Original Article

# Longitudinal Assessment of Glucocorticoid Toxicity Reduction in Patients With Severe Asthma Treated With Biologic Therapies

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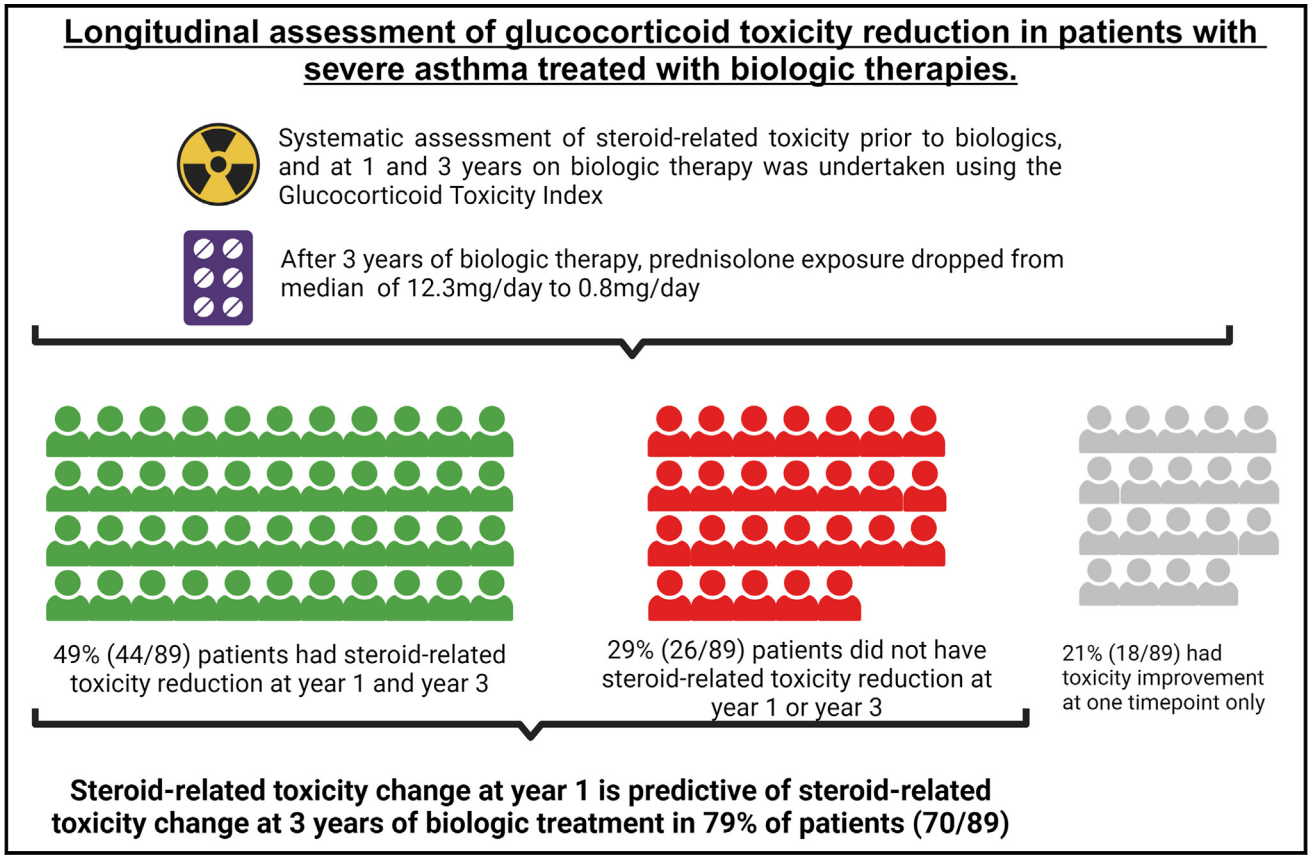
***What is already known about this topic?*** Patients with severe asthma are heavily exposed to oral corticosteroids (OCS) for disease management. OCS are known to be associated with ubiquitous adverse events or "toxicities," even at relatively low doses.

***What does this article add to our knowledge?*** This unique observation of the trajectory of accumulated steroid toxicity after biologic therapy–enabled reduction in OCS exposure shows that approximately one-third of patients do not have a reduction in their toxicity burden.

***How does this study impact current management guidelines?*** The lack or reversibility of OCS-related toxicities for a substantial proportion of individuals suggests that earlier intervention with biologic therapy, before substantial OCS exposure, is likely to result in improved patient outcomes.

**VISUAL SUMMARY**



*Abbreviations used*
*ACQ5- Asthma Control Questionnaire 5*
*AQLQ- Asthma Quality of Life Questionnaire*
*AIS- Aggregate Improvement Score*
*BEC- Blood eosinophil count*
*BMI- Body mass index*
*BP- Blood pressure*
*CWS- Cumulative Worsening Score*
*FeNO- Fractional exhaled nitric oxide*
*$FEV_1$- Forced expiratory volume in 1 second*
*FVC- Forced vital capacity*
*GC- Glucocorticoid*
*GINA- Global Initiative for Asthma*
*GTI- Glucocorticoid Toxicity Index*
*HbA1c- Hemoglobin A1c*
*HPA axis- Hypothalamic-pituitary-adrenal axis*
*ICS- Inhaled corticosteroid*
*IQR- Interquartile range*
*LDL- Low-density lipoprotein*
*MCID- Minimal clinically important difference*
*mOCS- Maintenance oral corticosteroid*
*OCS- Oral corticosteroid*
*PRO- patient-reported outcome*
*QoL- Quality of life*
*SA- Severe asthma*
*SGRQ- Saint George's Respiratory Questionnaire*
*T2- Type 2*

**BACKGROUND: Toxicities associated with oral corticosteroids (OCS) are well described. Targeted biologics for severe asthma (SA) substantially reduce OCS exposure with the potential to reduce cumulative OCS-related toxicities. The Glucocorticoid Toxicity Index (GTI) systematically assesses OCS-related toxicity; the GTI Aggregate Improvement Score (AIS) is a bidirectional measure of total toxicity change with a minimal clinically important difference (MCID) of ≤−10.**
**OBJECTIVE: This study was a longitudinal assessment of patients with SA treated with biologic therapies to assess the trajectory of OCS-related toxicity and predictors of toxicity improvement.**
**METHODS: A total of 89 patients with SA had GTI assessments at baseline and after 1 and 3 years of biologic therapy.**
**RESULTS: At 3 years, daily prednisolone use continued to decrease (6.9 mg/day [4.0, 9.4] year 1 vs 0.8 mg/day [0.0, 3.7] year 3, $P < .001$), OCS-related toxicity continued to decline (AIS at 3 years −36 [−94, 19]), and 61% (54 of 89) met the AIS MCID. There was a significant positive correlation between toxicity outcomes at years 1 and 3 (ρ 0.65, $P < .001$). Nearly half (49%) met the AIS MCID at both years 1 and 3, but 29% of the cohort did not meet the AIS MCID at either time point. Toxicity change at year 1 was predictive of toxicity change at year 3 for 79%. Toxicity reduction was not proportional to OCS reduction; there were no prebiologic characteristics that predicted toxicity reduction.**
**CONCLUSIONS: After 3 years of biologic treatment, 61% of patients with SA had clinically significant toxicity improvement. Individual toxicity outcomes at year 1 are associated with longitudinal outcomes, suggesting that for some, additional interventions are needed alongside OCS reduction to decrease morbidity.** **© 2024 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).** **(J Allergy Clin Immunol Pract 2024;■:■-■)**

***Key words:*** *Severe asthma; Biological therapies; Biologics; Oral corticosteroids; Steroids; Glucocorticoid Toxicity Index; Adverse events*

The biochemical compound "cortisone" was identified by biochemist Dr Edward Kendall and tested as an anti-inflammatory treatment for rheumatoid arthritis in 1949 by Dr Philip S. Hench. Their work led to a joint Nobel Prize in Medicine the following year.[1] The beneficial anti-inflammatory effects of cortisone were readily visible and lauded; however, within a year, their publications included a list of side effects associated with cortisone use, such as alterations of the psyche, salt retention and hypertension, hyperglycemia, weight gain with rounding of the face and deposition of retrocervical fat, transient paresthesias, muscular weakness, hypertrichosis, striae, and acneform eruptions.[2]

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Conflicts of interest: P. J. McDowell reports support to attend scientific meetings from Chiesi and speaker's honorarium from GSK. J. Busby reports a grant from AstraZeneca and personal fees from NuvoAir. J. H. Stone reports grants from Roche/Genentech, Sanofi, Bristol Myers Squib, ChemoCentryx, and Amgen; consultancy fees from Chemocentryx, Horizon, Argenx, Spruce, Amgen, Roche/Genentech, AbbVie, InflaRx, and Zenas, Kyverna, Q32 Bio, Novartis, and PPD; and payment honoraria for lectures at Bristol Myers Squibb, Chemocentryx, Argenx, Horizon, and Sanofi. The intellectual property of the GTI-MD is co-owned by the Massachusetts General Hospital (J. H. Stone's employer) and Steritas, LLC. The worldwide licensing rights to the GTI and GTI-MD are controlled by Steritas, LLC. J. H. Stone cofounded Steritas and is the unpaid chair of the Scientific Advisory Board but has no fiduciary responsibility at the company. He owns stock options in Steritas, LLC, and has consulted on glucocorticoid toxicity and FDA Advisory Committee preparations. L. G. Heaney reports grants from GSK; contracts with GSK, AstraZeneca, and Roche/Genentech for asthma clinical trials that were renumerated to his Institution; payment honoraria for lectures supported by AstraZeneca, Novartis, Roche/Genentech, Sanofi, Circassia, GlaxoSmithKline, Chiesi, and Teva; and funding to attend international respiratory meetings from AstraZeneca and GSK and attendance on advisory boards for Novartis, Roche/Genentech, GSK, Teva, and Celltrion. C. A. Butler has no relevant conflicts of interest to disclose.

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The anti-inflammatory effects of oral corticosteroids (OCS) were first applied to asthma in 1956,[3] with the efficacy of inhaled corticosteroids (ICS) demonstrated in 1972 and showing fewer side effects than with systemic administration.[4,5] Until recent years, OCS remained an essential treatment for patients with severe, uncontrolled asthma worldwide. The International Severe Asthma Registry reported that 49% of their Global Initiative for Asthma (GINA) step 5 patients were receiving daily maintenance OCS (mOCS) as part of their usual asthma treatment, and 52% of GINA step 4-5 patients had at least 2 bursts of OCS per year for asthma exacerbations.[6] A similar burden of OCS use is seen across other European severe asthma (SA) registries.[7,8]

Monoclonal antibodies targeting the type 2 (T2) inflammatory cascade known to drive eosinophilic airways inflammation in SA have been shown to reduce the burden of OCS exposure by permitting the weaning of mOCS and reduction of asthma exacerbations that require OCS treatment.[9-14]

The Glucocorticoid Toxicity Index (GTI) is a validated tool that systematically assesses and quantifies OCS-related toxicity in exposed individuals. We have previously published data showing that all individuals in a cohort of patients with SA who met UK prescribing criteria for biologics (see Online Repository at www.jaci-inpractice.org) had evidence of OCS-related toxicity.[15] Of these, 62% (62 of 101) met the minimal clinically important difference (MCID) for toxicity improvement after 1 year of biologic therapy.[16] However, improvement in some toxicity domains at 1 year was marginal, and the mean prednisolone exposure remained substantial (6 mg/day). A limitation of this study was its relatively short timeframe, which may have been insufficient to observe the reversal of some toxicities and was unable to offer insight into the trajectory of toxicity reduction.

