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Baseline Glucocorticoid-Related Toxicity Scores in Giant Cell Arteritis: A Post Hoc Analysis of the GiACTA Trial

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Objective. Giant cell arteritis (GCA) requires treatment with high-dose, long-term glucocorticoids (GCs). A score assessing and quantifying patients' baseline GC-related toxicity may be important to risk stratification and therapeutic decision-making in patients initiating immunosuppression.

Methods. We analyzed patients with GCA enrolled in the Tocilizumab in Giant Cell Arteritis (GiACTA) trial. Baseline GC-related toxicity scores for 12 domains were derived from the Glucocorticoid Toxicity Index using baseline medications, medical history, vital signs, and laboratory values. The 12 domains examined were body mass index, glucose tolerance, blood pressure, lipid metabolism, bone and/or tendon, GC myopathy, skin toxicity, neuropsychiatric effects, infection, ocular toxicity, gastrointestinal injury, and adrenal function. Potential scores ranged from 0 to 538. We compared differences between those with newly diagnosed versus relapsing disease at baseline.

Results. A total of 250 patients were included (75% female, mean age 69 years). The mean ± SD baseline GC-related toxicity score among all patients was 111.3 ± 53.2. The domains that contributed most to the overall scores were blood pressure (24.0% of the overall score), followed by glucose tolerance (22.6%) and neuropsychiatric effects (15.9%). Baseline GC-related toxicity scores were higher in patients with relapsing disease compared with those with newly diagnosed disease (mean of 122.5 vs. 98.9; $P < 0.001$). The body mass index and neuropsychiatric domain scores were significantly higher in patients with relapsing disease.

Conclusion. This approach to the assessment of baseline GC-related toxicity distinguished patients with relapsing GCA from those with newly diagnosed disease. Baseline GC-related toxicity scores may be useful in therapeutic decision-making for patients beginning immunosuppressive treatment.

INTRODUCTION

Giant cell arteritis (GCA), the most common primary form of systemic vasculitis, requires treatment with long-term, high-dose glucocorticoids (GCs). GCs are associated with numerous well-known toxicities, but until recently, there was no standardized way to quantify change in these toxicities (1–4).

The Glucocorticoid Toxicity Index (GTI) was developed for the purpose of measuring change in GC toxicity in clinical trials and other longitudinal research studies (5–7). The instrument has now been employed in dozens of studies, including phase 3 clinical trials (8–11). The core GTI instrument consists of nine weighted domains assessing GC toxicities that are both common and dynamic, ie, sensitive to changes in dose over time and likely to change over the course of a trial that involves varying GC doses (7). The GTI also includes three unweighted domains that incorporate toxicities that are not likely to change over time but that mark important chronic damage from GC toxicity.

The GTI domains can also be used to calculate a baseline GC-related toxicity score. This score addresses morbidities and potential for GC-related toxicity that are relevant regardless of the patient's current or prior exposure to GCs (Table 1). We hypothesize that patients' future development of GC toxicities can be predicted by their degree of GC-related toxicity at baseline and that such a baseline GC-related toxicity score might be an important factor in therapeutic decision-making and in the analysis of trial outcomes.

We analyzed data from Tocilizumab in Giant Cell Arteritis (GiACTA), a randomized, double-blind, placebo-controlled trial of tocilizumab in GCA in which patients with either newly diagnosed or relapsing disease received treatment with either prednisone

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SIGNIFICANCE & INNOVATIONS

- No approach to assessing the overall potential for glucocorticoid (GC) toxicity has been established for patients with rheumatic disease.
- Using data from the Tocilizumab in Giant Cell Arteritis (GiACTA) trial and the Glucocorticoid Toxicity Index, we assessed and quantified patients' baseline information from 12 different domains to derive a baseline GC-related toxicity score. The blood pressure and glucose tolerance domains contributed most substantially to the overall scores.
- Patients with relapsing disease at randomization had higher baseline GC-related toxicity scores than those with newly diagnosed disease.
- Baseline GC-related toxicity scores may serve as an important covariate in evaluating the risk of future GC toxicity over the course of treatment and in the decision to initiate GC-sparing therapies.

alone or prednisone in combination with tocilizumab, an interleukin-6 receptor blocker (12). In this study, we compared differences in baseline GC-related toxicity scores between those with newly diagnosed GCA and those with relapsing disease at the start of the trial, assessing the contributions of different GC-related toxicity domains to the overall scores.

