (18.8)
	Mood disturbance/mania	
	V1 (%)	V2 (%)
None	48 (47.5)	75 (74.3)
Mild	11 (10.9)	11 (10.9)
Moderate	14 (13.9)	8 (7.9)
Severe	28 (27.7)	7 (6.9)
	Insomnia	
	V1 (%)	V2 (%)
None	45 (44.6)	68 (67.3)
Without functional impairment	22 (21.8)	11 (10.9)
With functional impairment	34 (33.7)	22 (21.8)

Table E4: GTI 2.0: Changes in neuropsychiatric toxicity from V1 to V2.

N=101	V2 Depressive symptoms (%)				
V1 Depressive symptoms	Severe	Moderate	Mild	None	Total (%)
Severe	18 (43.9)	4 (9.8)	5 (12.2)	14 (34.1)	41 (40.6)
Moderate	1 (9.1)	1 (9.1)	0 (0)	9 (81.8)	11 (10.9)
Mild	0 (0)	0 (0)	2 (13.3)	13 (86.7)	15 (14.9)
None	0 (0)	2 (5.9)	2 (5.9)	30 (88.2)	34 (33.7)
Total (%)	19 (18.8)	7 (6.9)	9 (8.9)	66 (65.3)	101
	V2 Manic mood disturbance (%)				
V1 Manic mood disturbance	Severe	Moderate	Mild	None	Total (%)
Severe	5 (17.9)	6 (21.4)	2 (7.1)	15 (53.6)	28 (27.7)
Moderate	2 (14.3)	1 (7.1)	2 (14.3)	9 (64.3)	14 (13.9)
Mild	0 (0)	0 (0)	2 (18.2)	9 (81.8)	11 (10.9)
None	0 (0)	1 (2.1)	5 (10.4)	42 (87.8)	48 (47.5)
Total (%)	7 (6.9)	8 (7.9)	11 (10.9)	75 (74.3)	101
	V2 Insomnia (%)				
V1 Insomnia	With functional impairment	Without functional impairment	None	Total (%)	
Insomnia with functional impairment	17 (50)	1 (2.9)	16 (47.1)	34 (33.7)	
Insomnia without functional impairment	2 (9.1)	6 (27.3)	14 (63.6)	22 (21.9)	
None	3 (6.7)	4 (8.0)	38 (84.4)	45 (44.6)	
Total (%)	22 (21.8)	11 (10.9)	68 (67.3)	101	

Table E5: Change in patient reported outcomes across the whole cohort from v1 to V2.

ACQ5 change:	
MCID met, improvement (≥ 0.5)	58 (59.2%)
Improvement but less than MCID (0 to 0.4)	23 (23.5%)
Worsening (≤ 0.1)	17 (17.3%)
Mini-AQLQ change:	
MCID met, improvement (≥ -0.5)	58 (60.4%)
Improvement but less than MCID (0 to -0.49)	14 (14.6%)
Worsening (≤ 0.1)	24 (25.0%)
SGRQ change:	
MCID met, improvement (≥ 4)	68 (70.8%)
Improvement but less than MCID (0 to 3.9)	5 (5.2%)
Worsening (≤ -0.1)	23 (24.0%)
MCID: Mini-AQLQ and ACQ5: MCID 0.5 , SGRQ MCID: 4 units,	

Table E6: Change in Hospital Anxiety and Depression scores across the whole cohort from v1 to V2.

HADs Anxiety score (n=97)	Number of patients in HADs category at V1	Number of patients at V2
0-7	40 (41.2%)	49 (50.5%)
8-10	20 (20.6%)	21 (21.6%)
>11	37 (38.1%)	27 (27.8%)
HADs Depression score (n=98)	Number of patients at V1	Number of patients at V2
0-7	55 (56.1%)	62 (63.9%)
8-10	15 (15.3%)	19 (19.6%)
>11	28 (28.6%)	17 (17.5%)
HADS: 0-7=normal, 8-10 mildly disturbed, >11 psychiatric impairment		

Figure E1. Glycaemic control on commencing mepolizumab from baseline (V1) and after 12 months mepolizumab (V2).

Figure E2: Correlation between toxicity reduction measured by AIS and change in (a) mini AQLQ from V1 to V2 (Spearman's correlation=-0.039 p=0.71), (b) SGRQ from V1 to V2 (Spearman's correlation=-0.18 p=0.088) and (c) ACQ 5 from V1 to V2 (Spearman's correlation=-0.009 p=0.93), (d) HADS depression score from V1 to V2 (Spearman's correlation=-0.17 p=0.10), (e) HADS anxiety score from V1 to V2 (Spearman's correlation =-0.18 p=0.086).

Figure E2 (a)

Figure E2 (b)

Figure E2 (c)

Figure E2 (d)

Figure E2 (e)

Figure E3: Correlation between toxicity reduction measured by AIS and (a) percentage decrease in prednisolone exposure from V1 to V2 (Spearman's correlation=-0.18, p=0.076), (b) and decrease in prednisolone exposure (mg) from V1 to V2 (Spearman's correlation=-0.17, p=0.093) and (c) decrease in prednisolone GC rescue courses from V1 to V2 (Spearman's correlation=-0.066, p=0.51).

Figure E3 (a)

Figure E3 (b)

Figure E3 (c)

Figure E4: Correlation between presence of new toxicities at V2 measured by CWS and (a) percentage decrease in prednisolone exposure from V1 to V2 (Spearman's correlation=0.02, $p=0.84$), (b) decrease in cumulative prednisolone exposure (mg) from V1 to V2 (Spearman's correlation=0.008, $p=0.9$) and (c) decrease in prednisolone GC rescue courses from V1 to V2 (Spearman's correlation=0.04, $p=0.69$).

Figure E4 (a)

Figure E4 (b)

Figure E4 (c)

Figure E5. Curve illustrating the percentage decrease in annual oral glucocorticoid dosing (X-axis) versus the probability of achieving the minimal clinically important difference (MCID) in the Aggregate Improvement Score of the Glucocorticoid Toxicity Index (Y-axis). The upper and lower bounds of the confidence intervals are shown by the shaded area. The curve, has wide confidence intervals, illustrating that percentage reduction of systemic glucocorticoid use is an inadequate indicator of glucocorticoid toxicity.

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