

Original Article

Quantification of Glucocorticoid-Associated Morbidity in Severe Asthma Using the Glucocorticoid Toxicity Index

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What is already known about this topic? Morbidity from glucocorticoid (GC) exposure in severe asthma (SA) is described at population level, but because of the absence of a suitable tool, GC toxicity at the individual patient level has not been systematically captured and reported previously.

What does this article add to our knowledge? The Glucocorticoid Toxicity Index 2.0 identifies GC toxicity systematically in routine SA clinic, revealing unidentified toxicities and wide variation in cumulative toxicity in individual patients. Toxicity correlated poorly with prednisolone exposure compared with age and quality-of-life measures.

How does this study impact current management guidelines? This study proposes that measuring GC toxicity systematically in individual patients is an important part of routine care. Reliance on recent GC exposure as guidance for which patients would derive most benefit from biologic therapies may be imprecise.

BACKGROUND: Glucocorticoid (GC)-associated morbidity in severe asthma (SA) is well recognized but varies in individual patients; systematic measurement of GC toxicity is important to measure improvement with steroid-sparing monoclonal antibodies.

OBJECTIVE: To describe for the first time individual patient GC toxicity in steroid-dependent SA using the Glucocorticoid Toxicity Index (GTI).

METHODS: An observational consecutive patient cohort study was performed at a UK Regional SA Specialist clinic for systematic assessment of GC-associated morbidity using the GTI in routine clinical care. GTI was correlated with commonly used patient-reported outcome measures. An approach to GTI scoring, calculation of minimal clinically important difference

(MCID), and development of digital GTI application in routine clinical care are described.

RESULTS: All patients had significant oral GC exposure (cumulative prednisolone/prior year, 4280 [3083, 5475] mg) with wide distribution of toxicity in individual patients (mean GTI score, 177.5 [73.7]). GTI score had only modest correlation with recent prednisolone exposure: maintenance prednisolone dose ($\rho = 0.26$, $P = .01$), cumulative exposure/prior year ($\rho = 0.38$, $P < .001$), and GC boosts/prior year ($\rho = 0.25$, $P = .01$). GTI toxicity demonstrated stronger associations with asthma-related quality of life (mini-Asthma Quality of Life Questionnaire [mini-AQLQ] $r = -0.50$, $P < .001$ and St. George's Respiratory Questionnaire $r = 0.42$, $P < .001$). GTI MCID was calculated as 10 points. Multiple linear regression

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Abbreviations used

ACQ- Asthma Control Questionnaire
AIS- Aggregate Improvement Score
CI- Confidence interval
CWS- Cumulative Worsening Score
EQ5L5D- EuroQoL-5L5D
FEV ₁ - Forced expiratory volume in 1 second
GC- Glucocorticoid
GTI- Glucocorticoid Toxicity Index
HADS- Hospital Anxiety and Depression Score
ICC- Intraclass correlation coefficient
MCID- Minimal clinically important difference
Mini-AQLQ- Mini-Asthma Quality of Life Questionnaire
PROM- Patient-reported outcome measure
QoL- Quality of life
SD- Standard deviation
SEM- Standard error of measurement
SGRQ- St. George's Respiratory Questionnaire

demonstrated that age and mini-AQLQ were strongest predictors of GC toxicity.

CONCLUSIONS: The GTI is a useful tool to systematically capture and quantify GC toxicity at the individual patient level. GC toxicity varies widely between individual patients with SA and correlated only modestly with GC exposure over the preceding year. Age and mini-AQLQ are better predictors of GC toxicity. The GTI and MCID will facilitate assessment of individual SA response to steroid-sparing agents in clinical trials and routine care. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Severe asthma; Corticosteroid toxicity; Morbidity; Glucocorticoids

Systemic glucocorticoid (GC) therapy remains a necessity for a significant subset of patients with severe asthma. In 2012, approximately 60% of patients attending specialist severe asthma services in the United Kingdom received maintenance systemic GC to achieve disease control.¹ The morbidity associated with systemic GC exposure in asthma is well described in large population-based studies,²⁻⁴ and this toxicity adds not only to patients' burden of disease but also to the substantial economic burden associated with severe asthma.^{2,5,6}

Systemic GC exposure occurs due to standard treatment of acute asthma exacerbations ("boosts"), but additionally some patients require "low-dose" maintenance GCs for asthma control.² At population level, GC-related morbidity generally occurs in a dose-dependent manner,^{2,7,8} but disparities in the extent of GC-related morbidity according to age and gender have been highlighted.⁹ As an example, patients under the age of 60 with severe asthma have the greatest risk of GC-related toxicity when compared with age-matched controls who have received little or no GC exposure.⁹ It is also likely that the extent of GC-related morbidity varies according to the susceptibilities of individual patients, heightening the importance of tracking GC toxicity on a patient-level basis.

Despite the well-documented extent of GC-induced morbidity in severe asthma, and other immune-mediated diseases, measurement of the ability of new therapies to reduce GC toxicity has suffered from the lack of a validated tool that

measures a critical set of treatment-related adverse events both systematically and reliably.^{10,11} The arrival of effective GC-sparing therapies for severe asthma illustrates the importance of having such a tool to test whether or not these new biologic therapies actually reduce established GC-induced morbidity. The Glucocorticoid Toxicity Index (GTI) was developed by a group of international investigators from a broad array of medical subspecialties to measure GC toxicity.¹² The GTI is currently being used in a number of multicenter clinical trials (see this article's Online Repository at www.jaci-inpractice.org) and was used recently to demonstrate a reduction in GC toxicity in a multicenter, randomized, double-blind, placebo-controlled trial of a complement inhibitor in anti-neutrophil cytoplasmic antibodies-associated vasculitis.¹³

Assessment of GC toxicity is also an important part of routine clinical care. In this article, we describe the use of the GTI in routine care to capture GC-related morbidity in a cohort of patients with prednisolone-dependent asthma before biologic therapy. We explore the distribution of GC toxicity at the individual patient level and compare this toxicity score with both disease-specific and generic morbidity measures. We also calculate minimal clinically important difference (MCID) for change in toxicity (GTI Aggregate Improvement Score [AIS] and Cumulative Worsening Score [CWS] scores) describing how this tool can be used in routine care to evaluate the reduction in GC toxicity with novel treatment interventions.

METHODS

Severe asthma cohort

All patients were attending a Regional Severe Asthma Specialist clinic in the United Kingdom and had a diagnosis of severe asthma as defined by the Global Initiative for Asthma guidelines.¹⁴ All had undergone a systematic, multidisciplinary evaluation of their asthma.^{14,15} The GTI is included in routine care to systematically assess GC toxicity at the individual patient level in a biologic-naïve, GC-exposed population and facilitate management of GC-induced morbidity. All patients underwent a single measurement of GC toxicity using the GTI.