MATERIALS AND METHODS

GiACTA trial. Details of the GiACTA trial inclusion criteria and design have been published and are summarized briefly (12). Patients at least 50 years old with either newly diagnosed or relapsing GCA were included. The original clinical trial was approved by institutional review boards at each of the participating institutions, and written informed consent was obtained from all study participants. We considered only patients' baseline data in this study.

Calculation of baseline GC toxicity scores. The baseline GC-related toxicity score is calculated from the patient's medical history, medications, vital signs (blood pressure and body mass index [BMI]), and simple laboratory values, including hemoglobin A1c (HbA1c) and low-density lipoprotein (LDL). The GTI includes nine weighted domains of GC toxicity and three unweighted domains (Supplementary Table 1). The weighted domains are BMI, glucose tolerance, blood pressure, lipid metabolism, bone and/or tendon, GC myopathy, skin toxicity, neuropsychiatric effects, and infection. The unweighted domains are ocular, gastrointestinal, and adrenal function. We examined all 12 domains to derive a GC-related toxicity score based on the sum of all individual domain scores at week 0. Bone mineral density was not assessed uniformly at baseline and was excluded, but osteoporosis was scored if patients had a history of that diagnosis. Infections relevant to the GTI (Supplementary Table 1) were scored if they had occurred within 1 year before the baseline visit. Relevant gastrointestinal and endocrine toxicities were recorded if they were present in the patients' medical history. Table 1 demonstrates the approach to scoring baseline GC toxicity. The item associated with the highest weight within each domain is counted. The GC-related toxicity score ranges from 0 to 538 points, with higher scores indicating greater toxicity.

Statistical analysis. Continuous variables were reported as mean ± SD or 95% confidence interval. Categorical variables were reported as number (percentage). We assessed the contributions of each domain score to the overall score by evaluating the sum of all scores within each domain for all patients divided by the sum of all overall scores for all patients. We compared overall baseline GC toxicity scores using *t*-tests and the distribution of scores of each baseline GC toxicity domain using the Mantel–Haenszel chi-square test between patients with newly diagnosed and those with relapsing disease. We used SAS, version 9.4 (SAS Institute, Inc.), for all statistical analyses.

RESULTS

Baseline cohort demographics. All 250 patients with baseline visits were included in our analyses. The mean ± SD age was 69 ± 8 years, and 187 (75%) were female (Table 2). A slight majority of the patients (131; 52%) had relapsing disease at baseline. The remaining 119 patients (48%) had newly diagnosed disease.

Baseline metabolic features. The mean BMI for all patients was 25.9 ± 4.7. One hundred twenty-eight patients (51%) were either overweight (BMI 25 to <30) or obese (BMI ≥30) at baseline. Seven (3%) were classified as being underweight (BMI < 18.5), 115 (46%) were classified as having normal weight (BMI 18.5 to <25), 85 (34%) were classified as being overweight, and 43 (17%) were classified as obese.

Forty-nine patients (20%) had baseline HbA1c values in the diabetic range (HbA1c ≥ 6.5%), 136 (54%) had HbA1c values in the prediabetic range (HbA1c 5.7% to <6.5%), and 65 (26%) had normal HbA1c values (HbA1c < 5.7%). Thirty patients (12%) were on hypoglycemic medications at baseline.

The mean systolic and diastolic blood pressures were 135.1 ± 17.1 and 76.3 ± 10.8, respectively. Nearly half of the patients (119; 48%) were on antihypertensive medications at baseline. The mean LDL was 115.4 ± 38.7 mg/dl, and 57 patients (23%) were on lipid-lowering medications at baseline.

Forty-seven patients (19%) were known to have osteoporosis (Table 2).

Overall GC-related toxicity scores at baseline and contributions from different domains and components. The mean ± SD baseline GC-related toxicity score among all patients was 111.3 ± 53.2 (Figure 1A, Table 3). Of the GTI

