Evaluation of the toxicity of glucocorticoids in patients with autoimmune blistering disease using the Glucocorticoid Toxicity Index: A cohort study

Yicong Liang, MD,[a,b] Faith A. P. Zeng,[a,b] Tabrez Sheriff, MD,[a,b] Anna Wilson, MD,[a,b] Asli Bilgic, MD,[a,b,c] Grant Feng,[d] John H. Stone, MD, MPH,[e] and Dedee F. Murrell, MA, BMBCh, MD[a,b]
Sydney and XXX, New South Wales, Australia; Antalya, Turkey; and Boston, Massachusetts

Background: Glucocorticoids are the mainstay of treatment for autoimmune blistering diseases (AIBDs). The Glucocorticoid Toxicity Index (GTI) is a novel, outcome-based glucocorticoid-induced adverse effects monitoring instrument.

Objective: To investigate whether the GTI score was able to accurately quantify the glucocorticoid-induced toxicity in patients with AIBDs.

Methods: The prospective cohort study included patients with confirmed diagnoses of AIBDs (group1, currently receiving glucocorticoids; and group 2, had glucocorticoids ceased earlier). Data were collected minimally at baseline (V1) and 3 months (V2). Further data from patients who were able to complete the follow-up visits at 6 months (V3) and 12 months (V4) amid the COVID-19 pandemic were also included. GTI scores were calculated after data collection.

Results: Analysis of data from V1 and V2 found a linear correlation between GTI score and prednisone doses ($P < .05$) and a significant difference in GTI scores between group1 and group 2 ($P < .05$). Data from V3 and V4 suggested that GTI scores continued to rise progressively alongside increasing cumulative prednisone dose.

Limitations: Small sample size, further exacerbated by the COVID-19 pandemic. Single-center study.

Conclusion: The GTI sensitively and specifically captured the changes in glucocorticoids toxicity over time among patients with AIBDs. The GTI could be a feasible tool that can be used in future clinical trials as a glucocorticoid-induced toxicity outcome measure. (JAAD Int 2022;6:68-76.)

Key words: Autoimmune blistering disease; clinical research; Glucocorticoid Toxicity Index; glucocorticoid; side effect.

INTRODUCTION

Autoimmune blistering diseases

Autoimmune blistering diseases (AIBDs) are a group of skin disorders characterized by the presence of autoantibodies against certain structural proteins in the epidermis or dermoepidermal junction, causing blistering and erosions on the skin and mucous membranes.[1] The 1-year mortality rates are

From the Department of Dermatology, St George Hospital, Sydney[a]; Faculty of Medicine, University of New South Wales, Sydney[b]; Department of Dermatology, Akdeniz University, Antalya[c]; Data Science, WooliesX, Sydney[d]; and Department of Rheumatology, Massachusetts General Hospital, Harvard University, Boston.[e]
Authors Liang and Zeng are cofirst authors.
Funding sources: Dr Bilgic was supported by the Prof Dr Hulusi Behcet Scholarship from the Turkish Society of Dermatology to work with Dr Murrell.
IRB approval status: Not applicable.

Accepted for publication September 10, 2021.
Correspondence to: Dedee F. Murrell, MA, BMBCh, MD, Department of Dermatology, Ground Floor, James Laws House, St George Hospital, Gray St, Kogarah, NSW 2217, Australia. E-mail: d.murrell@unsw.edu.au.
2666-3287
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https://doi.org/10.1016/j.jdin.2021.09.003

reported to be high and range between 19% and 38% for bpullous emphigoid and 5% and 15% for pemphigus, respectively.[2-5]

Glucocorticoids have been the mainstay of treatment since the 1950s due to their potent immunosuppressive properties.[6] Although the mortality rate of AIBDs has been substantially reduced with the introduction of glucocorticoids, the use of glucocorticoids is associated with a myriad of glucocorticoid-induced adverse effects (GCAEs), ranging from mild to life-threatening conditions. Due to the relapsing nature of AIBDs, treatments often require long-term glucocorticoids exposure (1.5 to 20 years), which increases the risk of developing serious GCAEs.[7-9]

CAPSULE SUMMARY

- To our knowledge, this is the first study to apply the GTI to real patients with autoimmune blistering diseases in the clinical setting.
- This study suggests that the GTI is a feasible and responsive outcome measure that can be used in future clinical trials of AIBDs to quantify glucocorticoid-induced toxicity.