Glucocorticoid Toxicity Index

The details of the GTI development and components have been described elsewhere (paper by Miloslavsky et al¹² and this article's Online Repository at www.jaci-inpractice.org). In brief, the purpose of the GTI is to provide a validated tool permitting investigators to demonstrate not only that a new treatment approach enables the use of lower quantities of GCs compared with conventional therapies, but also that the new treatment approach is successful in reducing GC toxicity to a degree that is relevant to patients. The GTI is designed to measure change in GC toxicity between 2 points in time and includes 2 components, a Composite Index and a Specific List (Tables E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org), which together capture the full sweep of GC toxicity relevant to patients (details available in this article's Online Repository at www.jaci-inpractice.org). The GTI assigns systematically determined relative weights to each toxicity item in the Composite Index. These weights were developed through multicriteria decision analysis¹⁶ (see this article's Online Repository at www.jaci-inpractice.org for details). Given that change in GC toxicity over time or after an intervention is likely to be affected by baseline GC toxicity, the weighted scores from the Composite Index were used to establish a baseline GTI score (Table E3, available in

TABLE I. Demographics and asthma treatment

Number of patients = 101	
Age (y), mean (SD)	54.4 (11.9)
Female, n (%)	58 (57.4%)
Smoking status, n (%)	
Never smoker	60 (61.9%)
Ex-smoker	35 (36.1%)
Current smoker	2 (2.1%)
BMI (kg/m ²), mean (SD)	30.5 (5.8)
Age at onset of asthma, median [IQR]	30 [14, 40]
Atopic disease, n (%)	47 (48.5%)
Chronic rhinosinusitis, n (%)	31 (30.7%)
GORD, n (%)	27 (26.7%)
Seasonal allergic rhinitis, n (%)	27 (26.7%)
Nasal polyps, n (%)	21 (20.8%)
Eczema, n (%)	19 (18.8%)
Obstructive sleep apnoea, n (%)	8 (7.9%)
Hypothyroid, n (%)	6 (5.9%)
Anaphylaxis or urticaria, n (%)	5 (5.0%)
Aspirin sensitivity, n (%)	4 (4.0%)
Rescue courses of GCs/12 mo, median [IQR]	5 [2, 7]
Cumulative prednisolone dose (mg)/12 mo, median [IQR]	4280 [3082.5, 5475]
ED visits/12 mo	120/39 patients
Hospital admissions/12 mo	60/29 patients
Ever been ventilated, n (%)	14 (13.9%)
FEV ₁ (L), mean (SD)	2.0 (0.7)
FEV ₁ % predicted, mean (SD)*	68.9 (19.0)
FVC (L), mean (SD)	3.24 (0.9)
FVC % predicted, mean (SD)*	85.9 (16.0)
FEV ₁ /FVC %, mean (SD)	61.9 (14.6)
FeNO (ppb), median [IQR]	35 [20.3, 56.8]
Blood eosinophil (cells/μL), median [IQR]	280 [100, 600]
Highest blood eosinophils (cells/μL) in medical record, median [IQR]	860 [600, 1300]
IgE (kU/L), median [IQR]	117.5 [42.3, 351.3]
Bone density T score (hip), mean (SD)	−0.40 (1.1)
Bone density T score (spine), mean (SD)	−0.72 (1.1)
Daily prednisolone, n (%)	83 (82.2%)
Daily prednisolone dose (mg), median [IQR]	10 [10, 15]
ICS daily dose (BDP μg equivalent), median [IQR]	2000 [2000, 2000]
Long-acting β-agonist	101 (100%)
Long-acting muscarinic antagonist, n (%)	35 (36.5%)
Leukotriene receptor antagonists, n (%)	51 (51%)
Theophylline, n (%)	38 (38.4%)
Nebulized bronchodilators, n (%)	33 (34.4%)
Maintenance macrolide, n (%)	7 (7%)
ACQ5, mean (SD)	2.6 (1.3)
Mini-AQLQ, mean (SD)	3.6 (1.4)
SGRQ, mean (SD)	55.8 (20.9)
Euro-QoL 5D5L Index, median [IQR]	0.63 [0.4, 0.8]
Euro-QoL 5D5L Health Scale, median [IQR]	65 [50, 75]
HADS Depression, median [IQR]	6 [3, 11]
HADS Anxiety, median [IQR]	8 [5, 13.5]

this article's Online Repository at www.jaci-inpractice.org). This baseline GTI toxicity score facilitates examination of the distribution of toxicity scores and relationship with other asthma-specific patient-reported outcome measures (PROMs) and commonly used morbidity measures in severe asthma (see below).

A cloud-based digital interface—the GTI 2.0 app (© 2016, 2018, Massachusetts General Hospital. All rights reserved)—was developed to facilitate use and scoring of the GTI, which generates 2 scores: (1) the AIS and (2) the CWS. These subscores and their rationales, described in further detail in this article's Online Repository at www.jaci-inpractice.org, provide complementary information about the ability of a GC-sparing therapy to reduce toxicity and optimize the granularity with which GC toxicity can be captured and reported with the GTI.

Validated PROMs were used to measure quality of life (QoL) and asthma control to determine their relationship with GC toxicity. The EuroQoL-5L5D Health Scale (EQ5L5D-HS) is a visual analog scale that permits patients to report their overall health.¹⁷ A score of 100 represents the best health possible, and 0 the worst possible health state. The EuroQoL-5L5D Index value (EQ5L5D-I) reflects impairment of activities of daily living, and the closer EQ5L5D-I is to 1, the less the impairment of daily living. Asthma-specific QoL was measured by mini-Asthma Quality of Life Questionnaire (mini-AQLQ) and St. George's Respiratory Questionnaire (SGRQ).^{18,19} The mini-AQLQ consists of 15 questions scored on a scale of between 0 and 7; lower scores reflect greater impairment. The MCID for the mini-AQLQ is 0.5. The SGRQ assesses the impact of disease over the preceding 12 months, with scores ranging from 0 to 100. The higher the SGRQ score, the greater impact disease has on QoL with an MCID of 4. Asthma control was assessed by the Asthma Control Questionnaire (ACQ5)²⁰; a score of ≤0.75 reflects controlled asthma, whereas a score of ≥1.5 is uncontrolled asthma. The MCID for the ACQ5 is 0.5.²¹ 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 suggests requirement for psychiatric assessment.^{22,23}

Statistical analysis

Statistical analysis was performed on SPSS version 25 (IBM, Chicago, IL). We calculated frequencies (n, %) for binary and categorical variables, means and standard deviations (SDs) for continuous variables with normal distribution, or median and interquartile range for continuous variables with skewed distribution. Pearson's (*r*) correlation for assessing a linear relationship and Spearman's (*rho*) correlation for assessing a monotonic relationship were estimated between 2 variables when appropriate. Multiple linear regression was used to assess the association of several variables with GTI toxicity. The variables considered to be clinically relevant to GC toxicity were

ACQ, Asthma Control Questionnaire; BMI, body mass index; ED, emergency department; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GC, glucocorticoid; GORD, gastro-oesophageal reflux disease; HADS, Hospital Anxiety and Depression Scale; ICS, inhaled corticosteroids; mini-AQLQ, mini-Asthma Quality of Life Questionnaire; SGRQ, St. George's Respiratory Questionnaire.