Table 1. Domains of the baseline glucocorticoid-related toxicity score

Baseline glucocorticoid-related toxicity domain	Domain criteria	Weighted score
BMI	BMI < 27	0
	BMI ≥ 27 but < 30	21
	BMI ≥ 30	36
Glucose tolerance	HbA1c < 5.7%	0
	HbA1c < 5.7% and on medication	32
	HbA1c ≥ 5.7%	32
	HbA1c ≥ 5.7% and on medication	44
	Diabetic retinopathy, nephropathy, or neuropathy (count only one)	44
Blood pressure	Normotensive: systolic ≤ 120 mm Hg and diastolic ≤ 85 mm Hg on no medications	0
	Systolic ≤ 120 mm Hg and diastolic ≤ 85 mm Hg and on medications	19
	Systolic > 120 mm Hg or diastolic > 85 mm Hg on no medications	19
	Systolic > 120 mm Hg or diastolic > 85 mm Hg and on medications	44
	Hypertensive emergency or PRES (count only one)	44
Lipid metabolism	LDL ≤ target (70 mg/dl or 1.8 mmol/l)	0
	LDL ≤ target (70 mg/dl or 1.8 mmol/l) but on medications	10
	LDL > target (70 mg/dl or 1.8 mmol/l) on no medications	10
	LDL > target (70 mg/dl or 1.8 mmol/l) on treatment	30
Bone and/or tendon	Normal BMD or no known history of osteoporosis	0
	Osteoporosis (ever)	29
	Insufficiency fracture secondary to osteoporosis (ever)	29
	Osteonecrosis (ever)	29
	Tendon rupture while on steroids (ever)	29
Glucocorticoid myopathy	No myopathy	0
	Minor glucocorticoid myopathy	9
	Moderate glucocorticoid myopathy	63
	Severe glucocorticoid myopathy	63
Skin toxicity	No skin toxicity	0
	Minor skin toxicity (one or more than one minor skin item)	8
	Moderate skin toxicity (one or more than one moderate skin item)	26
	Severe skin toxicity (one or more than one moderate skin item)	26
Neuropsychiatric effects	No neuropsychiatric toxicity	0
	Minor (one or more than one minor item: insomnia, mania, depression, cognitive)	11
	Moderate (one or more than one moderate item: insomnia, mania, depression, cognitive)	74
	Severe (one or more than one severe item: insomnia, mania, depression, cognitive)	74
	Psychosis	74
	Glucocorticoid-induced violence	74
Infection (within 1 year)	No relevant infections within the prebaseline specified interval of the study	0
	Oral or vaginal candidiasis or noncomplicated zoster (<grade 3) within the prebaseline specified interval of the study	19
	Grade 3 or grade 4 infection within the prebaseline specified interval of the study	93
Ocular toxicity	Increased intraocular pressure	33
	Posterior subcapsular cataract	33
	Central serous retinopathy	33
Gastrointestinal (ever)	Gastrointestinal perforation in the absence of NSAIDs	33
	Peptic ulcer disease without *Helicobacter pylori*	33
Adrenal function (ever)	Adrenal insufficiency	33

Abbreviations: BMD, bone mineral density; BMI, body mass index; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; NSAID, nonsteroidal antiinflammatory drug; PRES, posterior reversible encephalopathy syndrome.

domains, blood pressure contributed the most points toward the overall scores (24.0% of the overall score), followed by glucose tolerance (22.6%), neuropsychiatric effects (15.9%), lipid metabolism (11.1%), BMI (9.5%), bone and/or tendon (7.1%), and ocular toxicity (7.0%) (Table 4).

In terms of the specific domains and manifestations within each domain, 76 patients (30%) had neuropsychiatric toxicity, with 49 (20%) having insomnia, none having mania, one (<1%) having cognitive impairment, and 41 (16%) having depression (Supplementary Table 2). Twelve patients (5%) had a recent or current infection, with 10 (4%) having oral or vaginal candidiasis or uncomplicated zoster and three (1%) having a grade 3 infection. No grade 4 infections or complicated zoster was noted. Fifty-nine patients (24%) had ocular toxicity, with 23 (9%) having increased ocular pressure, 46 (18%) having cataracts, and none having central serous retinopathy. Ten patients (4%) had a history of gastrointestinal injury, 10 (4%) had peptic ulcer disease in the absence of

Table 2. Baseline characteristics of GiACTA patients, stratified by disease status at baseline