Current methods of measuring glucocorticoid-induced adverse events: trends and limitations

Exposure to glucocorticoids is mainly quantified in 2 ways—daily dose and cumulative dose.[10] Several studies have illustrated different daily- and cumulative-dose–related patterns of individual GCAEs.[11-16] Assessing the relationship between glucocorticoid doses and the general impact of GCAEs remains challenging due to the differential impact of the wide variety of GCAEs on a patient's general health.[17] Systematic reviews have concluded that a comprehensive understanding of the dose-response relationship of GCAEs remains poorly understood.[18,19]

Daily and cumulative glucocorticoid doses are widely used in clinical trials as the primary indicator for the steroid-sparing ability of novel adjuvant therapies for AIBDs.[20] Although a significant reduction in glucocorticoid doses has been observed in several clinical trials, the ability of the adjuvant therapies to reduce the actual impact of GCAEs on patients remains poorly documented.[21-27] This highlights the need for a standardized, outcome-based GCAE quantification tool that allows direct measurement of glucocorticoid-induced toxicity.

The Glucocorticoid Toxicity Index

The Glucocorticoid Toxicity Index (GTI) is a comprehensive, outcome-based glucocorticoid toxicity-monitoring instrument developed by a multidisciplinary team of international experts during 2015 to 2016.[28] The GTI is composed of 9 domains and measures the change in glucocorticoid toxicity between 2 points in time. The GTI can measure not only the worsening of glucocorticoid toxicity but also its improvement. The minimal clinically important difference for the GTI scores is 10.[29]

The GTI can be used in a web-based application, the GTI 2.0 (Supplementary File 1, available via Mendeley at 10.17632/n6v5n8fms8.1).[29] Given the significant impact of GCAEs in patients with AIBDs, the validation and application of this novel tool in this patient population could lead to improved clinical outcomes, better treatment choices, and fewer drug-induced side effects.

Aims

Our research aimed to apply the GTI among patients with AIBDs to investigate the real-life validity of this tool, to our knowledge, for the first time in skin disease. We aimed to investigate whether the GTI score is able to accurately quantify the glucocorticoid-induced toxicity, whether it has high specificity for glucocorticoid-induced toxicity while not being confounded by other factors, and whether it reflects the impact of GCAEs on patients' quality of life.

MATERIALS AND METHODS

This prospective study was conducted in an academic blistering disease clinic in Sydney, Australia, in 2019. Ethics approval was obtained for this study (HREC STG/186).

Population

Patients with confirmed diagnoses of AIBDs based on typical clinical, histopathological, immunohistochemical, and enzyme-linked immunoassay/biochip/immunoblot testing who visited the Blistering Disease Centre during the enrolment period were eligible. The following inclusion criteria were used for the selection of the participants: confirmed diagnosis of AIBD; about to start glucocorticoids or increase the glucocorticoid dose for active AIBD (group 1, active treatment group) or previous receipt of glucocorticoids for AIBD treatment (group 2, control group); at least 2 visits to the Blistering Disease Centre during the study period; and ability to consent.