*Using GLI 2012 predictive values.

TABLE II. Glucocorticoid toxicities in the severe asthma cohort aligned with GTI scoring (n = 101)

Toxicity domain		Points	Number (%)
Body mass index (BMI)	BMI <27	0	31 (30.7)
	BMI ≥27 but <30	21	15 (14.9)
	BMI ≥30	36	55 (54.5)
Glucose metabolism	HgbA1c <5.7	0	35 (34.7)
	HgbA1c <5.7 but on medication	32	53 (52.5)
	HgbA1c ≥5.7	32	
	HgbA1c ≥5.7 and on medication	44	13 (12.9)
Blood pressure	Diabetic retinopathy, nephropathy, or neuropathy (count only one)	44	
	Normotensive: systolic ≤120 and diastolic ≤85 no medications	0	33 (32.7)
	Systolic ≤120 and diastolic ≤85 but on medications	19	51 (50.5)
	Systolic >120 or diastolic >85 on no medications	19	
	Systolic >120 or diastolic >85 and on medications	44	17 (16.8)
Lipid metabolism	Hypertensive emergency or PRES (count only one)	44	
	LDL ≤ target	0	43 (42.6)
	LDL ≤ target but on medications	10	51 (50.5)
	LDL > target on no medications	10	
Bone/tendon	LDL > target on treatment	30	7 (6.9)
	Normal BMD or no known history of osteoporosis		94 (93.1)
	Osteoporosis	29	7 (6.9)
	Insufficiency fracture secondary to osteoporosis	29	
	Osteonecrosis	29	
Glucocorticoid myopathy	Tendon rupture while on corticosteroids	29	
	No myopathy	0	95 (94.1)
	Minor GC myopathy	11	2 (2)
	Moderate GC myopathy	63	4 (4)
Skin	Severe GC myopathy	63	
	No skin toxicity	0	21 (20.8)
	*Minor skin toxicity (1 or more than 1 minor skin item)	8	50 (49.5)
	*Moderate skin toxicity (1 or more than 1 moderate skin item)	26	30 (29.7)
	*Severe skin toxicity (1 or more than 1 moderate skin item)	26	
Neuropsychiatric	*Select only 1 (minor, moderate, or severe)		
	No neuropsychiatric toxicity	0	19 (18.8)
	*Minor (1 or more than 1 minor NP item: insomnia, mania, depression, cognitive)	11	16 (15.8)
	*Moderate (1 or more than 1 moderate NP item: insomnia, mania, depression, cognitive)	74	66 (65.3)
	*Severe (1 or more than 1 severe NP item: insomnia, mania, depression, cognitive)	74	
	Psychosis	74	
Infection	Glucocorticoid-induced violence	74	
	*Select only 1 (minor, moderate, or severe)		
	No GTI-relevant infections within the prebaseline GTI interval of the study	0	59 (58.4)
Ocular	Oral or vaginal candidiasis or noncomplicated zoster (<grade 3) within the prebaseline GTI interval of the study	19	20 (19.8)
	Grade 3 or grade 4 infection within the prebaseline GTI interval of the study	93	21 (20.8)
	No ocular pathology	0	88 (87.1)
Gastrointestinal	Increased IOP	33	13 (12.9)
	Posterior subcapsular cataract	33	
	Central serous retinopathy	33	
	No GI pathology	0	98 (97.0)
Endocrine	GI perf absence of NSAIDs	33	3 (3)
	PUD without <i>Helicobacter pylori</i>	33	
	No endocrine pathology	0	100 (99)
	Symptomatic adrenal sufficiency	33	1 (1)

BMD, bone mineral density; GC, glucocorticoid; GI, gastrointestinal; GTI, Glucocorticoid Toxicity Index; HgbA1c, glycated haemoglobin; IOP, intraocular pressure; LDL, low density lipoprotein; NP, neuropsychiatric; NSAID, nonsteroidal anti-inflammatory drug; PRES, posterior reversible encephalopathy syndrome; PUD, peptic ulcer disease.

*Minor: Acneiform rash (grades 1-2), easy bruising (grade 1), hirsutism (grade 1), atrophy/striae (grade 1), erosions/ulceration (grade 1). Moderate: Acneiform rash (grades 3), easy bruising (grade 2), hirsutism (grade 2), atrophy/striae (grade 2), erosions/tears/ulceration (grade 2). Severe: Acneiform rash (grade 4), atrophy/striae (grade 3), erosions/tear/ulceration (grade 3).

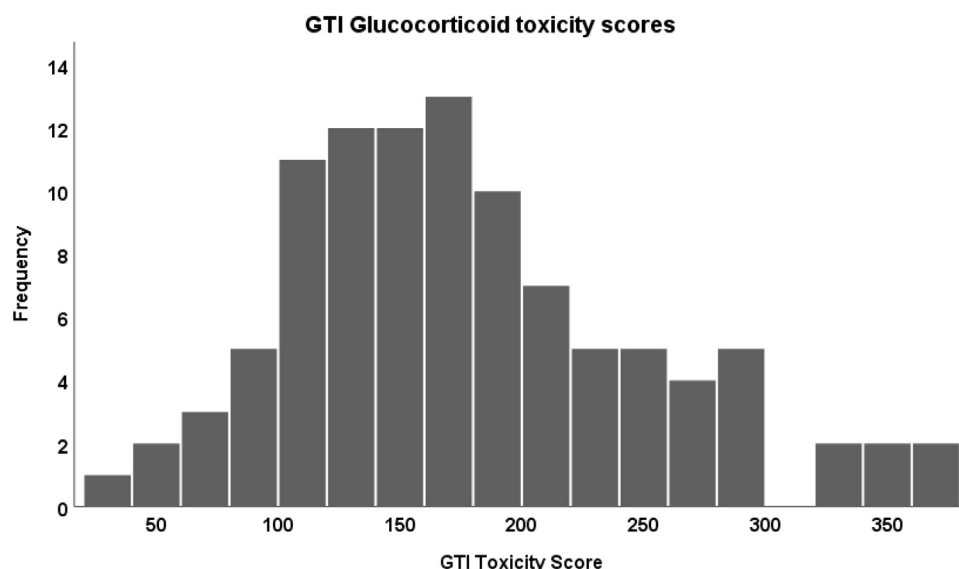


FIGURE 1. Distribution of baseline GTI toxicity scores. *GTI*, Glucocorticoid Toxicity Index.

prespecified, but those directly related to toxicity measurement and those likely to be associated with a high degree of collinearity were excluded. Adjusted regression coefficient and 95% confidence intervals (CIs) are reported. The threshold for statistical significance throughout was a *P* value of less than .05.