Characteristic	All patients (N = 250)	Relapsing disease (n = 131)	Newly diagnosed disease (n = 119)
Age, mean (SD)	69 (8)	69 (8)	69 (8)
Female, n (%)	187 (75)	98 (75)	89 (75)
Disease status, n (%)			
Newly diagnosed	119 (48)	0 (0)	119 (100)
Relapsing	131 (52)	131 (100)	0 (0)
BMI category, n (%)			
Underweight (BMI < 18.5)	7 (3)	4 (3)	3 (3)
Normal (BMI 18.5 to <25)	115 (46)	46 (35)	69 (58)
Overweight (BMI 25 to <30)	84 (34)	50 (38)	34 (29)
Obese (BMI 30)	44 (18)	31 (24)	13 (11)
HbA1c category, n (%)			
Diabetes (HbA1c 6.5%)	49 (20)	26 (20)	23 (19)
Prediabetes (HbA1c 5.7% to <6.5%)	136 (54)	71 (54)	65 (55)
Normal (HbA1c <5.7%)	65 (26)	34 (26)	31 (26)
Hypoglycemic medication use, n (%)	30 (12)	17 (13)	13 (11)
Systolic BP, mean (SD) mm Hg	135.1 (17.1)	135.1 (16.9)	135.1 (17.4)
Diastolic BP, mean (SD) mm Hg	76.3 (10.8)	76.3 (10.9)	76.4 (10.7)
Antihypertensive medication use, n (%)	119 (48)	68 (52)	51 (43)
Osteoporosis, n (%)	47 (19)	28 (21)	19 (16)
LDL, mean (SD) mg/dl	115.4 (38.7)	116.1 (39.2)	114.6 (38.4)
Lipid-lowering medication use, n (%)	57 (23)	31 (24)	26 (22)
Baseline prednisone dose, n (%)			
>30 mg daily	121 (48)	48 (37)	73 (61)
≤30 mg daily	129 (52)	83 (63)	46 (39)

Abbreviations: BMI, body mass index; BP, blood pressure; GiACTA, Tocilizumab in Giant Cell Arteritis; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein.

Helicobacter pylori, and none had a gastrointestinal perforation. Four patients (2%) had skin toxicity, with one (<1%) having acneiform rash, three (1%) having easy bruising, and none having hirsutism, atrophy/striae, or erosions, tears, or ulcerations. Two patients (1%) had GC myopathy. No patients had a known history of adrenal insufficiency.

Differences in GC-related toxicity scores between patients with newly diagnosed and those with relapsing disease at baseline. GC-related toxicity scores were higher in patients with relapsing disease compared with those with newly diagnosed disease (mean of 122.5 vs. 98.9, respectively; $P < 0.001$) (Figure 1B, Table 3). Multiple individual GC toxicity