Our aims were to measure clinical outcomes, OCS use, patient-reported outcomes (PROs), and OCS-related toxicity after 3 years of biologic therapy to assess the trajectory of toxicity change and determine if there are predictors of toxicity improvement.

## METHODS

This was a longitudinal assessment of OCS-related toxicity in a previously described cohort.[16] In summary, this was a single-center, prospective observational cohort of 101 sequential patients with SA assessed as they commenced biologics (visit 1), with repeated assessment at the end of 1 year (visit 2) and 3 years (visit 4) on biologic treatment.

All patients had SA as per the European Respiratory Society and American Thoracic Society definition[17] and met the UK's National Institute for Health and Care Excellence access criteria for biologic treatment (see Online Repository at www.jaci-inpractice.org for details). After receiving 3 months of biologic treatment, mOCS were weaned in keeping with the clinic's weaning protocol (see Online Repository at www.jaci-inpractice.org). Primary and secondary care records were used to verify patient-reported exacerbation count and acute care attendance.

At each assessment, patients had clinical review (history, medications review, and examination), spirometry, fractional exhaled nitric oxide (FeNO), and blood sampling (blood eosinophil count [BEC], hemoglobin A1c [HbA1c], and lipids). They also completed PRO measures and underwent systematic assessment of OCS-related toxicity using the GTI. PROs included both asthma-specific and quality-of-life (QoL) measures, including Asthma Control Questionnaire 5 (ACQ5), the mini—Asthma Quality of Life Questionnaire (mini-AQLQ), Saint George's Respiratory Questionnaire (SGRQ), Hospital Anxiety and Depression Score, and EuroQoL-5L5D (see Online Repository at www.jaci-inpractice.org for further information on PROs).

## GTI SCORING

The GTI (and its online application, GTI 2.0 app 2016, 2018, Massachusetts General Hospital, all rights reserved) is a validated tool developed to demonstrate whether a new treatment or intervention reduces steroid-associated toxicity to a degree that is relevant clinically and to patients. The GTI systematically measures steroid-associated toxicity burden before a treatment intervention and at designated time points after the introduction of the new treatment, evaluating change in OCS-related toxicity over time. The GTI captures the full sweep of steroid-associated toxicity, with the online application applying systematically determined relative weights to each toxicity item in the toxicity index. The weighting of each toxicity was determined through multicriteria decision analysis "forced choice" methods (MCDA, 1000minds platform, Dunedin, New Zealand) after which all toxicity items were ranked in severity and assigned a relative weighting or score.[18] Central to the scoring approach is that an improvement in each steroid-associated toxicity is given the same absolute weight as a worsening of that toxicity, but in the opposite direction. The MCID that quantifies a clinically significant change in toxicity over time was calculated using a distribution-based approach based on the standard error of measurement. The development and validation of the GTI, including the MCID, has been described.[14,18,19] The GTI has been used across multiple inflammatory diseases to measure OCS-related toxicity.[20-22] Because of the frequency of GTI assessment (0, 1, 3 years), bone densitometry was not included in the toxicity change assessment.

Two scores arise from this systematic assessment of glucocorticoid toxicities, the Aggregate Improvement Score (AIS) and the Cumulative Worsening Score (CWS). The AIS is a measure of change in total toxicity burden in an individual and can increase or decrease over time. A positive AIS score indicates increased total toxicity, and a negative AIS score signifies a reduction in total toxicity (maximum possible score +439, minimum −346). The MCID for the AIS is −10. The CWS is an additive score of all new toxicities accumulated; therefore, this score can only increase (maximum score of 439). Here we report toxicity change (AIS) and accumulated toxicities (CWS) for year 0-1 (year 1 outcomes) and years 1-3 (year 3 outcomes) of biologic therapy.

### Statistical analysis

Descriptive statistics were presented as mean (standard deviation), median (interquartile range [IQR]), or n (%) as appropriate. Demographic and clinical characteristics were compared between the 1-year and 3-year post—biologic initiation visits using paired *t* tests (normally distributed data), Wilcoxon signed-rank tests (non—normally distributed data), and McNemar's tests (categorical data). The independent *t* test (normally distributed data), Mann-Whitney *U* test (non—normally distributed data), and $\chi^2$ test (categorical data) were used to compare between independent groups. Pearson's correlation was used to describe the relationship between continuous variables. Observations with missing data were excluded from the analysis

**TABLE I.** Clinical and demographic characteristics at the time of commencing biologic therapy and after 1 and 3 years of biologic therapy

| Characteristics | n | Prebiologic (89) | One year after biologics (89) | Three years after biologics (89) | *P* value* |
|---|---|---|---|---|---|
| No. of patients | 267 | 89 | 89 | 89 | |
| Female sex | 267 | 49 (55.1%) | 49 (55.1%) | 49 (55.1%) | 1.000 |
| Age (y) | 266 | 54.9 (11.7) | 56.0 (11.7) | 58.0 (11.7) | - |
| Asthma duration (y) | 248 | 23.2 (12.0, 35.2) | 24.2 (13.3, 36.1) | 26.5 (15.1, 38.3) | |
| Age of onset (y) | 249 | 30.0 (14.0, 40.0) | 30.0 (14.0, 40.0) | 30.0 (14.0, 40.0) | |
| Blood eosinophil count ($\times 10^9$L) | 265 | 0.25 (0.08, 0.53) | 0.07 (0.04, 0.10) | 0.07 (0.02, 0.09) | .25 |
| FeNO (ppb) | 258 | 35 (22, 63) | 40 (24, 68) | 37 (23, 61) | .68 |
| $FEV_1$ (%) | 255 | 68.2 (18.3) | 69.2 (21.4) | 75.9 (21.8) | <.001 |
| FVC (%) | 249 | 85.4 (15.4) | 86.0 (17.6) | 93.4 (16.5) | <.001 |
| $FEV_1$/FVC | 251 | 62.3 (13.6) | 63.1 (14.8) | 63.3 (12.2) | .89 |
| Any prednisolone exposure/1 y | 267 | 89 (100.0%) | 84 (94.4%) | 56 (62.9%) | <.001 |
| Median daily prednisolone (mg)/1 y | 267 | 12.3 (9.0, 15.0) | 6.9 (4.0, 9.4) | 0.8 (0.0, 3.7) | <.001 |
| mOCS | 267 | 76 (85.4%) | 50 (56.2%) | 29 (32.6%) | <.001 |
| mOCS dose (mg) | 155 | 10 (10, 15) | 5 (5, 5) | 4 (3, 5) | .002 |
| mOCS with HPA axis suppression | 76 | | 28 (56.0%) | 23 (88.5%) | .22 |
| Any exacerbation/1 y | 267 | 79 (88.8%) | 55 (61.8%) | 39 (43.8%) | .011 |
| Median exacerbations/1 y | 267 | 5 (2, 7) | 1 (0, 2) | 0 (0, 1) | .005 |
| Any hospital admission/1 y | 263 | 27 (30.7%) | 9 (10.2%) | 4 (4.6%) | .11 |
| Any ED attendance/1 y | 264 | 26 (29.5%) | 9 (10.1%) | 14 (16.1%) | .38 |
| ACQ5 score | 251 | 2.6 (1.2) | 1.7 (1.3) | 1.7 (1.3) | .42 |
| mini-AQLQ score | 251 | 3.7 (1.4) | 4.5 (1.6) | 4.6 (1.8) | .51 |
| SGRQ total score | 253 | 56.0 (20.4) | 43.7 (23.6) | 40.8 (23.0) | .13 |
| EuroQoL health scale | 246 | 65 (50, 75) | 75 (60, 85) | 75 (60, 85) | .91 |
| EuroQoL utility index | 248 | 0.64 (0.42, 0.84) | 0.71 (0.52, 0.91) | 0.76 (0.62, 0.94) | .022 |
| HADS anxiety | 253 | 8 (5, 12) | 7 (3, 11) | 7 (2, 13) | .928 |
| HADS depression | 254 | 6 (3, 11) | 5 (2, 10) | 5 (1, 9) | .285 |
| Biologic therapy | 267 | | | | |
| Mepolizumab | | 89 (100.0%) | 89 (100.0%) | 66 (74.2%) | |
| Benralizumab | | 0 (0.0%) | 0 (0.0%) | 21 (23.6%) | |
| Dupilumab | | 0 (0.0%) | 0 (0.0%) | 2 (2.2%) | |
| Weight (kg) | 266 | 85.2 (18.7) | 83.2 (17.6) | 83.6 (18.8) | .85 |
| BMI (kg/m$^2$) | 266 | 30.4 (5.8) | 29.7 (5.5) | 29.8 (5.9) | 1.00 |
| Systolic BP (mm Hg) | 266 | 130.0 (15.9) | 129.4 (18.2) | 133.8 (17.7) | .019 |
| HbA1c (mmol/mol) | 267 | 43.0 (9.7) | 40.2 (6.7) | 39.1 (7.3) | .005 |
| LDL (mmol/L) | 267 | 2.8 (0.9) | 2.6 (0.9) | 2.6 (0.9) | .91 |
| Total cholesterol (mmol/L) | 266 | 5.3 (1.1) | 5.0 (1.2) | 5.0 (1.2) | .78 |
| AIS | 178 | | −34.0 (−74.0, 1.0)† | −36.0 (−94.0, 19.0)‡ | .79 |
| AIS change from previous visit | 178 | | | | .12 |
| Decrease | | | 63 (70.8%) | 55 (61.8%) | |
| Static/increase | | | 26 (29.2%) | 34 (38.2%) | |
| Met AIS MCID (%) | 178 | | 53/89 (60%) | 54/89 (61%) | .88 |
| CWS | 178 | | 18.0 (0.0, 27.0) | 48.0 (26.0, 101.0) | <.001 |
| CWS change from previous visit | 178 | | | | <.001 |
| No new toxicity | | | 35 (39.3%) | 5 (5.6%) | |
| Increased toxicity | | | 54 (60.7%) | 84 (94.4%) | |

Data are presented as mean (standard deviation), median (interquartile range), or n (%). n = number of assessments across the 3 time periods.
*ACQ5*, Asthma Control Questionnaire 5; *AIS*, Aggregate Improvement Score; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *BP*, blood pressure; *CWS*, Cumulative Worsening Score; *FeNO*, fractional exhaled nitric oxide; *$FEV_1$*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HADS*, Hospital Anxiety and Depression Score; *HbA1c*, hemoglobin A1c; *HPA*, hypothalamic-pituitary-adrenal; *LDL*, low-density lipoprotein; *MCID*, minimal clinically important difference; *mOCS*, maintenance oral corticosteroids (maintenance OCS refers to prednisolone dose); *SGRQ*, Saint George's Respiratory Questionnaire.
**P* value for comparison of outcomes between 1 and 3 years of treatment.
†Toxicity change (AIS score) from commencing biologic therapy to the end of 1 year of treatment.
‡Toxicity change (AIS score) between year 1 and year 3 on biologic therapy.