Clinical relevance of the GTI domains and weights was built into the Composite Index by expert investigator consensus during the development of the instrument.¹² To determine the MCID for the GTI 2.0, we used data collected during instrument development. We applied the GTI 2.0 weights and scoring approach to data from 15 paper case descriptions of real-life patients whose GC toxicity was assessed at 2 different time points during the development of the GTI instrument. To calculate the MCID, we used a distribution-based approach based on the standard error of measurement (SEM).²⁴ The SEM of effect size for the AIS can be interpreted as the smallest difference or change likely to reflect a true difference as opposed to a measurement error of the effect. The SEM was calculated according to the following formula: $SEM = SD * \sqrt{1 - ICC}$, where SD is the standard deviation of the AIS. An intraclass correlation coefficient (ICC) was estimated based on the GTI assessments of these cases by 34 different clinicians.

RESULTS

Assessment of GTI toxicity was undertaken in 101 GC-dependent, biologic-naïve patients with severe asthma between April 2017 and November 2018; demographic details are presented in Table I. The mean age was 54.4 (11.9) years with female preponderance (57.4%) and impaired lung function (forced expiratory volume in 1 second [FEV₁]% predicted, 68.1 [54.2, 84.6]%; FEV₁/forced vital capacity ratio%, 64 [53.9, 73.2]%). All patients received high-dose inhaled GC in combination with additional controller medications; 82.2% were also receiving daily maintenance prednisolone (median, 10 [10, 15] mg). The median number of GC rescue treatments (“boosts”) over the previous 12 months was 5 [2, 7], and the median cumulative prednisolone exposure for the preceding 12 months in this cohort was 4280 [3082.5, 5475] mg. Notably, despite substantial GC treatment, peripheral blood eosinophilia was still

evident (280 [100, 600] cells/μL) with persistent high symptom burden (ACQ5 score, 2.6 [1.3]) and substantial impairments of QoL (Table I).

All patients had some degree of GC-related toxicity, with a wide distribution of toxicity seen at individual level range, which was normally distributed (mean GTI score, 177.5 [73.7], Table II and Figure 1). GC toxicity showed modest correlations with maintenance prednisolone dose ($\rho = 0.26$, $P = .01$), cumulative prednisolone dosage in previous 12 months ($\rho = 0.38$, $P < .001$), and exacerbation rate in the preceding year ($\rho = 0.25$, $P = .01$).

Fifty-five (54.5%) patients had baseline body mass index values ≥ 30 . Median glycated haemoglobin A1c (HbA1c) was 41.0 [37, 46] mmol/mol with 44 patients (43.5%) having pre-diabetic HbA1c levels (HbA1c ≥ 42 mmol/mol). Two-thirds of patients were either hypertensive or receiving medications for hypertension (Table II).

Twenty-four (24%) patients had candidiasis (oral or vaginal) or herpes zoster in the preceding year; 2 zoster cases were accompanied by ophthalmic involvement or associated with postherpetic neuralgia. Nineteen grade 3 infections (19%) occurred in the preceding year, and 41 (41.6%) patients reported toxicity-related infections in the preceding year.

Neuropsychiatric morbidity was the most common morbidity in this population (81.2%), with depression (66.3%), insomnia (55.4%), and mania (52.5%) reported. Skin toxicity was also highly prevalent (79.2%) with cutaneous striae (34.7%) and 14 (13.9%) reporting widespread generalized easy bruising. Ocular complications were noted with 14 patients having posterior subcapsular cataracts, 2 with glaucoma and 2 with central serous retinopathy.

Age ($r = 0.27$, $P = .006$), cumulative prednisolone exposure over the 12 months before GTI measurement ($\rho = 0.38$, $P < .001$), and current asthma symptoms (ACQ5, $r = 0.34$, $P < .001$) correlated modestly with GTI score. GTI score demonstrated stronger associations with asthma-related QoL (mini-AQLQ $r = -0.50$, $P < .001$ and SGRQ $r = 0.42$, $P < .001$) and health state (EQ5L5D-I, $\rho = -0.49$, $P < .001$),