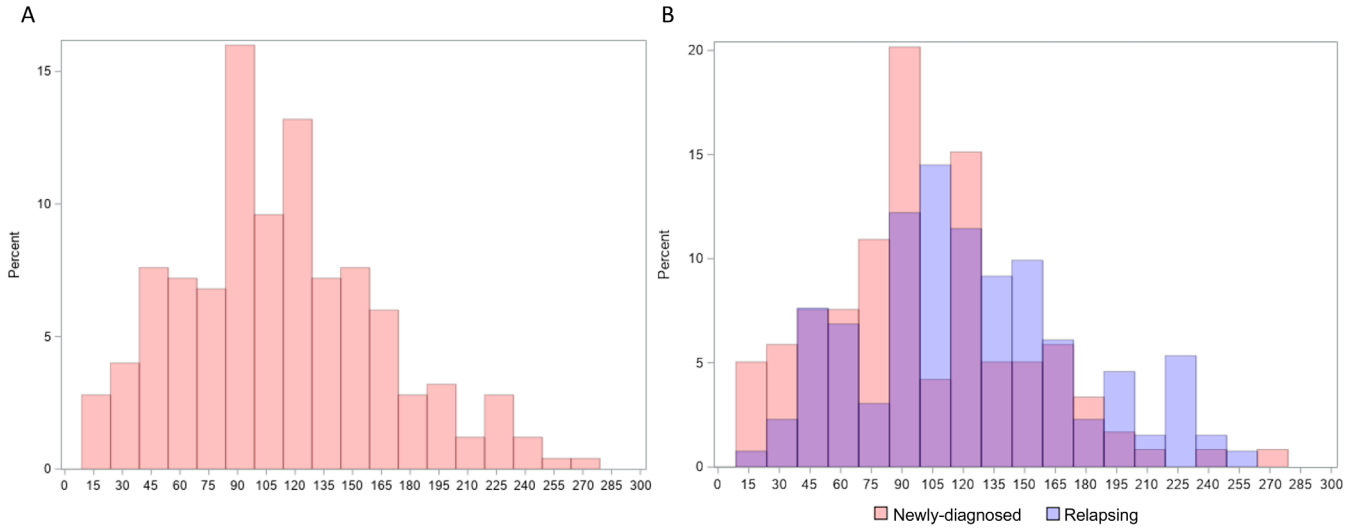

Figure 1. Histogram of glucocorticoid-related toxicity scores in all patients and in those with newly diagnosed versus relapsing disease at baseline. **A,** Distribution of baseline glucocorticoid toxicity scores in all patients. **B,** Distribution of baseline glucocorticoid toxicity scores in patients with newly diagnosed versus relapsing disease. Purple represents overlap in the percentages of patients with newly diagnosed and relapsing disease. Red represents excess percentage of patients with newly diagnosed disease over those with relapsing disease. Blue represents excess percentage of patients with relapsing disease over those with newly diagnosed disease.

Table 3. Differences in GC-related toxicity scores between those with newly diagnosed versus relapsing disease at baseline

Overall baseline GC-related toxicity or domain score	All patients (N = 250)	Relapsing disease (n = 131)	Newly diagnosed disease (n = 119)	*P* value (comparing relapsing to newly diagnosed)
Baseline GC-related toxicity score, mean (SD)	111.3 (53.2)	122.5 (53.4)	98.9 (50.4)	<0.01
Blood pressure, n (%)				0.45
Score of 0	35 (14)	16 (12)	19 (16)	
Score of 19	111 (44)	56 (43)	55 (46)	
Score of 44	104 (42)	59 (45)	45 (38)	
Body mass index, n (%)				<0.01
Score of 0	155 (62)	68 (52)	87 (73)	
Score of 21	51 (20)	32 (24)	19 (16)	
Score of 36	44 (18)	31 (24)	13 (11)	
Glucose tolerance, n (%)				0.74
Score of 0	64 (26)	34 (26)	30 (25)	
Score of 32	157 (63)	80 (61)	77 (65)	
Score of 44	29 (12)	17 (13)	12 (10)	
Lipid metabolism, n (%)				0.93
Score of 0	17 (7)	9 (7)	8 (7)	
Score of 10	188 (75)	100 (76)	88 (74)	
Score of 30	40 (16)	20 (15)	20 (17)	
Missing	5 (2)	2 (2)	3 (3)	
GC myopathy, n (%)				0.50
Score of 0	248 (99)	129 (98)	119 (100)	
Score of 9	2 (1)	2 (2)	0 (0)	
Score of 63	0 (0)	0 (0)	0 (0)	
Skin toxicity, n (%)				0.12
Score of 0	246 (98)	127 (97)	119 (100)	
Score of 8	4 (2)	4 (3)	0 (0)	
Score of 26	0 (0)	0 (0)	0 (0)	
Neuropsychiatric effects, n (%)				<0.01
Score of 0	174 (70)	88 (67)	86 (72)	
Score of 11	19 (8)	4 (3)	15 (13)	
Score of 74	57 (23)	39 (30)	18 (15)	
Infection, n (%)				0.35
Score of 0	238 (95)	123 (94)	115 (97)	
Score of 19	10 (4)	6 (5)	4 (3)	
Score of 93	2 (1)	2 (2)	0 (0)	
Bone and/or tendon, n (%)				0.21
Score of 0	182 (73)	91 (69)	91 (76)	
Score of 29	68 (27)	40 (31)	28 (24)	
Ocular toxicity, n (%)				0.53
Score of 0	191 (76)	98 (75)	93 (78)	
Score of 33	59 (24)	33 (25)	26 (22)	
Gastrointestinal, n (%)				1.00
Score of 0	240 (96)	126 (96)	114 (96)	
Score of 33	10 (4)	5 (4)	5 (4)	
Adrenal function, n (%)				—
Score of 0	250 (0)	131 (100)	119 (100)	
Score of 33	0 (0)	0 (0)	0 (0)	

Abbreviation: GC, glucocorticoid.

domain scores were higher in patients with relapsing disease compared with those with newly diagnosed disease, including BMI (highest score of 36 was seen in 24% vs. 11%; $P = 0.002$) and neuropsychiatric effects (highest score of 74 was seen in 30% vs. 15%; $P = 0.001$) (Table 3). BMI contributed to 11.1% of the overall scores among the patients with relapsing disease, compared with 7.4% in patients with newly diagnosed disease. Neuropsychiatric effects contributed to 18.3% of the score among those with relapsing disease, compared with 12.7% in patients with newly diagnosed disease (Table 4). The remaining domains (blood pressure, glucose tolerance, lipid metabolism, GC myopathy, skin toxicity, infection, bone and/or tendon, ocular toxicity, gastrointestinal injury, and endocrine) were not significantly different between those with relapsing disease and those with newly diagnosed disease.