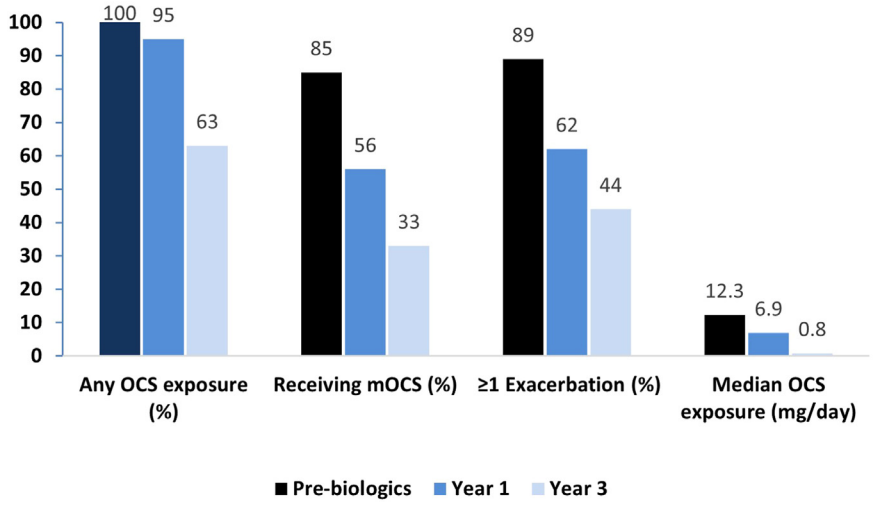


**FIGURE 1.** OCS use before commencing biologic therapy, compared with 1 and 3 years on biologic therapy. Bar graph showing OCS use prebiologics, and at 1 and 3 years after commencing biologics, including any OCS use in the last year n (%), patients receiving mOCS n (%), patients with 1 or more asthma exacerbations requiring OCS treatment in the last year n (%), and median OCS exposure for the whole cohort in the last year (mg/day). *OCS*, Oral corticosteroids; *mOCS*, maintenance oral corticosteroids.

without any attempt to impute values. All analyses were conducted using STATA version 16 (StataCorp).

## RESULTS

A total of 89 of the 101 patients had assessment after 3 years on biologics (consort diagram for patient follow-up in Online Repository at www.jaci-inpractice.org; Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). The population had a female preponderance and were middle-aged, with a median duration of asthma of 23 years (IQR: 12, 35 years) at the time they commenced biologics (Table I).

### Clinical characteristics

With regard to asthma outcomes, forced expiratory volume in 1 second ($FEV_1$) did not change in the first year of biologic treatment, but after 3 years, there was a significant improvement in $FEV_1$ ($FEV_1$: 68.9% [21.2] vs 75.9 % [21.8], $P < .001$). Forced vital capacity (FVC) also improved significantly by year 3, with no change in the $FEV_1$/FVC ratio. FeNO and BECs remained suppressed across the 3 years of treatment (Table I, Table E1, available in this article's Online Repository at www.jaci-inpractice.org, for a change in clinical characteristics with effect size).

Prednisolone use decreased substantially across the 3 years of treatment with fewer patients receiving mOCS and at a reduced mean mOCS dose; most mOCS use was for hypothalamic-pituitary-adrenal (HPA) axis suppression (23 of 29, 89%) at year 3 (see Online Repository at www.jaci-inpractice.org for further details of HPA axis suppression). There was an ongoing fall in OCS-requiring exacerbations (Table I and Figure 1), and 37% of patients did not have any OCS exposure in their third year on biologic therapy. Acute secondary care utilization fell substantially across the first year of biologic treatment, and this reduction in acute care use was maintained to year 3 (Table I, Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). PRO measures showed improvement in the first year of treatment, and although this improvement was maintained, there was no ongoing improvement from year 1 to 3 except for the EuroQoL utility index, which continued to improve with a longer duration on biologic therapy (Table I). At the end of 3 years of biologic therapy, 74% of patients remained on mepolizumab therapy, 24% on benralizumab, and 2% on dupilumab.

Between year 1 and year 3 of biologic therapy, there was no significant reduction in mean weight, body mass index (BMI), low-density lipoprotein (LDL), or total cholesterol for this cohort. There was a reduction in mean HbA1c but an increase in mean systolic BP (Table I).

### The AIS: toxicity change

There was an overall reduction in OCS-associated toxicity for this cohort at year 1 and year 3 assessments (year 1 AIS: −34 [−74, 1.0] vs year 3 AIS: −36 [−94, 19], $P = .79$); 60% of the cohort met the toxicity change MCID at year 1 and 61% at year 3, $P = .88$ (Table I). At the individual patient level, there was a significant positive correlation between toxicity outcomes at year 1 (reflecting toxicity change in year 0-1) and year 3 (reflecting toxicity change from years 1 to 3 on biologics), ρ 0.65, $P < .001$ (Figure 2). Nearly half (44 of 89, 49%) of the cohort met the AIS MCID at both year 1 and year 3, but 29% (26 of 89) of the cohort did not meet the AIS MCID at either year. Thus, toxicity change at the end of year 1 was predictive of toxicity change at year 3 for 79% (70 of 89) of the cohort.

Comparing those who had a sustained reduction in toxicity (met AIS MCID at both year 1 and year 3, n = 44) and those who did not have toxicity improvement (did not meet AIS MCID at year 1 or year 3, n = 26), there was no difference in OCS use from baseline across the 3 years of biologic treatment. Specifically, both groups had a similar total (mg) and proportional reduction (%) in mean daily OCS exposure from commencing biologics to 3 years on biologics; prednisolone data are presented in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org).

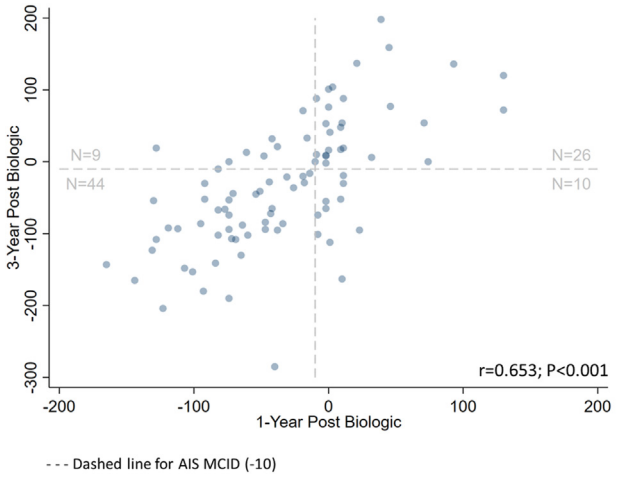


**FIGURE 2.** Correlation of toxicity change (AIS) in the first year of biologic therapy, compared with toxicity change from years 1 to 3 of biologic therapy. Scatter graph showing AIS at 1 and 3 years after biologics (*x* and *y* axis, respectively). The dashed line marks AIS at −10 (the MCID) at 1 and 3 years. The bottom-left quarter met the AIS toxicity change MCID at year 1 and year 3 (n = 44). The top-left quarter met the AIS MCID at year 1 but not at year 3 (n = 9). The bottom-right quarter met the AIS MCID at year 3 but not at year 1 (n = 10). The top-right quarter did not meet the MCID at year 1 or year 3 (n = 26). *AIS*, Aggregate Improvement Score; *MCID*, minimal clinically important difference.

There were no prebiologic patient characteristics that differentiated those who went on to meet the toxicity change MCID and those who did not (Tables E3 and E4, available in this article's Online Repository at www.jaci-inpractice.org), specifically no differences in recent OCS use, age, or sex (Figure E3, available in this article's Online Repository at www.jaci-inpractice.org). After 3 years of biologic therapy, those who met the toxicity change MCID had a lower BMI and better patient-reported QoL (EuroQoL utility score: 0.81 [0.65, 0.95] vs 0.69 [0.51, 0.81], $P = .01$). The patients who achieved the AIS MCID had also accumulated fewer new OCS-associated toxicities, as illustrated by a substantially lower CWS (29 [18, 51] vs 114 [74, 167], $P < .001$) although there was no difference in OCS exposure (Table II).

### Toxicity change via domains

When considering toxicity change by domain across the whole cohort (Figure 3), the toxicity domain in which the most individuals saw improvement was the psychiatric/mood domain with an impressive reduction in the burden of depression, elevated mood, and insomnia. Improvement in skin complaints (bruising, hirsutism, and striae) was also observed, with more modest improvement in metabolic domains. Systolic blood pressure was the only toxicity that worsened over time. Figure 4 shows the change in individual toxicities in those who met the toxicity change (AIS) MCID and those who did not meet the toxicity change MCID at year 3. Those who did not meet the toxicity change MCID had less improvement in each of the individual toxicity domains than those who met the AIS MCID. The cohort who did not meet the AIS MCID at year 3 did not see any decrease in BMI.

### CWS: toxicity accumulation

New toxicity accumulation was greater in years 1 to 3 than in the first year of treatment (CWS 48 in year 3 vs 18 in year 1, $P \leq .001$), with more patients having new GTI toxicities recorded (94% in year 3 vs 61% in year 1, $P < .001$) (Table I, Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Those who met the AIS MCID at year 3 had a substantially lower accumulation of new toxicities (CWS: 29 [18, 51] vs 114 [74, 167], $P < .001$) (Table II).

New toxicity accumulation (CWS) was not directly associated with ongoing OCS exposure, as there was no difference in CWS in those who continued to have prednisolone exposure in their third year on biologics and those who had no OCS exposure at all in their third year on biologics (CWS: 59.6 [20, 112] vs CWS: 48 (27, 93], $P = .686$) (Table E5, available in this article's Online Repository at www.jaci-inpractice.org).

## DISCUSSION

This cohort of patients with SA achieved a substantial reduction in exacerbation rate and OCS exposure, reduction in acute care attendance, and improvement in PROs sustained across 3 years of biologic therapy. Consistent with the reduction in OCS, there was a reduction in OCS-related toxicity burden with biologic therapy. However, approximately one-third of individuals did not have a clinically significant toxicity improvement at either year 1 or year 3, and these patients had a higher rate of ongoing new toxicity accumulation despite a substantial reduction in OCS exposure. Importantly, toxicity outcomes at year 1 were predictive of toxicity outcomes at year 3 for the majority of patients, suggesting that patients who are not going to achieve toxicity reduction with OCS reduction alone can be identified early, and additional strategies can be implemented to manage OCS-induced morbidity.