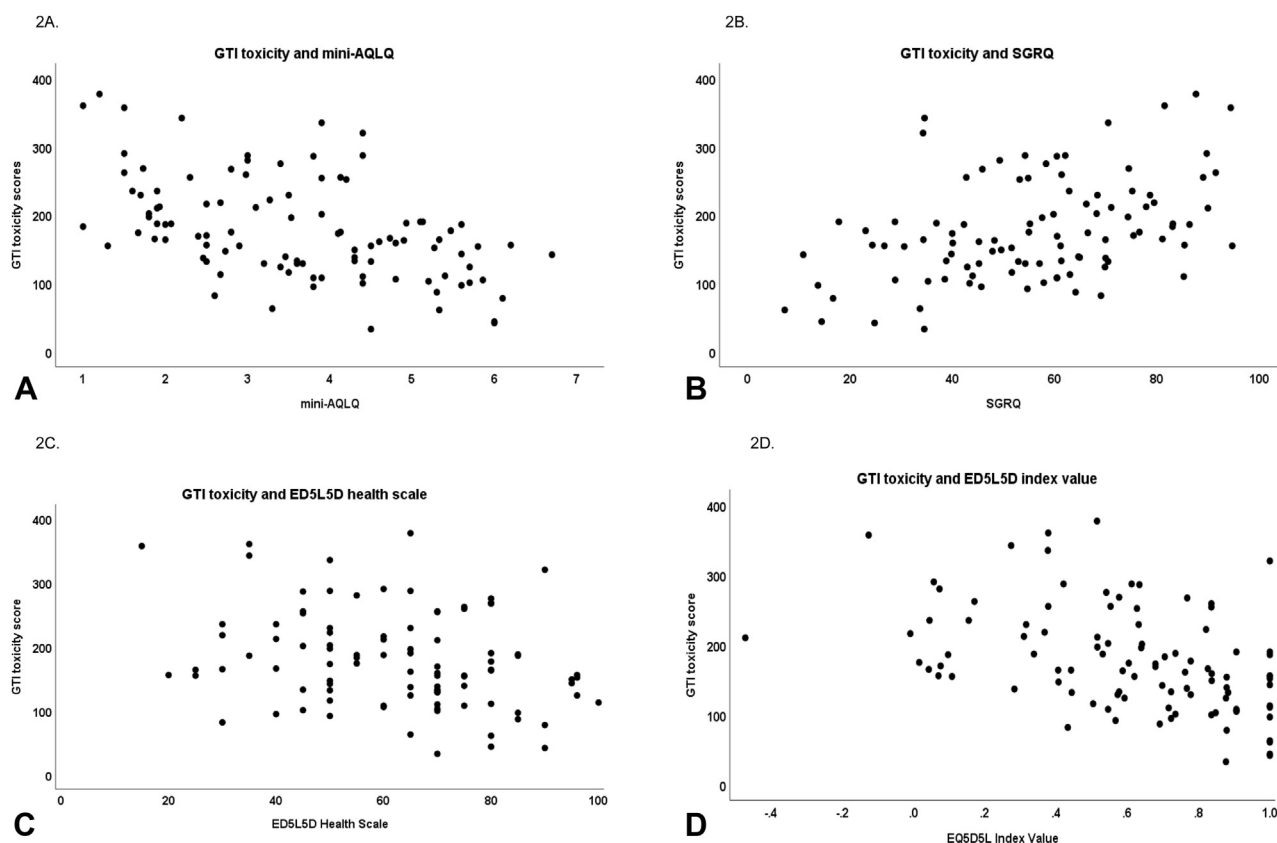


FIGURE 2. Correlations between GC Toxicity Score and Quality of Life Measures in severe asthma. **A**, Pearson's correlation GTI toxicity and mini-AQLQ $r = -0.50$, $P < .001$. **B**, Pearson's correlation GTI toxicity and SGRQ $r = 0.42$, $P < .001$. **C**, Spearman's correlation GTI toxicity and ED5L5D Health Scale, $\rho = -0.28$, $P = .006$. **D**, Spearman's correlation GTI toxicity and ED5L5D Index value, $\rho = -0.5$, $P < .001$. EQ5L5D, EuroQoL-5L5D; GC, glucocorticoid; GTI, Glucocorticoid Toxicity Index; mini-AQLQ, mini-Asthma Quality of Life Questionnaire; SGRQ, St. George's Respiratory Questionnaire.

TABLE III. Multiple linear regression for variables influencing GTI score

	Beta coefficients (95% CI)	P
Gender	-7.4 (-32, 17)	.55
Annual prednisolone exposure last 12 mo	0.002 (-0.002, 0.006)	.41
Age (y)	2.0 (0.9, 3.0)	<.001
mini-AQLQ	-26.0 (-35, -17)	<.001

CI, Confidence interval; GTI, Glucocorticoid Toxicity Index; mini-AQLQ, mini-Asthma Quality of Life Questionnaire.

though patient self-rated health demonstrated a modest association (EQ5L5D-HS, $\rho = -0.28$, $P = .006$) (Figure 2). HADS also demonstrated modest correlation with GTI score (anxiety score $r = 0.35$, $P < .001$ and depression score $\rho = 0.47$, $P < .001$).

The relationship between clinical and demographic variables and GTI toxicity was explored using multiple linear regression. Predictor variables thought to be clinically relevant to GC toxicity included age, gender, cumulative GC exposure in the year before mepolizumab, and patient-reported outcomes. Because of

collinearity among PROMs, we added only mini-AQLQ into the regression model because it had the strongest correlation with GTI toxicity score ($r = -0.50$, $P < .001$). The other variables in the model were age, gender, and cumulative GC exposure. We assessed collinearity among the predictor variables using the P-P plot of regression standardized residuals. The scatterplot and residuals statistics showed no outliers present; Cook's distance was <1 . Both mini-AQLQ and age were significant contributors to toxicity, but neither age nor cumulative prednisolone in the last 12 months was statistically significantly associated with GTI toxicity. Overall, the model explained 35.6% of the variance in GTI toxicity ($P \leq .001$). For every 0.5 point increase in the mini-AQLQ, GTI toxicity was lowered by 13.0 (95% CI: 8.5, 17.5), and for every increasing year of age, there was a 2.0 (95% CI: 0.9, 3.0) point increase in GTI toxicity (Table III).

To determine the MCID for the GTI, 34 clinicians evaluated 15 different paper cases independently in validation exercises during the original GTI development. The GTI 2.0 weights and scoring approach were applied to those data. The ICC for the AIS in these evaluations was 0.97. The SD of the AIS at the follow-up was 57.42. Thus, the MCID was $57.42 \times \sqrt{1 - 0.971} = 9.8$, or approximately 10 points.

DISCUSSION

This article describes the use of the GTI 2.0 in a cross-sectional cohort of patients with severe asthma and provides detailed background on the approach to scoring and analyzing GTI 2.0 data. The article also introduces the concept of calculating a baseline GC toxicity score, the first attempt, to our knowledge, to systematically assess and quantify the degree of GC toxicity at individual patient level in routine clinical care.

Demographic features were consistent with other severe asthma cohorts with the mean age of 54.4 years, female preponderance, and substantial asthma-related morbidity despite high-dose treatment (lung function impairment, high symptom scores, and impaired disease-specific QoL). Despite significant GC exposure, the cohort had evidence of persistent type 2-mediated inflammation, including elevated peripheral blood eosinophil counts and fractional exhaled nitric oxide.

GC toxicity was extremely high, consistent with longstanding severe asthma with the median daily prednisolone dose of 10 mg and 5 GC boosts for asthma exacerbation in the prior year. GC toxicity scores correlated variably with PROMs that address activities of daily living, asthma-related QoL, anxiety, and depression. Mini-AQLQ correlated with GTI toxicity more than EQoL5D5L, SGRQ, and HADS, suggesting that the effects of GC toxicity are reflected in the questions across the 4 questionnaire domains (symptoms, activities, emotions, and environment). In multiple regression analysis, mini-AQLQ and age explained 32.9% of the variance in GC toxicity; the MCID value for mini-AQLQ exceeded the MCID for GTI supporting the impact of GC toxicity being reflected in this asthma-specific QoL tool. It remains to be seen what level of toxicity reversal is delivered by biologic therapies in patients with severe asthma with established GC morbidity, and how changes in mini-AQLQ relate to these toxicity changes.