DISCUSSION

Using data from a large randomized trial of GCA, we assessed and compared the baseline GC-related toxicity scores

Table 4. Contributions of each GC-related toxicity score domain to the overall baseline GC-related toxicity score, stratified by disease status at baseline

Domain	Proportion of overall baseline GC-related toxicity score, %		
	All patients (N = 250)	Relapsing disease (n = 131)	Newly diagnosed disease (n = 119)
BP	24.0	22.8	25.7
Glucose tolerance	22.6	20.6	25.4
Neuropsychiatric effects	15.9	18.3	12.7
Lipid metabolism	11.1	9.9	12.6
BMI	9.5	11.1	7.4
Bone and/or tendon	7.1	7.2	6.9
Ocular toxicity	7.0	6.8	7.3
Infection	1.4	1.9	0.6
Gastrointestinal	1.2	1.0	1.4
GC myopathy	0.1	0.1	0.0
Skin toxicity	0.1	0.2	0.0
Adrenal function	0.0	0.0	0.0

Abbreviations: BMI, body mass index; BP, blood pressure; GC, glucocorticoid.

for patients with newly diagnosed or relapsing disease. We found that scores were significantly higher in those with relapsing disease at baseline compared with those with newly diagnosed disease (mean score of 122.5 vs. 98.9; $P < 0.001$) and that the blood pressure, glucose tolerance, and neuropsychiatric effects domains contributed the largest proportion of points toward the overall scores. Higher scores in the BMI and neuropsychiatric effects domains were observed in those with relapsing disease at baseline, driven by higher BMI values as well as numerically higher rates of depression in those with relapsing disease compared with those with newly diagnosed disease at baseline. These data suggest that baseline GC-related toxicity and risk factors for future GC toxicity can be quantified at the start of trials.

The retrospective nature of this study imposed important limitations on the ability to fully assess baseline GC toxicity. Nevertheless, the prevalence of risk factors for poor outcomes on GC treatment in the GiACTA trial was extremely high. Seventy-four percent of patients were classified as either diabetic or prediabetic at baseline simply on the basis of their HbA1c values. Fifty-one percent of the patients were either overweight or obese at baseline, and 48% were on antihypertensive medications. In addition, although bone mineral density studies were not performed in this population at baseline, 19% of the patients were already known to have osteoporosis at baseline. This population of patients, already at risk for GC toxicity by virtue of their mean age (69 ± 8 years) and sex distribution (75% female), then embarked on a treatment course heavily dependent on GCs. At the baseline visit, 121 (48%) of these patients were started on a prednisone dose greater than 30 mg/day, which was to be tapered to discontinuation over either 6 or 12 months according to the protocol. In addition, most patients had already been treated with moderate to high doses of prednisone for up to 6 weeks at the time of their baseline visit.

The domains included in the score and their respective items are relevant regardless of whether or not the patient has been exposed to GCs before the calculation is performed. The design of the GTI and its derivative GC-related toxicity score is such that each item is scored regardless of whether or not its presence is attributable to GC use. The GC-related toxicity score provides a comprehensive overview of morbidity that may either be due to GC use or be directly relevant to the potential for further GC toxicity in those initiating or receiving GCs. These results may have important implications for the counseling and monitoring of patients regarding weight changes during treatment, monitoring for impaired glucose tolerance or diabetes, and counseling regarding neuropsychiatric adverse effects of GCs or management of existing symptoms such as insomnia, anxiety, or others. Indeed, the Outcome Measures in Rheumatology (OMERACT) working group has identified GC-related complications as a core outcome measure for polymyalgia rheumatica, and these data would be valuable in large-vessel vasculitis and other autoimmune diseases treated with GCs as well (13–16).

The mean scores in our cohort were lower than those seen in a real-world cohort of patients with asthma (mean score was 177.5 [SD: 73.7]), likely reflecting differences in the patient cohorts (6). Patients in the asthma study all had longstanding disease, with a mean of 23 years between the onset of asthma and the assessment of GC toxicity. The investigators in that study also found that GC toxicity had only a modest correlation with both daily GC dose at the time of assessment and cumulative GC exposure over the preceding 12 months, underscoring the importance of quantifying GC toxicity itself as opposed to simply GC dose or cumulative exposure.