Abbreviations used:

AIBD:	autoimmune blistering disease
ABQOL:	Autoimmune Bullous Disease Quality of Life
BMI:	body mass index
GCAE:	glucocorticoid-induced adverse effect
GTI:	Glucocorticoid Toxicity Index
GTI-AIS:	Glucocorticoid Toxicity Index Aggregate Improvement Score
GTI-CWS:	Glucocorticoid Toxicity Index Cumulative Worsening Score

Study design

For each patient, the parameters for GTI calculation were collected from routinely collected data twice during 2 visits, namely the baseline visit (V1) and follow-up visit at 3 months (V2). Data were included if patients were able to attend follow-up visits at 6 months (V3) and at 12 months (V4) amid the COVID-19 pandemic. The treatment plans were decided by dermatology professionals clinically based on the patient's condition.

Parameters collected

During each visit, patients routinely completed the validated Autoimmune Bullous Disease Quality of Life (ABQOL) questionnaire and the Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) questionnaire.[30,31] Body mass index (BMI) and blood pressure were measured at the time of the visit. The muscle strength of both upper and lower extremities was physically measured (the degrees correspond to the mild, moderate, and severe ratings of the standard Medical Research Council rating scale).[29,32] The skin assessment was conducted by accredited dermatology professionals, and the neuropsychiatric toxicity was assessed by patient interview. Glycated hemoglobin and low-density lipoprotein cholesterol level were included in routine safety blood. The bone mineral density domain was not assessed in this study as the study duration of change was <1 year.[28]

Any change in medications related to blood pressure, glucose tolerance, or lipid metabolism between V1 and any of the follow-up visits (V2, V3, or V4), where available, was recorded. The cumulative glucocorticoid doses were calculated in prednisone equivalents.

Final GTI score

The GTI 2.0 app, a cloud-based digital interface, was developed to facilitate the use and scoring of the GTI (Supplementary File 1). The final GTI score contains 2 components. The GTI Cumulative Worsening Score (GTI-CWS) calculates the worsening of GCAEs, assessing cumulative glucocorticoid toxicity, regardless of whether the toxicity has lasting effects or is transient. The GTI Aggregate Improvement Score (GTI-AIS) assesses improvement and worsening of GCAEs.

Statistical analysis

After data collection was completed, all the patients were classified into 2 groups based on their treatment during the study. The active treatment group (group 1) included patients who received glucocorticoids from baseline (V1) to the end point of their data collection (V2, V3, or V4). The control group (group 2) included patients who had taken glucocorticoids before V1 and received no glucocorticoid from baseline (V1) to the end point of their data collection (V2, V3, or V4).

Where possible, analysis using statistical and correlation tests was performed. SPSS version 25.0 (IBM Corporation) was applied, where a P value of $<.05$ (2-sided) was considered significant. The correlations between GTI-CWS and GTI-AIS and cumulative and average daily glucocorticoid doses were analyzed using Pearson correlation test. Pearson correlation and Spearman correlation tests were performed to assess the relationship between GTI-CWS, GTI-AIS, ABQOL, and TABQOL. One-way analysis of variance analysis and Kruskal-Wallis H test were performed to investigate a significant difference in GTI scores between the 2 study groups.

RESULTS

Population characteristics

A convenience sample of 80 patients was considered for entry in the study. Of these, 33 patients were enrolled in this study, and 27 patients completed the follow-up. Six (18%) participants were unavailable for the follow-up. The final population included in this study consisted of 27 patients aged 62.2 ± 18 years. Sixteen patients, classified in the active treatment group (group 1), received an average cumulative prednisone dose of 886.1 mg (range, 30-2318 mg) between V1 and V2. Eleven patients who received no glucocorticoid during the study were classified into the control group (group 2). The mean length of the interval between V1 and V2 was 106.1 and 108.5 days for group 1 and group 2, respectively. Both GTI-CWS and GTI-AIS scores of all 27 patients were calculated. The population characteristics are listed in Table I. The mean GTI scores, standard deviations, and ranges are listed in Table II. Due to the COVID-19 pandemic, only 4 patients from group 1 attended face-to-face follow-up visits beyond V2 (Supplementary Table I, available via