The benefit of biologic therapies has been widely reported in both clinical trials and real-world cohorts.[9-14,23,24] In this cohort, we see a substantial ongoing reduction in OCS exposure; in the third year of biologic therapy, fewer than half of the patients in the cohort experienced an asthma exacerbation, and the majority of mOCS use during that time was for HPA axis suppression, with a mean total daily prednisolone exposure for the cohort of less than 1 mg/day. At 3 years, there was also an improvement in lung function, which may reflect the decrease in recent asthma exacerbations that are associated with accelerated lung function decline[25] and an overall reduction in T2 airway inflammation known to drive mucus production, mucosal inflammation, and smooth muscle constriction, leading to lung function impairment and chronically to airways remodeling.[26] PRO measures show substantial improvement at year 1, which is sustained across the 3 years. The only PRO that showed ongoing improvement from year 1 to year 3 for the whole cohort was the EuroQoL utility index, which reflects improved health-associated QoL.[27] Improved QoL is important socially and financially for individual patients but is also important for health economies. This cohort experienced a median 0.9-point improvement in EuroQoL utility score; if this QoL improvement was then sustained over an 11-year period (note QoL may continue to improve), it would equate to a gain of 1 quality-adjusted life year with an economic value of approximately £20-30,000 per patient.[27] This figure does not include the direct health care costs saved from reduced exacerbations and acute care use.

**TABLE II.** Cohort characteristics at 3 years: those who met the AIS MCID and those who did not after 3 years of biologic therapy

| Characteristics | n | Did not meet AIS MCID | Met AIS MCID | *P* value |
|---|---|---|---|---|
| No. of patients | 89 | 35 | 54 | |
| Female sex | 89 | 21 (60.0%) | 28 (51.9%) | .450 |
| Age (y) | 89 | 57.7 (12.1) | 58.3 (11.5) | .821 |
| Age at asthma onset (y) | 83 | 28.0 (12.0, 40.0) | 32.0 (14.8, 36.3) | .291 |
| Asthma duration (y) | 83 | 30.5 (16.5, 39.5) | 25.4 (14.8, 36.3) | .291 |
| Blood eosinophil count ($\times 10^9$L) | 87 | 0.07 (0.02, 0.11) | 0.06 (0.02, 0.08) | .278 |
| FeNO (ppb) | 83 | 36 (21, 56) | 39 (24, 70) | .234 |
| $FEV_1$ (%) | 79 | 77.9 (20.5) | 74.6 (22.8) | .511 |
| FVC (%) | 77 | 95.5 (16.3) | 92.1 (16.6) | .387 |
| $FEV_1$/FVC | 78 | 64.3 (12.6) | 62.6 (12.1) | .562 |
| Any prednisolone exposure/1 y | 89 | 22 (62.9%) | 34 (63.0%) | .992 |
| Median daily prednisolone (mg)/1 y | 89 | 0.8 (0.0, 3.7) | 0.8 (0.0, 3.7) | .938 |
| mOCS (mg) | 89 | 10 (28.6%) | 19 (35.2%) | .516 |
| mOCS dose (mg/day) | 29 | 5 (3, 5) | 4 (3, 5) | .451 |
| mOCS with HPA axis suppression | 26 | 9 (100.0%) | 14 (82.4%) | .180 |
| Any exacerbation/1 y | 89 | 18 (51.4%) | 21 (38.9%) | .244 |
| Median exacerbations/1 y | 89 | 1 (0, 2) | 0 (0, 1) | .172 |
| ACQ5 score | 74 | 1.8 (1.3) | 1.7 (1.3) | .841 |
| mini-AQLQ score | 77 | 4.5 (1.6) | 4.7 (1.9) | .521 |
| SGRQ—total score | 80 | 42.7 (20.1) | 39.7 (24.8) | .567 |
| EuroQoL health scale | 77 | 70 (60, 83) | 78 (63, 88) | .180 |
| EuroQoL utility index | 74 | 0.69 (0.51, 0.81) | 0.81 (0.65, 0.95) | .010 |
| HADS anxiety | 79 | 7 (3, 10) | 6 (2, 13) | .394 |
| HADS depression | 79 | 5 (3, 9) | 5 (1, 9) | .257 |
| Weight (kg) | 89 | 90.0 (19.9) | 79.4 (17.0) | .009 |
| BMI ($kg/m^2$) | 89 | 32.2 (6.1) | 28.2 (5.3) | .001 |
| Systolic BP (mm Hg) | 89 | 137.2 (20.5) | 131.5 (15.5) | .138 |
| HbA1c (mmol/mol) | 89 | 39.7 (7.4) | 38.6 (7.2) | .476 |
| LDL (mmol/L) | 89 | 2.8 (1.0) | 2.5 (0.9) | .062 |
| Total cholesterol (mmol/L) | 89 | 5.3 (1.3) | 4.8 (1.1) | .076 |
| CWS | 89 | 114 (74.0, 167.0) | 29 (18.0, 51.0) | <.001 |
| CWS change from previous visit | 89 | | | .064 |
| No new toxicity | | 0 (0.0%) | 5 (9.3%) | |
| Increased toxicity | | 35 (100.0%) | 49 (90.7%) | |

Data are presented as mean (standard deviation), median (interquartile range), or n (%). n = number of paired assessments.
*ACQ5*, Asthma Control Questionnaire 5; *AIS*, Aggregate Improvement Score; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *BP*, blood pressure; *CWS*, Cumulative Worsening Score; *FeNO*, fractional exhaled nitric oxide; *$FEV_1$*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HADS*, Hospital Anxiety and Depression Score; *HbA1c*, hemoglobin A1c; *HPA*, hypothalamic-pituitary-adrenal; *LDL*, low-density lipoprotein; *MCID*, minimal clinically important difference; *mOCS*, maintenance oral corticosteroids (maintenance OCS refers to prednisolone dose); *SGRQ*, Saint George's Respiratory Questionnaire.

Aside from HbA1c measurements, which improved significantly at year 1 and continued to improve at year 3, there was little movement in the mean values of the metabolic-cardiovascular domains for this cohort. Mean BMI, LDL, and total cholesterol remained relatively static, whereas mean systolic blood pressure increased. At the individual patient level, however, there was a proportion of patients who demonstrated improvement in the metabolic domains (Figure 3).

Overall, the cohort had a reduction in the burden of OCS-related toxicity with biologic therapy, but approximately 30% of patients did not meet the toxicity change MCID at either year 1 or 3 biologic therapy despite minimal ongoing OCS exposure. There were no differences in the baseline characteristics of those who met the toxicity change (AIS) MCID and those who did not; therefore, we lack reliable predictors of patients who are likely to have toxicity reduction with biologics. In a previous publication, we showed that an individual patient's recent OCS and toxicity burden before commencing biologics are not directly related.[15] This work confirms that there is no difference in recent OCS exposure in those who achieve significant toxicity reduction with biologics and those who do not. It is a limitation that we cannot report on lifetime oral steroid exposure, although the lack of difference in duration of asthma and recent OCS use between the cohort who persistently achieve toxicity reduction and those who do not implies that this is unlikely to be different. Taken together, this suggests that individual susceptibility to OCS-related toxicities is a key issue, as the burden of harm for the same OCS exposure will vary from individual to individual. Importantly, for the majority of patients, early toxicity changes on biologic therapy correlate with longitudinal toxicity outcomes.

Some toxicity accumulation may not be surprising as many of the OCS-related toxicities are age-related, but the burden of new toxicity accumulation (CWS) was substantially greater in those

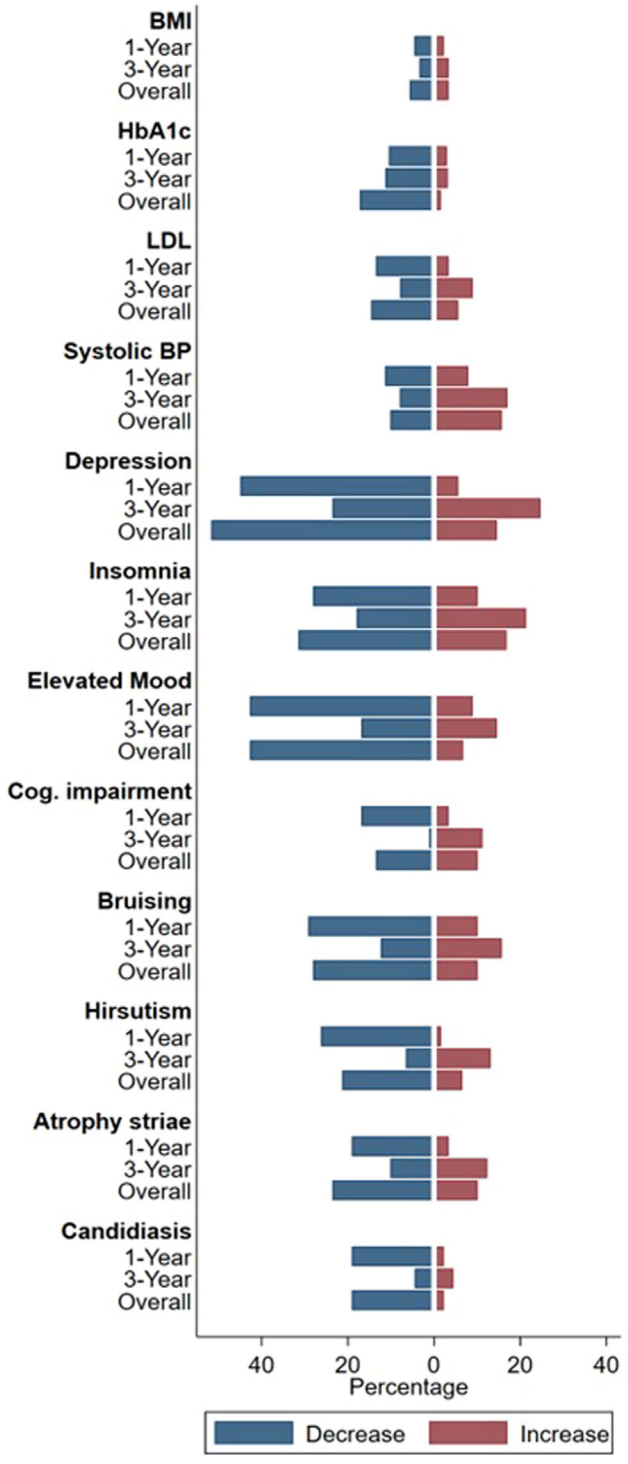


**FIGURE 3.** Proportion of patients with improvement or worsening toxicity across toxicity domains after 1 year of biologic therapy, between 1 and 3 years of biologic therapy, and overall across the 3 years. Bar chart showing each individual's overall movement in each toxicity domain across year 1 of biologic therapy, across years 1 to 3 of biologic treatment, and overall across the 3 years of biologic treatment (top, middle, and lower bar of each toxicity domain, respectively). *BMI*, Body mass index; *BP*, blood pressure; *HbA1c*, hemoglobin A1c; *LDL*, low-density lipoprotein.