Because the median time between age of asthma onset and GC toxicity assessment was 23 years, age as a predictor of greater GC toxicity probably reflects both the prolonged duration of GC exposure and the background increasing prevalence of these morbidities with age.⁹ Cumulative GC exposure in the 12 months before GTI toxicity assessment was not a significant predictor of GC toxicity, suggesting that recent GC exposure is a poor predictor of toxicity at the individual patient level and that recent GC exposure may not be the best criterion on which to make decisions regarding commencing biologic therapies. Furthermore, reduction in GC exposure from the 12 months before biologic therapy is used to decide continuation of biologic therapy,²⁵⁻²⁸ but our data would suggest that this will align poorly with toxicity at baseline and likelihood of reduction with treatment. In addition, GC exposure in the prior 12 months may not reflect total GC exposure, and given the greater association with age, duration of GC exposure may be of greater importance to GC toxicity load than recent GC intake. However, in those older patients with low levels of toxicity despite significant long-term GC exposure, the level of toxicity improvement by definition is likely to be small and this should form part of the discussion with the patient.

The need to define a response to biologic therapy for severe asthma is pressing. In the United Kingdom, the National Institute for Health and Care Excellence has linked the decision to continue or discontinue biologic therapy to assessments of an adequate response, defined as a “clinically significant reduction

in GC requiring exacerbations” or a “clinically significant reduction in continuous oral GCs.” There is, however, no clear guidance about what constitutes a clinically significant reduction in these parameters.²⁵⁻²⁸ In other countries, variable stopping rules exist for biologic therapies, but again there is no consistent guidance on GC reduction, which is the primary benefit of these treatments.²⁹ In addition, there is an inherent assumption that a reduction of GC will always cause a reduction in GC toxicity and that this will be related directly to the degree of GC reduction in individual patients. We demonstrate here that when using a tool designed to capture GC toxicity systematically, there was a wide distribution of toxicity across individual patients. This toxicity was only weakly associated with baseline prednisolone dose, cumulative GC exposure in the previous 12 months, and asthma exacerbation rate in the previous year, suggesting that patients differ substantially in their susceptibility to GC toxicity. It is also clear that the spectrum of toxicities seen in individual patients is different, many of which are asymptomatic and at an early preclinical stage, supporting systematic individualized assessment. Given the distribution of baseline GC toxicity scores derived from weights of the GTI 2.0 domains, these baseline scores will need to be included as a potential explanatory variable in multivariate analyses of similar clinical cohorts as biologic therapies are introduced and GC exposure reduced over time. The GTI 2.0 was designed for use in prospective, randomized, controlled clinical trials in which GCs are part of the treatment protocol. Use of the GTI 2.0 in clinical trials is advantageous and logical because randomization and blinding serve the critical purposes of controlling for the background rate of adverse events and prior GC treatment. The procedure of randomization also eliminates the requirement for study investigators to attribute an adverse event observed to either GCs or a confounding factor—a task that is often difficult and prone to bias. In this assessment of baseline toxicity in a severe asthma cohort, we applied the same GTI principle to attribution as used in randomized clinical trials; that is, the clinician made no attempt to parse whether a particular morbidity had been caused by GCs or not, but simply recorded the morbidity if it was present. This approach will permit an assessment of improvement in these morbidities in longitudinal assessment.

The GTI 2.0 provides a mechanism for measuring GC toxicity in routine clinical care using a standardized, weighted, and validated instrument that has already been used in clinical trials.¹³ Clinical relevance of the GTI domains was built into the instrument during its design by medical experts from a wide range of specialties, who considered what changes in GC toxicity in each GTI domain would be important to both clinicians and patients. For example, a 10% change in HbA1c was deemed clinically significant to patients’ long-term health. Such a change would have important implications for patients and motivate clinicians to alter management approaches to glucose tolerance. This level of change was therefore incorporated into the definition of a significant improvement or worsening for the glucose tolerance domain. The MCID calculated in this study takes into account the precision of the GTI, therefore reflecting a true difference as opposed to a measurement error. As patients routinely take their systemic GC therapy in the morning, no comment can be made on the possible effects of administration later in the day or slow release-formulation GC.

In conclusion, we have described the clinical features of a biologic-naïve, severe asthma cohort and described substantial individual variation in patient toxicity levels that only weakly correlates with the usual clinical measures of GC exposure. We have also provided a detailed explanation on the background of GTI 2.0, a weighted measure of GC toxicity, and described the approach to scoring and analyzing data from this instrument in routine clinical care. The description of an MCID will facilitate understanding the impact and clinical relevance of GC-sparing treatments in longitudinal assessments of these patients and how toxicity measurement aligns with commonly used PROMs, and indices of the improvements in asthma control as measures of therapeutic response.

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These data on GTI toxicity and development of GTI 2.0 with MCID have not previously been presented.

Other than the named authors, there are no persons who have made substantial contributions to the work in this article.

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ONLINE REPOSITORY

TRIALS WITH GLUCOCORTICOID TOXICITY INDEX (GTI)

Trials in antineutrophil cytoplasmic antibody—associated vasculitis (ClinicalTrials.gov Identifiers: NCT03895801, NCT02994927), sarcoidosis (NCT03593759), giant cell arteritis (NCT03600805, NCT03765788), polymyalgia rheumatica (NCT03600818), minimal change nephropathy (NCT03210688), and pemphigus vulgaris (NCT03762265).

DEVELOPMENT OF THE GTI

The original version of the GTI (GTI 1.0) underwent preliminary validation by a multispecialty group of 19 physician experts.^{E1} These experts represented 10 medical subspecialties: pulmonary medicine, rheumatology, pediatric 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 multicriteria decision analysis (MCDA).^{E2}

A full explanation of how the items required to give a complete quantification of glucocorticoid (GC)-related toxicity were determined is outlined in the paper by Miloslavsky et al.^{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 (ie, to either improve or worsen over a period of at least 3 months); and (5) they can be measured simply and noninvasively. 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 patients with severe asthma treated with GC.^{E1} 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 MCDA^{E2} using pairwise “forced-choice” methods within the 1000Minds 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.

The GTI 2.0 app

A cloud-based digital interface—the GTI 2.0 app—was developed to facilitate the use of the GTI. With the app, investigators record a few data points and the app tabulates, analyzes, and scores the GTI in real time. The app’s algorithms, essential to reporting accuracy, assign the appropriate weights to the Composite Index to ensure the integrity of the Aggregate Improvement Score (AIS) and Cumulative Worsening Score (CWS). The platform also captures toxicities relevant to the Specific List and catalogues them on the scoring page. Data from the patient visit can be recorded by the app in 2 or 3 minutes, and integration with other databases (eg, electronic data capture systems, if available) minimizes redundancy and eliminates user

error. Data from the app can be downloaded into a.csv file for analysis.

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 multicenter clinical trials. This approach generated 2 scores from the Composite Index data called: (1) the AIS and (2) the CWS. These scores and their rationales are outlined briefly below.

Aggregate Improvement Score. 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 toward 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. 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.