Table I. Population characteristics

Characteristic	Value	
	Active treatment group (group 1)	Control group (group 2)
No. of patients	16	11
Age at baseline, years (SD)	60.4 (19)	65.6 (20)
Sex		
Female (%)	12 (75%)	7 (64%)
Male (%)	4 (25%)	4 (36%)
Diagnosis		
Pemphigus vulgaris (%)	8 (50%)	5 (46%)
Bullous pemphigoid (%)	4 (25%)	3 (27%)
Pemphigus foliaceus (%)	2 (13%)	2 (18%)
Mucous membrane pemphigoid (%)	2 (13%)	0 (0%)
Pemphigoid gestationis (%)	0 (0%)	1 (9%)
Mean duration of disease since diagnosis, years	4.5	6.7
Mean duration on prednisone before V1, years	2.3	2.2
Mean cumulative prednisone dose between V1 and V2, mg (range)	886.1 (30-2318)	0 (0-0)
Mean average daily prednisone dose between V1 and V2, mg (range)	8.5 (0.2-23.4)	0 (0-0)
Average time between V1 and V2, days (SD)	106.1 (16)	108.5 (19)

SD, Standard deviation; *V1*, baseline visit; *V2*, follow-up visit at 3 months.

Table II. Between V1 and V2: mean Glucocorticoid Toxicity Index scores, standard deviation, and range

Value	Active treatment group (group 1)	Control group (group 2)
No. of Patients	16	11
GTI-CWS		
Mean (SD)	42.8 (39)	7.5 (14)
Range	0-132	0-44
GTI-AIS		
Mean (SD)	37.1 (40)	−13.9 (42)
Range	−21 to 132	−114 to 34

GTI-AIS, Glucocorticoid Toxicity Index Aggregate Improvement Score; *GTI-CWS*, Glucocorticoid Toxicity Index Cumulative Worsening Score; *SD*, standard deviation; *V1*, baseline visit; *V2*, follow-up visit at 3 months.

Mendeley at 10.17632/n6v5n8fms8.1). From these, 1 patient had data up to 6 months (V3), and 3 patients had follow-up data up to 12 months (V4). The latter 3 patients with complete V1 to V4 data had their bone mineral density scores included in the final GTI score calculation.

Improvement and worsening of GTI scores

Between V1 and V2. The improvement and worsening of GCAEs identified by the GTI is presented in Table III. In the active treatment group, 13 (81%) patients experienced worsening of at least 1 GCAE. Neuropsychiatric toxicity had the highest rate of worsening (69%) in the active treatment group. No infections, significant weight change, or cases of glucocorticoid-induced myopathy were observed. In the control group, 7 (64%) patients experienced improvements in one or more GTI domains. Three (27%) patients experienced no change in GCAEs during the study. Neuropsychiatric toxicity had the highest rate of improvement (36%). The worsening of GCAEs was only observed in the blood pressure domain (3 patients).

Beyond V2. The GTI scores continued to worsen at V3 and V4 in the subset of 4 patients who continued low dose prednisone for 6 months and the 3 who continued prednisone for 12 months. However, the only patient in the control group with follow-up data beyond V2 showed worsening GTI scores despite no steroid use. Later, it was found that the patient had undiagnosed clinical anxiety and depression, which falsely elevated her GTI scores (Supplementary Table I).

Correlation between the GTI score and other domains between V1 and V2

GTI-CWS and GTI-AIS with prednisone dose. The relationships and correlations between GTI-AIS and GTI-CWS and cumulative and daily prednisone doses are shown in Table IV and Fig 1.