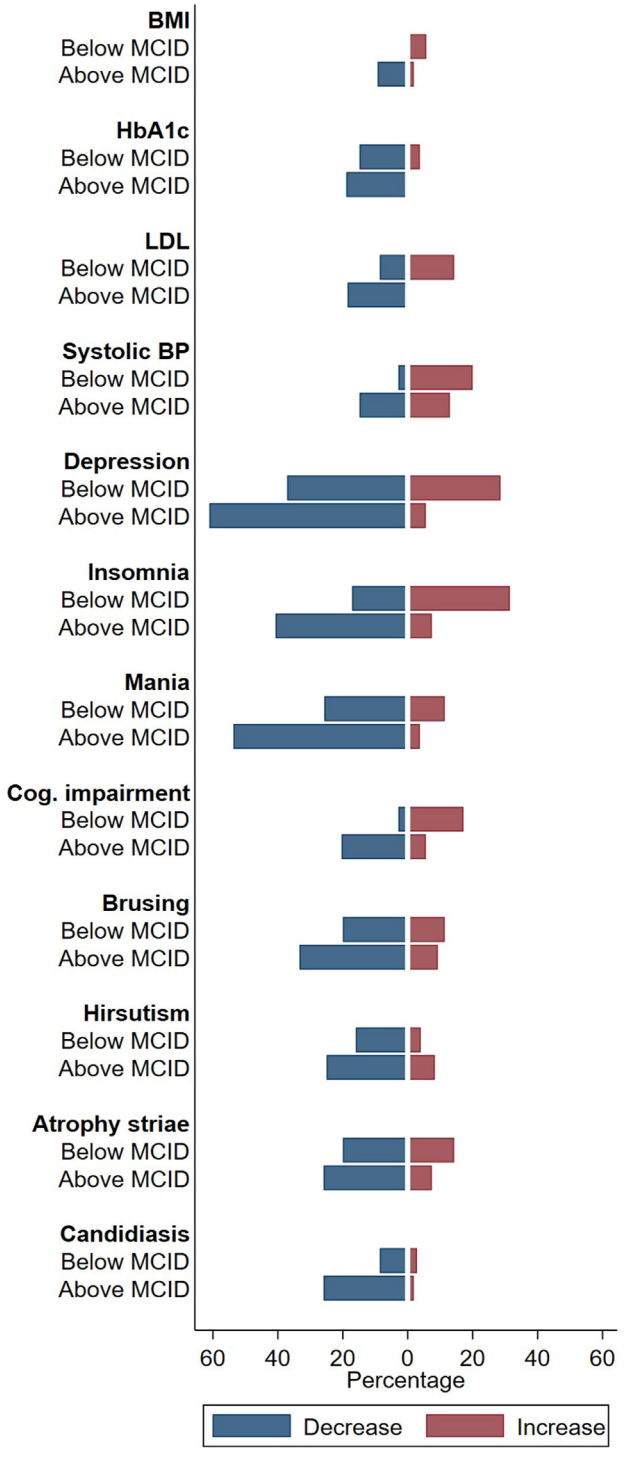


**FIGURE 4.** Comparison of toxicity change for each domain for those who meet the MCID and those who do not. Bar chart showing each overall movement in each toxicity domain across years 1 to 3 of biologic for those who meet the AIS MCID and those who do not meet the AIS MCID at year 3. *AIS*, Aggregate Improvement Score; *BMI*, Body mass index; *BP*, blood pressure; *HbA1c*, hemoglobin A1c; *LDL*, low-density lipoprotein; *MCID*, minimal clinically important difference.

who did not meet the AIS MCID, and there was no difference in age of those who met the AIS MCID and those who did not. The accumulation of new toxicities was not associated with ongoing low-dose prednisolone exposure at the individual patient level. Taken together, this suggests that with biologic therapies, some patients will have a substantial reduction in total OCS-related toxicity with a slowing of new toxicity accumulation and subsequent improved QoL, whereas other patients will continue to accumulate OCS-related toxicities even when the initiating trigger (OCS) has been removed or substantially reduced. We are unable to comment on the magnitude of reduction in accumulation of new toxicities compared with a nonbiologic-treated SA cohort, but the AIS improvement group acts as a comparator to show that not all individuals will have the same OCS-related toxicity trajectory when OCS are removed.

Many of the toxicities related to OCS use have been shown to have a negative impact on asthma control and symptom burden. In an elegant study, McDonald et al[28] showed that an increase in the number of treatable traits in asthma (including obesity, anxiety-depression, and cardiovascular comorbidity) was associated with greater health impairment as captured by the SGRQ, and the relationship between obesity, anxiety, depression, and poor asthma outcomes has been shown repeatedly.[29,30] Further, recent asthma studies assessing the impact of clinical remission definitions in SA treated with biologics have shown that the presence of some of these OCS-related comorbidities is associated with poorer outcomes with biologic therapies, that is, a decreased likelihood of clinical remission after 1 year of biologic therapy.[31,32] This implies that for some patients, these comorbidities, which are known to have a higher prevalence with OCS use, have an ongoing impact on clinical outcomes even when OCS use has stopped or substantially reduced. With this new era of biologic therapy for SA, one would hope that the magnitude and longevity of OCS exposure seen in the current generation of patients with SA will become a thing of the past, but careful consideration of the threshold for access to biologics is required as the accumulation of OCS-associated toxicities occurs at relatively low OCS exposure.[33] As this work demonstrates, patterns of OCS-related toxicity reduction established in the first year of treatment appear to set the patient's course for longer periods of follow-up. Given that there is a group of patients who do not have toxicity reversal when OCS are removed, further research is required to assess if earlier intervention with biologic therapies may prevent the onset of toxicities and comorbidity burden, which is difficult to reverse in some patients. Multidisciplinary approaches to toxicity resolution can also be considered for those who do not see toxicity resolution on reduction of OCS alone, for instance, dietetics input for obesity, clinical psychology input for mood disturbance, and endocrinology input for osteopenia/osteoporosis or adrenal suppression. This work also highlights the need for assessment of the consequences of OCS use in other inflammatory diseases where OCS continue to be central in management algorithms for both adult and pediatric populations.[33-35]

In conclusion, the use of targeted biologics for SA results in reduced OCS exposure and a reduction in total OCS-related toxicity for most patients. Approximately 30% of patients did not experience a clinically significant improvement in toxicity burden; in fact, they continued to accumulate new toxicities, and there are no baseline characteristics that predict toxicity response. Toxicity outcomes at year 1 are predictive of ongoing toxicity trajectory and suggest that for some, interventions may be needed alongside OCS reduction to decrease morbidity.

## Acknowledgments

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## PATIENT-REPORTED OUTCOME MEASURES IN THIS STUDY ADDRESSED THE CHANGE IN QUALITY OF LIFE (QOL) AND ASTHMA SEVERITY

### Asthma Control Questionnaire 5

**Asthma control.** Asthma control was assessed by the 5-item Asthma Control Questionnaire (ACQ5).[E1] An ACQ5 score of 0.75 reflects adequate asthma control, whereas a score of 1.5 or over signals inadequate asthma control. The minimal clinically important difference (MCID) is a reduction in the ACQ5 score of 0.5 or greater.[E2]

### EuroQoL

**Quality of life.** The EuroQoL-5L5D health scale is a visual analog scale with which patients report their overall health;[E3] 100 is the best health possible and 0 reflects the worst overall health. The EuroQoL-5L5D index value reflects the 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 after an intervention allows evaluation of the health economics of the intervention through the calculation of quality-adjusted life years.

### mini—Asthma Quality of Life Questionnaire

The mini—Asthma Quality of Life Questionnaire (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.[E4]

### St George's Respiratory Questionnaire

The St George's Respiratory Questionnaire (SGRQ) assesses the impact of disease over the preceding 12 months; the higher the score the greater impact disease has on QoL. The MCID is a score reduction of 4 units.[E5]

### Hospital Anxiety Depression Scale

The Hospital Anxiety and Depression Score (HADS) is a validated tool with outputs that quantify anxiety and depression. A score of 0 to 7 is defined as normal, 8 to 10 indicates mild anxiety and depression, and 11 or more suggests requirement for psychiatric assessment.[E6,E7]

### Definition of severe asthma: American Thoracic Society/European Respiratory Society[E8]

Severe asthma is defined as asthma that requires Global Initiative for Asthma (GINA) step 4-5 asthma treatment (high-dose inhaled corticosteroid [ICS] and long-acting β-agonist or leukotriene modifier/theophylline) and/or systemic corticosteroids (OCS) for 50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy.

- Uncontrolled asthma is defined as at least one of the following:
  1. Poor symptom control: ACQ consistently ≥1.5, Asthma Control Test <20 (or "not well controlled" by National Asthma Education and Prevention Program/GINA guidelines)
  2. Frequent severe exacerbations: 2 or more bursts of systemic OCS (3 days each) in the previous year
  3. Serious exacerbations: at least 1 hospitalization, intensive care unit stay, or mechanical ventilation in the previous year
  4. Airflow limitation: after appropriate bronchodilator withhold forced expiratory volume in 1 second ($FEV_1$), 80% predicted (in the face of reduced $FEV_1$/forced vital capacity [FVC] defined as less than the lower limit of normal)
- Controlled asthma that worsens on tapering of these high doses of ICS or systemic OCS (or additional biologics)

### NICE criteria for commencing biologics in the UK for uncontrolled asthma despite optimization and assessment of adherence:

**Benralizumab[E9].** Benralizumab, as an add-on therapy, is recommended as an option for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose ICS and long-acting β-agonists, only if:

- the person has agreed to and followed the optimized standard treatment plan and
- the blood eosinophil count has been recorded as 300 cells per microliter or more, and the person has had 4 or more exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous OCS of at least the equivalent of prednisolone 5 mg per day over the previous 6 months (ie, the person is eligible for mepolizumab) or
- the blood eosinophil count has been recorded as 400 cells per microliter or more with 3 or more exacerbations needing systemic corticosteroids in the past 12 months (ie, the person is eligible for reslizumab).

**Dupilumab[E10].** Dupilumab as add-on maintenance therapy is recommended as an option for treating severe asthma with type 2 inflammation that is inadequately controlled in people 12 years and older, despite maintenance therapy with high-dose ICS and another maintenance treatment, only if:

- the dosage used is 400 mg initially and then 200 mg subcutaneously every other week,
- the person has agreed to and follows an optimized standard treatment plan,
- the person has a blood eosinophil count of 150 cells per microliter or more and fractional exhaled nitric oxide of 25 parts per billion or more, and has had at least 4 or more exacerbations in the previous 12 months, and
- the person is not eligible for mepolizumab, reslizumab, or benralizumab, or has asthma that has not responded adequately to these biologic therapies.

**Mepolizumab[E11].** Mepolizumab, as an add-on therapy, is recommended as an option for treating severe refractory eosinophilic asthma, only if:

- the adults have agreed to and followed the optimized standard treatment plan and
- the blood eosinophil count has been recorded as 300 cells per microliter or more and the person has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous OCS of at least the equivalent of prednisolone 5 mg per day over the previous 6 months or
- the blood eosinophil count has been recorded as 400 cells per microliter or more and the person has had at least 3

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exacerbations needing systemic corticosteroids in the previous 12 months (so they are also eligible for either benralizumab or reslizumab).