THE GTI: COMPOSITE INDEX AND SPECIFIC LIST

The GTI is designed to measure change in GC toxicity between 2 points in time and includes 2 components, a Composite Index and a Specific List. The full Composite Index includes 9 domains and a total of 31 unique weighted items (see below). The Composite Index captures information about common GC-induced morbidities that distinguish high GC users from low GC users. The domains of toxicity represented in the Composite Index are well recognized by both clinicians and patients as being important: BMI, glucose tolerance, blood pressure, lipids, GC-induced myopathy, bone mineral density, skin toxicity, neuropsychiatric effects and infections. Important to the GTI’s purpose of recording change in GC toxicity, the domains of the Composite Index all represent elements of GC toxicity that are expected to either worsen or improve with variations in GC doses over time.

The Specific List was created as the second component of the GTI because not all GC toxicities are either sufficiently common or easily measurable for inclusion in the Composite Index. Nevertheless, even relatively uncommon or difficult-to-measure toxicities are important to record because such morbidities contribute substantially to the overall burden of GC use. The Specific List permits a more complete accounting of cumulative GC toxicity than that afforded by the Composite Index alone. Examples of toxicities included in the Specific List are osteonecrosis and posterior subcapsular cataracts, reflecting GC-induced damage that is irreversible. Because items in the Specific List occur rarely, often reflect cumulative GC toxicity, and frequently have a disproportionate impact on patients' quality of life, weights are not assigned to Specific List items. The Specific List includes 11 domains (9 of which are also shared by the Composite Index) and 23 unique items (see below). Together, the Composite Index and the Specific List aspire to capture the full sweep of GC toxicity that is relevant to patients.

WEIGHTS

The GTI assigns systematically determined relative weights to each toxicity item in the Composite Index. These weights were developed through MCDA.^{E2} Using pairwise "forced-choice" methods within the 1000Minds 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. The MCDA method is more systematic than group consensus methods such as Delphi exercises, in which investigators are asked to order all possible toxicities or assign relative weights. The MCDA method also carries a lower cognitive burden for investigators involved in a consensus exercise, because investigators are required to compare only 2 items at a time. This MCDA approach has been employed now in multiple studies developing classification criteria for immune-mediated diseases.^{E3-E6}

DEFINITIONS

Hypertensive emergency: The blood pressure has reached levels that are damaging organs. Hypertensive emergencies generally occur at blood pressure levels exceeding 180 mm Hg systolic or 120 mm Hg diastolic, but can occur at even lower levels in patients whose blood pressure have not been elevated before. Complications can include stroke, loss of consciousness, memory loss, myocardial infarction, hypertensive retinopathy or nephropathy, aortic dissection, angina, and pulmonary edema.

Posterior reversible leukoencephalopathy syndrome (PRES): A clinical radiological entity. Clinical features may include headaches, altered mental status, seizures, and visual loss, depending on the affected neuroanatomy. Characteristic magnetic resonance imaging (MRI) findings include vasogenic edema involving the white matter that predominantly affects the

posterior occipital and parietal lobes of the brain, although other brain regions may also be affected. Confirmation by MRI is required as is exclusion of other potential causes (including hypertensive emergency).

Severe glucocorticoid myopathy: Grade 3 or worse myopathic weakness or respiratory myopathic weakness attributable to glucocorticoid myopathy.

Central serous retinopathy: A fluid detachment of macula layers from their supporting tissue. Requires formal ophthalmology examination, typically accompanied by optical coherence tomography and/or fluorescein angiography for diagnostic confirmation.

Infection definitions

No significant infection = no specific infections or serious infections, grade 3 or greater.

Specific infections = oral or vaginal candidiasis or zoster infections without postherpetic neuralgia or eye involvement.

Grade 3 = intravenous antibiotic, antifungal, or antiviral intervention or hospitalization indicated OR radiologic or operative intervention indicated OR herpes zoster complicated by postherpetic neuralgia or eye involvement.

Grade 4 or 5 = Life-threatening consequences; urgent intervention indicated OR death from infection (included in the Specific List).

Diabetic nephropathy: Macroalbuminuria, that is, a urinary albumin excretion >300 mg in a 24-hour collection or a urinary protein: creatinine ratio >300 mg/g.

Diabetic neuropathy: Any of 4 types of peripheral neuropathy occurring in the setting of diabetes mellitus, namely: (1) a distal sensory polyneuropathy; (2) autonomic neuropathy (hypoglycemia unawareness, bladder or bowel problems, erectile dysfunction, and other autonomic nervous system issues); (3) diabetic amyotrophy (muscle infarction); or (4) mononeuritis (eg, a diabetic sixth cranial nerve palsy).

Diabetic retinopathy: Any form of retinopathy associated with diabetes mellitus, including both nonproliferative and proliferative forms of diabetic retinopathy as well as diabetic macular edema. These complications must be confirmed by an ophthalmologist.

Severe skin toxicity: Any of the following 3 manifestations:

Grade 4 acneiform lesions = papules and/or pustules covering any % body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated or life-threatening consequences.

Grade 3 striae = covering >30% BSA or associated with ulceration.

Grade 3 ulcers = combined area of ulcers >2 cm or full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia.

TABLE E1. Approach to calculating the baseline GTI score: toxicities assigned weighted scores from the Composite Index to establish a baseline GTI score

Toxicity domain		Points
Body mass index (BMI)	BMI < 27	0
	BMI ≥ 27 but < 30	21
	BMI ≥ 30	36
Glucose metabolism	HgbA1c < 5.7	0
	HgbA1c < 5.7 but on medication	32
	HgbA1c ≥ 5.7	32
	HgbA1c ≥ 5.7 and on medication	44
Blood pressure	Diabetic retinopathy, nephropathy, or neuropathy (count only one)	44
	Normotensive: systolic ≤ 120 and diastolic ≤ 85 no medications	0
	Systolic ≤ 120 and diastolic ≤ 85 but on medications	19
	Systolic > 120 or diastolic > 85 on no medications	19
	Systolic > 120 or diastolic > 85 and on medications	44
Lipid metabolism	Hypertensive emergency or PRES (count only one)	44
	LDL ≤ target	0
	LDL ≤ target but on medications	10
	LDL > target on no medications	10
	LDL > target on treatment	30
Bone/tendon	Normal BMD or no known history of osteoporosis	0
	Osteoporosis	29
	Insufficiency fracture secondary to osteoporosis	29
	Osteonecrosis	29
	Tendon rupture while on corticosteroid	29
Glucocorticoid myopathy	No myopathy	0
	Minor glucocorticoid myopathy	9
	Moderate glucocorticoid myopathy	63
	Severe glucocorticoid myopathy	63
Skin	No skin toxicity	0
	*Minor skin toxicity (1 or more than 1 minor skin item)	8
	*Moderate skin toxicity (1 or more than 1 moderate skin item)	26
	*Severe skin toxicity (1 or more than 1 moderate skin item)	26
	*Select only 1 (minor, moderate, or severe)	
Neuropsychiatric	No neuropsychiatric toxicity	0
	*Minor (1 or more than 1 minor NP item: insomnia, mania, depression, cognitive)	11
	*Moderate (1 or more than 1 moderate NP item: insomnia, mania, depression, cognitive)	74
	*Severe (1 or more than 1 severe NP item: insomnia, mania, depression, cognitive)	74
	Psychosis	74
	Glucocorticoid-induced violence	74
	*Select only 1 (minor, moderate, or severe)	
Infection	No GTI-relevant infections within the prebaseline GTI interval of the study	0
	Oral or vaginal candidiasis or noncomplicated zoster (<grade 3) within the prebaseline GTI interval of the study	19
	Grade 3 or grade 4 infection within the pre-baseline GTI interval of the study	93
Ocular	Increased IOP	33
	Posterior subcapsular cataract	33
	Central serous retinopathy	33
Gastrointestinal	GI perf absence of NSAIDs	33
	PUD without <i>Helicobacter pylori</i>	33
Endocrine	Adrenal insufficiency	33