The Pearson correlation test showed that the GTI-CWS had a statistically significant positive linear correlation with both cumulative ($r = 0.727$, $P = .001$) and average daily ($r = 0.700$, $P = .003$) glucocorticoid doses. GTI-AIS was also shown to have a statistically significant positive linear correlation with both cumulative ($r = 0.665$, $P = .005$) and

Table III. Improvement and worsening of specific GTI domains between V1 and V2

Group	GTI domain	Worsening (%)	Improvement (%)	No change (%)
Active treatment group (N = 16)	BMI	0 (0%)	0 (0%)	16 (100%)
	Glucose tolerance	1 (6%)	0 (0%)	15 (93%)
	Blood pressure	5 (31%)	1 (6%)	10 (63%)
	Lipids	2 (13%)	2 (13%)	12 (75%)
	Steroid myopathy	0 (0%)	0 (0%)	16 (100%)
	Skin toxicity	5 (31%)	0 (0%)	11 (69%)
	Neuropsychiatric toxicity	11 (69%)	2 (13%)	3 (19%)
	Infection	0 (0%)	0 (0%)	16 (100%)
Control group (N = 11)	BMI	0 (0%)	0 (0%)	11 (100%)
	Glucose tolerance	0 (0%)	1 (9%)	10 (91%)
	Blood pressure	3 (27%)	1 (9%)	7 (64%)
	Lipids	0 (0%)	2 (18%)	9 (82%)
	Steroid myopathy	0 (0%)	0 (0%)	11 (100%)
	Skin toxicity	0 (0%)	2 (18%)	9 (82%)
	Neuropsychiatric toxicity	0 (0%)	4 (36%)	7 (64%)
	Infection	0 (0%)	0 (0%)	11 (100%)

BMI, Body mass index; *GTI*, Glucocorticoid Toxicity Index; *V1*, baseline visit; *V2*, follow-up visit at 3 months.

Table IV. Between V1 and V2: Pearson Correlations between GTI-AIS and GTI-CWS with cumulative prednisone dose and daily prednisone dose

GTI score		Cumulative prednisone dose	Average daily prednisone dose
GTI-CWS	Pearson correlation	0.727	0.700
	Significance (2-tailed)	0.001	0.003
GTI-AIS	Pearson correlation	0.665	0.628
	Significance (2-tailed)	0.005	0.009

GTI-AIS, Glucocorticoid Toxicity Index Aggregate Improvement Score; *GTI-CWS*, Glucocorticoid Toxicity Index Cumulative Worsening Score; *V1*, baseline visit; *V2*, follow-up visit at 3 months.

average daily (r = 0.628, P = .003) glucocorticoid doses.

GTI-AIS and GTI-CWS with quality of life indexes (ABQOL and TABQOL). The correlations between GTI-AIS and GTI-CWS and the change in ABQOL and TABQOL between the 2 visits (calculated by the score at V2 minus the score at V1) are shown in Table V. The Pearson correlation and Spearman correlation tests showed no significant correlation between GTI score (GTI-AIS and GTI-CWS) and the changes in the Quality of Life indexes (ABQOL and TABQOL) ($P > .05$).

The difference in GTI score between V1 and V2

The 1-way analysis of variance analysis showed that the GTI-CWS was significantly higher in the active treatment group (42.8 ± 38.7) than in the control group (7.5 ± 14.3) (F [1,25] = 8.301, P = .008). The GTI-AIS was also significantly higher in the active treatment group (37.1 ± 40.0) than in the control group (−13.9 ± 41.7) (F [1,25] = 10.254, P = .004). The difference between the active treatment group and the control group exceeded the minimal clinically important difference of 10 for both GTI-CWS and GTI-AIS.

The Kruskal-Wallis H test showed that GTI-CWS and GTI-AIS scores were significantly higher in the active treatment group than in the control group ($\chi 2$ = 8.218 and 8.392, P = .004 and .004), with a mean rank score of 8.91 and 8.68 for the control group and 17.50 and 17.66 for the active treatment group (Supplementary Table II, available via Mendeley at 10.17632/n6v5n8fms8.1).