**Reslizumab**[E12]**.** Reslizumab, as an add-on therapy, is recommended as an option for the treatment of severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose ICS plus another drug, only if:

- the blood eosinophil count has been recorded as 400 cells per microliter or more and
- the person has had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months.

### Maintenance OCS weaning

After 12 weeks on mepolizumab, participants receiving maintenance oral glucocorticoids (GC) for asthma control began a process of GC weaning in a stepwise manner. Weaning was based on clinical response (symptoms and exacerbation history) until a dose of 5 mg of prednisolone per day, at which time hypothalamic-pituitary-adrenal (HPA) axis function was checked using 9 AM cortisol and short Synacthen testing given the high prevalence of HPA axis suppression in those treated with oral GC. Further weaning was based on adequate HPA axis function, until complete GC withdrawal as described in detail in the PONENTE study.[E13]

### HPA axis suppression

In this cohort, 28 patients had HPA axis suppression at the end of 1-year biologic treatment. Of these, 9 (32%) had adrenal recovery by year 3 and 19 (68%) had ongoing HPA axis suppression at 3 years. A further 4 patients who had weaned off their mOCS by 3-year biologic treatment were found to have HPA axis suppression, giving a total of 23 of 89 patients with HPA axis suppression at 3 years.

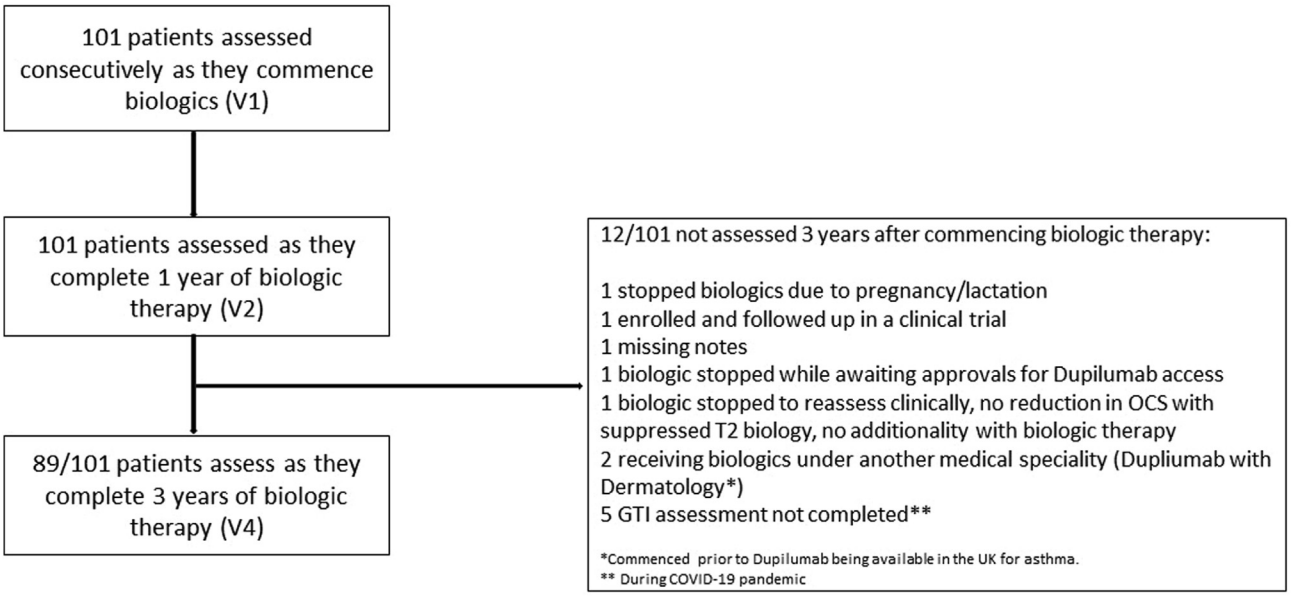


**FIGURE E1.** Consort diagram showing patient assessment over 3 years. Consort diagram showing GTI assessments on commencing biologics (n = 101), after 1 year of biologics (n = 101), and after 3 years of biologics (n = 89). *GTI*, Glucocorticoid Toxicity Index; *OCS*, oral corticosteroids.

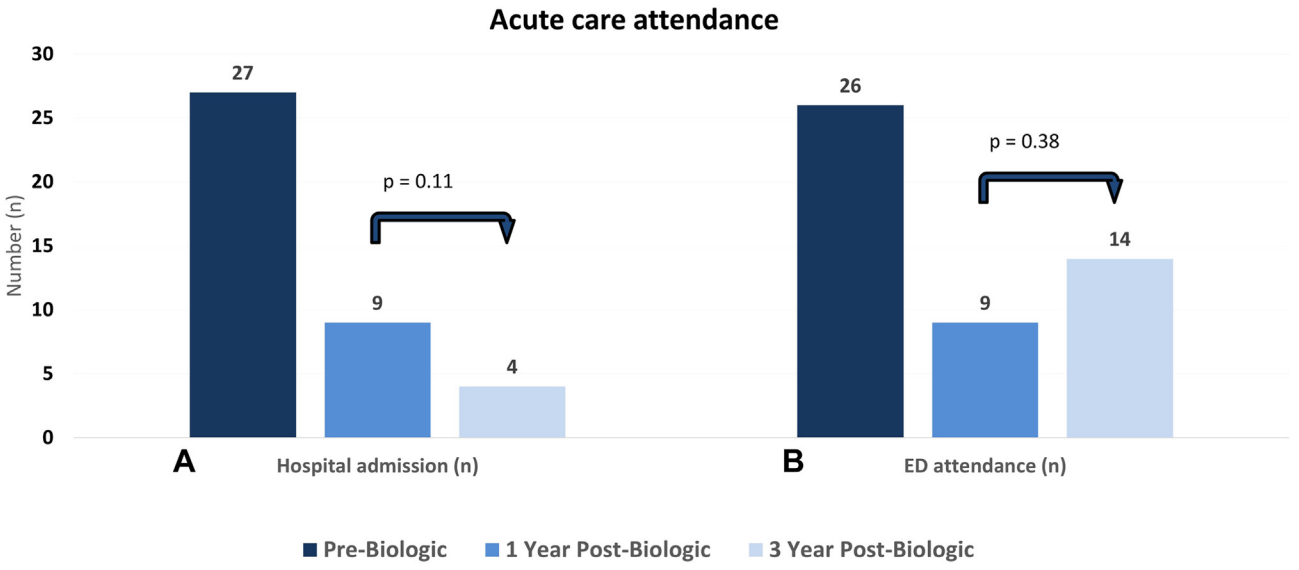


**FIGURE E2.** Acute care use before commencing biologic therapy and after 1 and 3 years on biologic therapy. Bar chart showing the number of patients with at least 1 (**A**) hospital admission and (**B**) ED attendance in the last 12 months. *ED*, Emergency department.

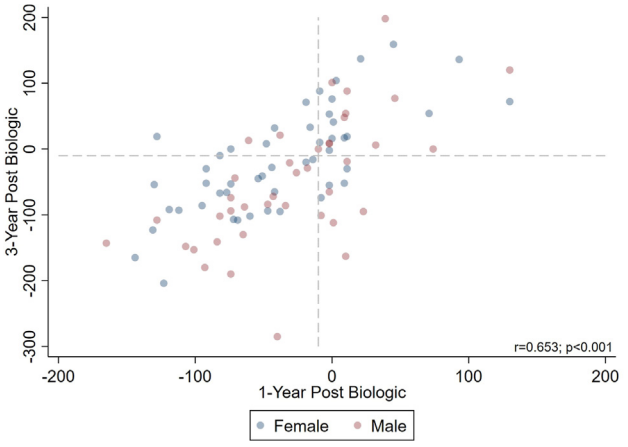


**FIGURE E3.** Correlation of toxicity change (AIS) in the first year of biologic therapy, compared with toxicity change from years 1 to 3 of biologic therapy. Distribution by sex. Scatter graph showing AIS at 1 and 3 years after biologics (*x* and *y* axis, respectively). The dashed line marks AIS at −10 (the MCID) at 1 and 3 years. The blue dots represent female participants, and the red dots male participants. *AIS*, Aggregate Improvement Score; *MCID*, minimal clinically important difference.