BMD, bone mineral density; GI, gastrointestinal; GTI, Glucocorticoid Toxicity Index; HgbA1c, glycated haemoglobin; IOP, intraocular pressure; LDL, low density lipoprotein; NP, neuropsychiatric; NSAID, nonsteroidal anti-inflammatory drug; PRES, posterior reversible encephalopathy syndrome; PUD, peptic ulcer disease.

*Minor: Acneiform rash (grades 1-2), easy bruising (grade 1), hirsutism (grade 1), atrophy/striae (grade 1), erosions/ulceration (grade 1). Moderate: Acneiform rash (grades 3), easy bruising (grade 2), hirsutism (grade 2), atrophy/striae (grade 2), erosions/tears/ulceration (grade 2). Severe: Acneiform rash (grade 4), atrophy/striae (grade 3), erosions/tear/ulceration (grade 3).

TABLE E2. GTI 2.0 Composite Index: domains and weights of the 31 unique items in 9 domains

	Domain	Score
1. Change in body weight (BMI)	Decrease by ≥ 5 BMI units	−36
	Decrease by >2 but <5 BMI units	−21
	No significant change (± 2 BMI units)	0
	Increase of >2 to <5 BMI units	21
	Increase of 5 or more BMI units	36
2. Glucose metabolism	Improvement in HbA1c AND decrease in medication	−44
	Improvement in HbA1c OR decrease in medication	−32
	No significant change	0
	Increase in HbA1c OR increase in medication	32
	Increase in HbA1c AND increase in medication	44
3. Blood pressure (BP)	Improvement in BP AND decrease in medication	−44
	Improvement in BP OR decrease in medication	−19
	No significant change	0
	Increase in BP OR increase in medication	19
	Increase in BP AND increase in medication	44
4. Hyperlipidemia	Decrease in LDL AND decrease in medication	−30
	Decrease in LDL OR decrease in medication	−10
	No significant change	0
	Increase in LDL OR increase in medication	10
	Increase in LDL AND increase in medication	30
5. Bone health (BMD)	Increase in BMD (gain of more than 0.5)	−29
	No significant change in BMD (± 0.5)	0
	Decrease in BMD (loss of more than 0.5)	29
6. Corticosteroid myopathy	Moderate weakness to none	−63
	Moderate-to-mild weakness	−54
	Mild weakness to none	−9
	No significant change	0
	None-to-mild weakness (without functional limitation)	9
	Mild-to-moderate weakness	54
7. Skin corticosteroid-related toxicity	None-to-moderate weakness (with functional limitation)	63
	Decrease in skin toxicity—moderate to none	−26
	Decrease in skin toxicity—moderate to mild	−18
	Decrease in skin toxicity—mild to none	−8
	No significant change	0
	Increase in skin toxicity—none to mild	8
	Increase in skin toxicity—mild to moderate	18
8. Neuropsychiatric—corticosteroid-related symptoms	Increase in skin toxicity—none to moderate	26
	Decrease in NP toxicity—moderate to none	−74
	Decrease in NP toxicity—moderate to mild	−63
	Decrease in NP toxicity—mild to none	−11
	No significant change	0
	Increase in NP toxicity—none to mild	11
	Increase in NP toxicity—mild to moderate	63
9. Infection	Increase in NP toxicity—none to moderate	74
	No infection	0
	Oral or vaginal candidiasis or uncomplicated zoster ($<$ grade 3)	19
	Grade 3, 4, or 5 infection	93

BMD, bone mineral density; GTI, Glucocorticoid Toxicity Index; HgbA1c, glycated haemoglobin; LDL, low density lipoprotein; NP, neuropsychiatric.

TABLE E3. GTI 2.0 specific list: 11 domains (9 of which are shared by the Composite Index) and 23 unique items

	At baseline or before	New since baseline
Body mass index (BMI)		
• An absolute increase in BMI of more than 8 units (and >24.9 kg/m ²)		
Blood pressure		
• Hypertensive emergency (see definition, below)		
• PRES (posterior reversible encephalopathy syndrome) (see definition, below)		
Endocrine		
• Symptomatic adrenal insufficiency		
Bone health		
• Osteonecrosis of one joint		
• Osteonecrosis of more than one joint		
• Bone mineral density decrease >6%		
• Insufficiency fracture		
• Insufficiency fracture in more than one bone		
Muscle and tendon		
• Severe glucocorticoid myopathy (see definition)		
• Tendon rupture		
• More than 1 tendon rupture		
Eye		
• Central serous retinopathy		
• New-onset or worsened elevation of intraocular pressure requiring treatment or change in treatment		
• Posterior subcapsular cataracts (or history of same)		
Infection		
• Grade 4 infection (see definition, below)		
• Grade 5 infection (death from infection)		
Glucose tolerance		
• Diabetic nephropathy		
• Diabetic neuropathy		
• Diabetic retinopathy		
Gastrointestinal tract		
• Gastrointestinal perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use)		
• Peptic ulcer disease confirmed by endoscopy (excluding <i>Helicobacter pylori</i>)		
Skin		
• Severe skin toxicity (see definition, below)		
Neuropsychiatric		
• Psychosis, defined as hallucinations, delusions, or disorganized thought processes (occurring in the absence of mania, delirium, or depression)		
• Glucocorticoid-induced violence toward self or others		
Other glucocorticoid toxicities		
Please specify: _____		

GTI, Glucocorticoid Toxicity Index.

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