DISCUSSION

Patient demographics and GTI scores

Patients receiving a wide range of cumulative prednisone doses (30 to 2318 mg) were enrolled in this study. Neuropsychiatric toxicity, hypertension, and skin toxicity were the most common GCAEs observed in the active treatment group, which is consistent with the literature.[33,34] The GTI captured a significantly higher rate of neuropsychiatric toxicities among the active treatment group than other GCAEs during this study. This is consistent with studies demonstrating that neuropsychiatric symptoms have an acute onset after starting glucocorticoids, which may be observed as early as the first week of treatment.[33,35] The findings are also highly concordant with a study of the GTI in routine clinical practice in the care of patients with severe asthma.[29]

Barrimi et al,[36] also reported that female sex, active pemphigus, and age >40 years were risk factors for glucocorticoid-induced neuropsychiatric

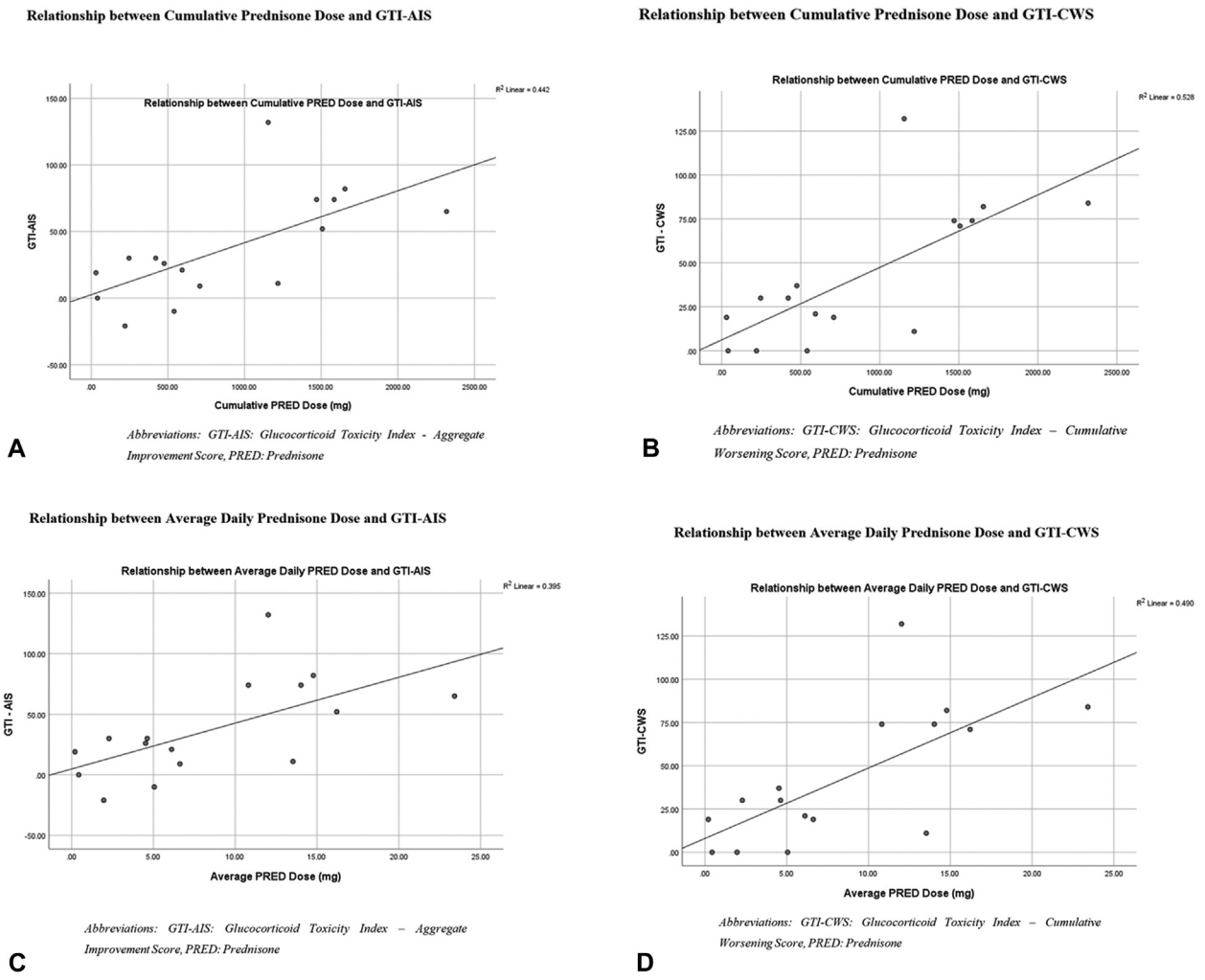

Fig 1. Relationship between GTI and prednisone doses. (**A**) Relationship between cumulative prednisone dose and GTI-AIS; (**B**) Relationship between cumulative prednisone dose and GTI-CWS; (**C**) Relationship between average daily prednisone dose and GTI-AIS; (**D**) Relationship between average daily prednisone dose and GTI-CWS. Both GTI-AIS and GTI-CWS were significantly correlated with pred doses (P <.05).

disorders, which matches the patient demographics of this study. Patients in the control group had a high rate of improvement in neuropsychiatric toxicity, which is also consistent with another study showing that glucocorticoid-induced neuropsychiatric toxicity could be resolved in 90% of the patients shortly after stopping glucocorticoids (average 5.4 days for delirium and 19.3 days for depression, psychosis, and mania).[37]