GC-related toxicity accounts for a substantial percentage of the adverse effects seen in clinical trials involving GCs as part of the treatment regimen, and many patients may have received GCs prior to their enrollment in trials. For example, in a phase 3 trial investigating avacopan for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis in which the GTI was analyzed as a secondary outcome measure, 91% of the patients had GC-related toxicity at 26 weeks and 67% of the patients had toxicity involving between two and six domains (17). Future GC toxicity may be predicted by baseline toxicity, and thus careful assessment and quantification of baseline GC toxicity in clinical trials and other clinical settings is essential to evaluating these relationships. In the GiACTA trial, evaluation of the impact of GC tapering on HbA1c values in the setting of GCA treatment demonstrated that daily prednisone dose had a more profound impact on the HbA1c levels of those with diabetes compared with those without diabetes, indicating that those with preexisting diabetes were more susceptible to worsening of glucose tolerance caused

by GCs received in the trial (18). The distribution of glucose tolerance categories is similar in our population compared with patients of similar age and sex from the general population; despite prior use of GCs, HbA1c values may normalize with tapering or time off of GCs in many patients (18–20).

Our study has important strengths. This is the first attempt to quantify baseline GC toxicity in a clinical trial population. Because of the clinical trial setting, data for certain GTI domains were collected thoroughly and systematically, and the baseline data for those domains were largely complete. In addition, because we only analyzed information that was available at baseline, our results are likely generalizable to the general population of patients with GCA and offer a reasonable reflection of baseline GC-related toxicity in patients embarking on a treatment course for new or relapsing disease, at least in the domains for which data capture was complete. In this context, it is worth bearing in mind that GC use in real-world practice has been shown to be substantially heavier than in clinical trial settings, likely placing patients at greater risk of GC toxicity (4).

Our study also has certain limitations. Although data were collected prospectively in the trial, the GTI did not exist at the time GiACTA began. Therefore, neither GTI scores nor baseline GC toxicity scores were calculated prospectively in the trial. This imposed significant limitations on the data available for GC toxicity domains that require focused physical examinations, particularly the skin toxicity and GC myopathy domains. In addition, active and prior severe infections were exclusion criteria of the trial, which could contribute to underestimation of the infection domain scores, and bone mineral density was not systematically assessed as part of GiACTA, so it is likely that the prevalence of osteoporosis at baseline was underestimated. The baseline GC toxicity scores as calculated in this study therefore likely represent underestimates of the actual baseline GC-related toxicity scores. Nevertheless, despite these data collection constraints, the higher baseline GC-related toxicity scores in those with relapsing disease compared with those with newly diagnosed disease provide convergent validity to this approach. Additionally, cumulative GC use prior to enrollment in GiACTA was not available. Next, BMI was higher in those with relapsing disease than in those with newly diagnosed disease at the time of enrollment in GiACTA and higher than that of the general population; we hypothesize that this is primarily due to prior exposure to GCs, though other considerations include a bidirectional relationship in which BMI may impact the risk of relapse of GCA, potentially related to lower weight-based GC dosing (21–24). Our findings suggest that evaluations focusing on the collection of data specific to baseline GC-related toxicity in future studies may lead to more robust assessments of this phenomenon and to more intentional and individualized management of patients' medications.

In conclusion, we found that multiple GC toxicity domains contributed to the degree of baseline GC-related toxicity seen in patients with GCA and that scores were significantly higher in those with relapsing disease at baseline compared with those with newly diagnosed disease. Future directions could include comparing prospectively collected GTI data with retrospectively collected data (eg, from the electronic health record, routine clinic notes, and other sources) in the same data set to provide further validation of the retrospective approach to calculating scores. Such baseline scores could be used to develop a risk prediction model for further GC toxicity, and patients with high risk of subsequent GC toxicity would warrant earlier initiation of GC-sparing therapies, when appropriate, and/or close monitoring for GC-related adverse effects. Finally, GC-related toxicity scores may also be analyzed in future studies as potential explanatory variables in future studies evaluating risk factors associated with subsequent GC toxicity during the course of treatment.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Stone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Patel, Fu, Zhang, Stone.
Acquisition of data. Stone.
Analysis and interpretation of data. Patel, Fu, Zhang, Stone.

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