**TABLE E1.** Clinical and demographic characteristics after 1 and 3 years of biologic therapy

| Characteristics | n | One-year postbiologic | Three-year postbiologic | Effect size (95% CI) | *P* value |
|---|---|---|---|---|---|
| No. of patients | 178 | 89 | 89 | | |
| Time in study (y) | 178 | 1.0 (1.0, 1.1) | 3.1 (3.0, 3.2) | 2.07 (2.01, 2.11) | <.001 |
| Age (y) | 177 | 56.0 (11.7) | 58.0 (11.7) | 2.13 (2.07, 2.19) | <.001 |
| Duration of asthma (y) | 165 | 24.4 (13.3, 36.1) | 26.5 (15.1, 38.3) | 2.15 (2.12, 2.23) | <.001 |
| Blood eosinophil count ($\times 10^9$L) | 176 | 0.07 (0.04, 0.10) | 0.07 (0.02, 0.09) | −0.010 (−0.010, 0.000) | .253 |
| FeNO (ppb) | 170 | 40 (24, 68) | 37 (23, 61) | −1.5 (−6.0, −1.0) | .679 |
| $FEV_1$ (%) | 167 | 69.2 (21.4) | 75.9 (21.8) | 7.00 (3.69, 10.31) | <.001 |
| FVC (%) | 163 | 86.0 (17.6) | 93.4 (16.5) | 7.21 (4.61, 9.81) | <.001 |
| $FEV_1$/FVC | 164 | 63.1 (14.8) | 63.3 (12.2) | 0.19 (−2.34, 2.71) | .886 |
| Any prednisolone exposure/1 y | 178 | 84 (94.4%) | 56 (62.9%) | 0.07 (0.01, 0.26) | <.001 |
| Median daily prednisolone (mg)/1 y | 178 | 6.9 (4.0, 9.4) | 0.8 (0.0, 3.7) | −4.22 (−4.90, −2.73) | <.001 |
| mOCS | 178 | 50 (56.2%) | 29 (32.6%) | 0.00 (0.00, 0.19) | <.001 |
| mOCS dose | 79 | 5 (5, 5) | 4 (3, 5) | −1.0 (−2.0, 0.0) | .002 |
| mOCS with HPA axis suppression | 76 | 28 (56.0%) | 23 (88.5%) | 5.00 (0.56, 236.49) | .219 |
| Any exacerbation/1 y | 178 | 55 (61.8%) | 39 (43.8%) | 0.38 (0.17, 0.82) | .011 |
| Median exacerbations/1 y | 178 | 1 (0, 2) | 0 (0, 1) | 0.0 (0.0, 0.0) | .005 |
| Any hospital admission/1 y | 175 | 9 (10.2%) | 4 (4.6%) | 0.25 (0.03, 1.25) | .109 |
| Any ED attendance/1 y | 176 | 9 (10.1%) | 14 (16.1%) | 1.63 (0.62, 4.52) | .383 |
| ACQ5 score | 162 | 1.7 (1.3) | 1.7 (1.3) | 0.09 (−0.13, 0.32) | .424 |
| mini-AQLQ—score | 163 | 4.5 (1.6) | 4.6 (1.8) | 0.10 (−0.19, 0.38) | .512 |
| SGRQ—total score | 166 | 43.7 (23.6) | 40.8 (23.0) | −2.85 (−6.46, 0.76) | .126 |
| EuroQoL health scale | 162 | 75 (60, 85) | 75 (60, 85) | 0.0 (−5.0, 5.0) | .914 |
| EuroQoL utility | 161 | 0.71 (0.52, 0.91) | 0.76 (0.62, 0.94) | 0.043 (0.000, 0.049) | .022 |
| HADS anxiety | 164 | 7 (3, 11) | 7 (2, 13) | 0.0 (0.0, 0.0) | .928 |
| HADS depression | 165 | 5 (2, 10) | 5 (1, 9) | 0.0 (0.0, 0.0) | .285 |
| Asthma duration (y) | 165 | 24.4 (13.3, 36.1) | 26.5 (15.1, 38.3) | 2.15 (2.12, 2.23) | <.001 |
| Biologic therapy | 178 | | | | |
| Mepolizumab | | 89 (100.0%) | 66 (74.2%) | | |
| Benralizumab | | 0 (0.0%) | 21 (23.6%) | | |
| Dupilumab | | 0 (0.0%) | 2 (2.2%) | | |
| AIS | 178 | −34.0 (−74.0, 1.0) | −36.0 (−94.0, 19.0) | 8.00 (−1.00, 16.00) | .790 |
| Weight (kg) | 177 | 83.2 (17.6) | 83.6 (18.8) | −0.13 (−1.46, 1.19) | .845 |
| BMI (kg/m$^2$) | 177 | 29.7 (5.5) | 29.8 (5.9) | −0.00 (−0.50, 0.49) | .995 |
| Systolic BP (mm Hg) | 177 | 129.4 (18.2) | 133.8 (17.7) | 4.32 (0.78, 7.86) | .019 |
| HbA1c (mmol/mol) | 178 | 40.2 (6.7) | 39.1 (7.3) | −1.17 (−1.97, −0.36) | .005 |
| LDL (mmol/L) | 178 | 2.6 (0.9) | 2.6 (0.9) | 0.01 (−0.14, 0.16) | .910 |
| Total cholesterol | 178 | 5.0 (1.2) | 5.0 (1.2) | 0.03 (−0.16, 0.21) | .783 |
| AIS change from previous visit | 178 | | | 2.33 (0.84, 7.41) | .115 |
| Decrease | | 63 (70.8%) | 55 (61.8%) | | |
| Static/Increase | | 26 (29.2%) | 34 (38.2%) | | |
| CWS | 178 | 18.0 (0.0, 27.0) | 48.0 (26.0, 101.0) | 29.00 (21.00, 52.00) | <.001 |
| CWS change from previous visit | 178 | | | | <.001 |
| No new toxicity | | 35 (39.3%) | 5 (5.6%) | | |
| Increased toxicity | | 54 (60.7%) | 84 (94.4%) | | |

n = number of assessments across the 3 time periods.

*ACQ5*, Asthma Control Questionnaire 5; *AIS*, Aggregate Improvement Score; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *BP*, blood pressure; *CI*, confidence interval; *CWS*, Cumulative Worsening Score; *ED*, emergency department; *FeNO*, fractional exhaled nitric oxide; *$FEV_1$*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HADS*, Hospital Anxiety and Depression Score; *HbA1c*, hemoglobin A1c; *HPA*, hypothalamic-pituitary-adrenal; *LDL*, low-density lipoprotein; *mOCS*, maintenance oral corticosteroids; *SGRQ*, Saint George's Respiratory Questionnaire.

**TABLE E2.** Comparison of OCS use across 3 years of biologic therapy for those with a sustained reduction in toxicity (AIS $\leq -10$ at years 1 and 3) versus those without toxicity improvement (AIS $> -10$ at years 1 and 3)

| Characteristics | n | No toxicity improvement years 1 and 3 (AIS $> -10$) | Sustained toxicity improvement years 1 and 3 (AIS $\leq -10$) | *P* value |
|---|---|---|---|---|
| No. of patients* | 70 | 26 | 44 | |
| Female sex | 70 | 15 (57.7%) | 15 (57.7%) | .798 |
| Age (y) | 70 | 58.6 (10.6) | 58.1 (11.8) | .882 |
| Weight (kg) | 70 | 92.4 (19.3) | 80.6 (17.5) | .01 |
| BMI (kg/m$^2$) | 70 | 32.6 (5.8) | 28.7 (5.6) | .006 |
| Asthma duration (y) | 66 | 31.7 (17.9, 47.9) | 25.4 (14.9, 33.9) | .156 |
| Asthma duration (y) | 66 | 28.5 (8.0, 39.0) | 32.0 (16.0, 41.0) | .214 |
| Blood eosinophil count ($\times 10^9$L) | 68 | 0.07 (0.02, 0.10) | 0.07 (0.02, 0.08) | .542 |
| FeNO (ppb) | 67 | 33 (21, 46) | 39 (22, 73) | .114 |
| $FEV_1$ (%) | 63 | 75.5 (21.1) | 74.4 (23.7) | .857 |
| FVC (%) | 61 | 93.2 (16.5) | 91.7 (17.4) | .741 |
| $FEV_1$/FVC | 62 | 63.3 (12.7) | 62.7 (12.4) | .845 |
| ACQ5 score | 58 | 1.8 (1.4) | 1.8 (1.2) | .929 |
| mini-AQLQ score | 62 | 4.4 (1.7) | 4.6 (1.8) | .583 |
| SGRQ—total score | 63 | 43.5 (21.1) | 39.9 (24.3) | .551 |
| EuroQoL health scale | 63 | 70 (58, 79) | 75 (60, 85) | .181 |
| EuroQoL utility | 61 | 0.63 (0.51, 0.73) | 0.78 (0.65, 0.94) | .006 |
| HADS anxiety | 62 | 8 (4, 12) | 6 (2, 13) | .314 |
| HADS depression | 62 | 5 (2, 10) | 6 (1, 9) | .463 |
| Exacerbations | 70 | 1 (0, 2) | 0 (0, 1) | .157 |
| Year 3 mOCS | 70 | 9 (34.6%) | 14 (31.8%) | .810 |
| Year 3 mOCS dose | 23 | 5 (3, 5) | 4 (3, 5) | .539 |
| Year 3 mOCS and HPA axis suppression | 20 | 8 (100.0%) | 10 (83.3%) | .224 |
| Year 3 daily prednisolone exposure (mg) | 70 | 1.2 (0.0, 3.8) | 0.8 (0.0, 3.1) | .576 |
| Year 3 any prednisolone exposure | 70 | 16 (61.5%) | 26 (59.1%) | .840 |
| Difference from baseline daily prednisolone dose (mg) | 70 | −8.0 (−12.7, −5.6) | −10.9 (−14.9, −7.2) | .141 |
| Difference from 1-year daily prednisolone dose (mg) | 70 | −3.6 (−6.6, −1.5) | −4.5 (−7.6, −1.8) | .458 |
| % Difference from baseline daily prednisolone dose (mg) | 70 | −88.0 (−100.0, −61.7) | −94.2 (−100.0, −77.2) | .389 |
| % Difference from 1-year daily prednisolone dose (mg) | 67 | −79.8 (−100.0, −35.4) | −86.4 (−100.0, −60.0) | .564 |
| Year 3 AIS | 70 | 54.0 (16.0, 101.0) | −87.0 (−115.5, −48.5) | <.001 |
| AIS change years 1-3 | 70 | | | <.001 |
| Decrease | | 1 (3.8%) | 44 (100.0%) | |
| Static/Increase | | 25 (96.2%) | 0 (0.0%) | |
| Year 3 CWS | 70 | 129.5 (73.0, 177.0) | 28.0 (14.5, 45.5) | <.001 |
| CWS change years 1-3 | 70 | | | .074 |
| No new toxicity | | 0 (0.0%) | 5 (11.4%) | |
| Increased toxicity | | 26 (100.0%) | 39 (88.6%) | |

Data are presented as mean (standard deviation), median (interquartile range), or n (%). n = number of paired assessments.

*ACQ5*, Asthma Control Questionnaire 5; *AIS*, Aggregate Improvement Score; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *CWS*, Cumulative Worsening Score; *FeNO*, fractional exhaled nitric oxide; *$FEV_1$*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HADS*, Hospital Anxiety and Depression Score; *HPA*, hypothalamic-pituitary-adrenal; *mOCS*, maintenance oral corticosteroids; *OCS*, oral corticosteroids; *SGRQ*, Saint George's Respiratory Questionnaire.

*Patient characteristics from assessment at 3 years on biologics.

**TABLE E3.** Baseline cohort characteristics: those who met the AIS MCID, and those who did not after 1 year of biologic therapy

| AIS after 1 y of biologic therapy | n | Did not meet AIS MCID | Met AIS MCID | *P* value |
|---|---|---|---|---|
| No. of patients | 89 | 36 | 53 | |
| Female sex | 89 | 19 (52.8%) | 30 (56.6%) | .722 |
| Age (y) | 89 | 55.4 (10.4) | 54.5 (12.6) | .743 |
| Asthma duration (y) | 83 | 28.1 (13.3, 41.2) | 22.4 (11.9, 31.2) | .150 |
| Blood eosinophil count ($\times 10^9$L) | 89 | 0.29 (0.10, 0.53) | 0.18 (0.08, 0.53) | .700 |
| FeNO (ppb) | 88 | 29 (16, 55) | 36 (24, 68) | .302 |
| $FEV_1$ (%) | 88 | 66.3 (19.4) | 69.4 (17.6) | .439 |
| FVC (%) | 86 | 83.3 (14.6) | 86.9 (15.9) | .288 |
| $FEV_1$/FVC | 87 | 60.9 (15.4) | 63.3 (12.2) | .412 |
| Any prednisolone exposure/1 y | 89 | 36 (100.0%) | 53 (100.0%) | 1.00 |
| Median daily prednisolone (mg)/1 y | 89 | 12.0 (8.6, 15.0) | 12.3 (9.8, 15.0) | .713 |
| mOCS | 89 | 31 (86.1%) | 45 (84.9%) | .874 |
| mOCS dose (mg/d) | 76 | 10 (8, 13) | 10 (10, 15) | .219 |
| Exacerbations/1 y | 89 | 5 (3, 8) | 4 (2, 7) | .262 |
| Any exacerbation/1 y | 89 | 34 (94.4%) | 45 (84.9%) | .162 |
| Any hospital admission/1 y | 88 | 14 (38.9%) | 13 (25.0%) | .165 |
| Any ED attendance/1 y | 88 | 13 (36.1%) | 13 (25.0%) | .261 |
| ACQ5 score | 89 | 3.0 (1.2) | 2.3 (1.2) | .009 |
| mini-AQLQ score | 88 | 3.5 (1.2) | 3.7 (1.5) | .452 |
| SGRQ score | 87 | 56.5 (18.4) | 55.7 (21.9) | .870 |
| EuroQoL health scale | 84 | 63 (50, 70) | 70 (50, 80) | .195 |
| EuroQoL utility | 87 | 0.59 (0.39, 0.77) | 0.70 (0.43, 0.91) | .121 |
| HADS anxiety | 89 | 8 (5, 13) | 9 (5, 12) | .725 |
| HADS depression | 89 | 6 (3, 11) | 6 (3, 11) | .897 |
| Weight (kg) | 89 | 87.4 (19.4) | 83.7 (18.3) | .360 |
| BMI ($kg/m^2$) | 89 | 30.9 (5.9) | 30.0 (5.8) | .490 |
| Systolic BP (mm Hg) | 89 | 130.8 (16.6) | 129.5 (15.4) | .707 |
| HbA1c (mmol/mol) | 89 | 44.7 (8.5) | 41.8 (10.3) | .161 |
| LDL (mmol/L) | 89 | 2.6 (0.9) | 2.9 (0.9) | .198 |
| Total cholesterol (mmol/L) | 88 | 5.1 (1.2) | 5.4 (1.1) | .273 |