Glucocorticoid-induced myopathy, weight gain, and infection were not observed in the active treatment group. This could be explained by the nature of glucocorticoid-induced myopathy. Acute glucocorticoid-induced myopathy was mainly observed among patients in the intensive care unit who were immobile, which did not match the patient demographics in this study. The chronic form of glucocorticoid-induced myopathy has slow progression and is usually painless or mildly painful, which may not have been evident during the short study period (average interval between V1 and V2 = 107.4 days).[38,39] Furthermore, myopathy has been more frequently reported with the use of fluorinated glucocorticoids, such as dexamethasone and betamethasone, which were not prescribed to any of the participants in this study.[40]

Similarly, studies have reported that glucocorticoid-induced weight gain was only observed among patients who took prednisone >5 mg/day or equivalent for at least 6 months.[16,41] Weight gain is defined as "increase by >2 but <5 BMI units, to above the upper limit of normal BMI [24.9 kg/m^2]" according to the GTI definition.[28] Moreover, none of the 4 patients who were on steroids for at least 6 months

Table V. Between V1 and V2: Pearson and Spearman correlations between GTI-AIS, GTI-CWS, ABQOL change, and TABQOL change

GTI score		Difference in ABQOL score between V1 and V2	Difference in TABQOL score between V1 and V2
GTI-CWS	Pearson correlation	0.029	0.027
	Significance (2-tailed)	0.894	0.894
	Spearman correlation coefficient	−0.047	−0.110
	Significance (2-tailed)	0.817	0.585
	N	27	27
GTI-AIS	Pearson correlation	−0.037	−0.044
	Significance (2-tailed)	0.854	0.827
	Spearman correlation coefficient	−0.111	−0.165
	Significance (2-tailed)	0.581	0.410
	N	27	27

ABQOL, Autoimmune Bullous Disease Quality of Life; *GTI-AIS*, Glucocorticoid Toxicity Index Aggregate Improvement Score; *GTI-CWS*, Glucocorticoid Toxicity Index Cumulative Worsening Score; *TABQOL*, Treatment of Autoimmune Bullous Disease Quality of Life; *V1*, baseline visit; *V2*, follow-up visit at 3 months.

had an increase in BMI of >2 units. Although glucocorticoid-induced immunosuppression could occur after short-term treatment, only oral or vaginal candidiasis, zoster infections, and grade 3 or higher infections are scored in the GTI infection domain.[28] The relatively short time interval of this study also likely explains the absence of infections observed in this cohort.

Correlation between GTI scores and prednisone dose

This study showed that both GTI scores (GTI-AIS and GTI-CWS) have positive linear correlations with cumulative prednisone dose and average daily prednisone dose. This is consistent with a concurrent prospective study in the United States, which, to our knowledge, was the first study to be published, using GTI among patients with systemic vasculitis, which showed that the cumulative prednisone dose correlated strongly with an increase in the Cumulative Worsening Score.[42] Our results were also consistent with other studies showing that the risk of GCAEs is both dose- and duration-dependent.[16,43,44]

Notably, previous studies showed limited information on the relationship between glucocorticoid doses and the overall burden of GCAEs due to the lack of a comprehensive GCAE quantification tool. In the GTI, each toxicity was assigned a relative weight based on the significance of the toxicity, showing the actual degrees of both worsening and improvement. The significant correlation between GTI-CWS and GTI-AIS and glucocorticoid doses ($P < .05$) observed in our study suggested a linear relationship between the glucocorticoid dose and overall burden of GCAEs, which corroborates the current understanding of the dose-related pattern of GCAEs. Since it is not always feasible to determine glucocorticoid exposure in patients who have been treated at different centers over years, the GTI score can act as a surrogate marker for glucocorticoid-induced toxicity.

Correlation between GTI scores (GTI-AIS, GTI-CWS) and quality of life indexes (ABQOL, TABQOL)

Our results showed no significant correlation between GTI scores and either the ABQOL index or the TABQOL. These results contrast with those from a study of the GTI in patients with severe asthma, in which moderate correlations between the GTI and asthma-related quality of life were observed using both the mini Asthma Quality of Life Questionnaire ($r = -0.50$, $P < .001$) and the St George's Respiratory Questionnaire ($r = 0.42$, $P < .001$).[45,46] The follow-up period in the asthma study was 1 year, which was 4 times longer than that in this study.[29] Further studies of the relationship between GTI scores and quality of life are indicated in larger groups of patients followed for longer periods, with investigations of various patient-reported instruments such as the SF-36, the EuroQoL 5D-5L, and the Hospital Anxiety and Depression Score.[47-49]

Difference in GTI score between groups 1 and 2

The significant difference in the GTI score between the 2 groups suggested that the GTI score was not easily confounded by the underlying disease, residual side effects from previous treatments, or real-life issues. This is important since the GTI could be potentially confounded by long-lasting GCAEs from previous glucocorticoid use and the psychological impact of the disease.[50-54] The ability to differentiate between GCAEs and confounding

factors allows the GTI to demonstrate the severity of GCAEs with a high specificity.

To our knowledge, this is the first prospective study investigating the real-life application of GTI among patients with AIBDs. There were some limitations of the present study, including the single site, limited patient demographic, and small sample size. Furthermore, the COVID-19 pandemic resulted in many patients opting for telehealth consultations, which meant that the components of the GTI that required physician physical examination could not be evaluated. This was the main contributor to patient dropout beyond V2, leading to only 5 patients with a minimum of 6 months follow-up. In conclusion, the results from this study suggest that the GTI is effective in capturing GCAEs among this patient cohort in short-term clinical trials and provide a strong basis for future independent studies investigating the application of GTI among other patient cohorts and the application of GTI in long-term studies. Finally, since many clinical trials are beginning to compare new therapies with traditional steroid-based therapies, it would be useful for these trials to include the GTI as one of their secondary safety outcome measures.

The authors acknowledge the BSc (Med) Honours Program by the University of New South Wales, Sydney, which enabled authors Liang and Zeng to participate in this research study. The authors thank all the staff at the Blistering Disease Centre for their support in the project, patients with AIBDs who kindly participated in this project, and the Australasian Blistering Diseases Foundation for providing great support.

Conflicts of interest

Drs Stone and Murrell are codevelopers of the Glucocorticoid Toxicity Index (GTI). The GTI license is held by the Harvard University, Boston. Authors Liang, Zeng, Sheriff, Wilson, Bilgic, and Feng do not have any conflicts of interest to disclose.

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