Data are presented as mean (standard deviation), median (interquartile range), or n (%). n = number of paired assessments.
*ACQ5*, Asthma Control Questionnaire 5; *AIS*, Aggregate Improvement Score; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *BP*, blood pressure; *ED*, emergency department; *FeNO*, fractional exhaled nitric oxide; *$FEV_1$*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HADS*, Hospital Anxiety and Depression Score; *HbA1c*, hemoglobin A1c; *LDL*, low-density lipoprotein; *MCID*, minimal clinically important difference; *mOCS*, maintenance oral corticosteroids; *SGRQ*, Saint George's Respiratory Questionnaire.

**TABLE E4.** Baseline cohort characteristics: those who met the AIS MCID, and those who did not after 3 years of biologic therapy

| AIS after 3 y of biologic therapy | n | Did not meet AIS MCID | Met AIS MCID | *P* value |
|---|---|---|---|---|
| No. of patients | 89 | 35 | 54 | |
| Female sex | 89 | 21 (60.0%) | 28 (51.9%) | .450 |
| Age (y) | 89 | 54.5 (12.1) | 55.1 (11.5) | .802 |
| Asthma duration (y) | 83 | 27.3 (13.3, 36.4) | 22.3 (11.6, 33.2) | .291 |
| Blood eosinophil count ($\times 10^9$L) | 89 | 0.34 (0.15, 0.68) | 0.17 (0.07, 0.49) | .097 |
| FeNO (ppb) | 88 | 27 (16, 62) | 37 (25, 63) | .168 |
| $FEV_1$ (%) | 88 | 67.4 (19.4) | 68.7 (17.7) | .737 |
| FVC (%) | 86 | 84.2 (16.3) | 86.2 (14.9) | .559 |
| $FEV_1$/FVC | 87 | 63.0 (12.0) | 61.8 (14.7) | .692 |
| Any prednisolone exposure | 89 | 35 (100.0%) | 54 (100.0%) | |
| Median daily prednisolone (mg)/1 y | 89 | 11.2 (7.7, 14.3) | 12.4 (10.0, 16.7) | .122 |
| mOCS | 89 | 28 (80.0%) | 48 (88.9%) | .246 |
| mOCS dose (mg/d) | 76 | 10 (8, 13) | 10 (10, 15) | .250 |
| Exacerbations/1 y | 89 | 5 (3, 7) | 5 (2, 7) | .707 |
| Any exacerbation/1 y | 89 | 32 (91.4%) | 47 (87.0%) | .522 |
| Any hospital admission/1 y | 88 | 10 (28.6%) | 17 (32.1%) | .727 |
| Any ED attendance/1 y | 88 | 12 (34.3%) | 14 (26.4%) | .428 |
| ACQ5 score | 89 | 2.7 (1.2) | 2.5 (1.3) | .642 |
| mini-AQLQ score | 88 | 3.6 (1.2) | 3.7 (1.5) | .870 |
| SGRQ total score | 87 | 53.5 (17.2) | 57.6 (22.3) | .364 |
| EuroQoL health scale | 84 | 65 (50, 70) | 65 (50, 80) | .541 |
| EuroQoL utility | 87 | 0.62 (0.44, 0.78) | 0.69 (0.41, 0.88) | .388 |
| HADS anxiety | 89 | 8 (6, 10) | 9 (3, 12) | .680 |
| HADS depression | 89 | 6 (3, 9) | 7 (2, 11) | .850 |
| Weight (kg) | 89 | 88.9 (19.7) | 82.8 (17.9) | .137 |
| BMI ($kg/m^2$) | 89 | 31.8 (6.0) | 29.4 (5.6) | .058 |
| Systolic BP (mm Hg) | 89 | 130.6 (14.9) | 129.6 (16.6) | .757 |
| HbA1c (mmol/mol) | 89 | 43.5 (10.0) | 42.6 (9.6) | .687 |
| LDL (mmol/L) | 89 | 2.7 (0.9) | 2.8 (0.9) | .699 |
| Total cholesterol (mmol/L) | 88 | 5.2 (1.2) | 5.3 (1.1) | .675 |

Data are presented as mean (standard deviation), median (interquartile range), or n (%). n = number of paired assessments.

*ACQ5*, Asthma Control Questionnaire 5; *AIS*, Aggregate Improvement Score; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *BP*, blood pressure; *ED*, emergency department; *FeNO*, fractional exhaled nitric oxide; *$FEV_1$*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HADS*, Hospital Anxiety and Depression Score; *HbA1c*, hemoglobin A1c; *LDL*, low-density lipoprotein; *MCID*, minimal clinically important difference; *mOCS*, maintenance oral corticosteroids; *SGRQ*, Saint George's Respiratory Questionnaire.

**TABLE E5.** Outcomes at year 3 of biologics for those with ongoing OCS exposure in the third year of biologic therapy, compared with no ongoing OCS exposure

| Prednisolone status at year 3 on biologics | n | No OCS exposure year 3 | OCS exposure year 3 | *P* value |
|---|---|---|---|---|
| No. of patients | 89 | 33 | 56 | |
| Female sex | 89 | 20 (60.6%) | 29 (51.8%) | .419 |
| Age (y) | 89 | 57.3 (9.9) | 58.5 (12.6) | .631 |
| Asthma duration (y) | 83 | 32.2 (15.1, 41.1) | 25.4 (15.4, 37.4) | .706 |
| Blood eosinophil count ($\times 10^9$L) | 87 | 0.07 (0.03, 0.11) | 0.06 (0.01, 0.08) | .191 |
| FeNO (ppb) | 83 | 36 (25, 60) | 38 (23, 65) | .985 |
| Any prednisolone exposure year 3 | 89 | 0 (0.0%) | 56 (100.0%) | <.001 |
| Daily prednisolone exposure (mg) year 3 | 89 | 0.0 (0.0, 0.0) | 2.2 (1.0, 5.0) | <.001 |
| Difference from baseline daily prednisolone dose (mg) | 89 | −12.3 (−15.0, −5.6) | −8.6 (−12.9, −6.3) | .181 |
| % Difference from baseline daily prednisolone dose (mg) | 89 | −100.0 (−100.0, −100.0) | −80.0 (−92.0, −59.4) | <.001 |
| Maintenance OCS | 89 | 0 (0.0%) | 29 (51.8%) | <.001 |
| Maintenance OCS dose | 29 | | 4 (3, 5) | |
| HPA axis suppression | 26 | | 23 (88.5%) | |
| Exacerbations | 89 | 0 (0, 0) | 1 (0, 2) | <.001 |
| Any exacerbation/1 y | 89 | 0 (0.0%) | 39 (69.6%) | <.001 |
| Any hospital admission/1 y | 87 | 0 (0.0%) | 4 (7.4%) | .109 |
| Any AE attendance/1 y | 87 | 2 (6.1%) | 12 (22.2%) | .047 |
| FEV1 (L) | 79 | 2.19 (0.99) | 2.24 (0.68) | .829 |
| FVC (%) | 77 | 92.9 (20.7) | 93.6 (13.7) | .857 |
| FEV1-FVC | 78 | 62.5 (12.5) | 63.7 (12.2) | .684 |
| FEV1 (%) | 79 | 75.8 (25.9) | 75.9 (19.4) | .985 |
| FVC (L) | 78 | 3.42 (1.24) | 3.49 (0.87) | .793 |
| ACQ5 score | 74 | 1.8 (1.4) | 1.7 (1.2) | .547 |
| mini-AQLQ score | 77 | 4.8 (2.0) | 4.5 (1.6) | .498 |
| SGRQ—total score | 80 | 39.2 (24.5) | 41.7 (22.4) | .650 |
| EuroQoL health scale | 77 | 75 (60, 90) | 75 (65, 84) | .723 |
| EuroQoL utility | 74 | 0.76 (0.65, 0.94) | 0.75 (0.52, 0.94) | .559 |
| HADS anxiety | 79 | 5 (2, 10) | 7 (3, 13) | .254 |
| HADS depression | 79 | 6 (1, 10) | 5 (1, 9) | .510 |
| Weight (kg) | 89 | 83.2 (19.2) | 83.8 (18.7) | .896 |
| BMI | 89 | 29.6 (5.2) | 29.9 (6.4) | .840 |
| Systolic BP (mm Hg) | 89 | 133.6 (17.7) | 133.9 (17.9) | .943 |
| HbA1c (mmol/mol) | 89 | 38.5 (5.9) | 39.4 (8.0) | .551 |
| LDL (mmol/L) | 89 | 2.8 (1.0) | 2.5 (0.9) | .209 |
| Total cholesterol | 89 | 5.2 (1.3) | 4.9 (1.1) | .298 |
| AIS year 1 | 89 | −26.0 (−54.0, −2.0) | −38.0 (−79.5, 9.5) | .815 |
| AIS year 3 | 89 | −28.0 (−84.0, 10.0) | −48.0 (−94.5, 20.0) | .766 |
| CWS year 1 | 89 | 19.0 (0.0, 26.0) | 11.0 (0.0, 38.5) | .749 |
| CWS year 3 | 89 | 48.0 (27.0, 93.0) | 59.5 (20.0, 112.0) | .686 |

Data are presented as mean (standard deviation), median (interquartile range), or n (%). n = number of paired assessments.

*ACQ5*, Asthma Control Questionnaire 5; *AE*, any ED attendance/1 year; *AIS*, Aggregate Improvement Score; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *BP*, blood pressure; *CWS*, Cumulative Worsening Score; *FeNO*, fractional exhaled nitric oxide; *ED*, emergency department; *$FEV_1$*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HADS*, Hospital Anxiety and Depression Score; *HbA1c*, hemoglobin A1c; *HPA*, hypothalamic-pituitary-adrenal; *LDL*, low-density lipoprotein; *OCS*, oral corticosteroids; *SGRQ*, Saint George's Respiratory Questionnaire.

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