acta medica

INVITED REVIEW

Glucocorticoid toxicity index

Sema Kaymaz Tahra[1], Melda Bahap Kara[2]

[1] Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Bahcesehir University, İstanbul, Türkiye.

[2] Department of Clinical Pharmacy, Faculty of Pharmacy, Hacettepe University, Ankara, Türkiye.

Corresponding Author: Sema Kaymaz Tahra ▪ Email: dr.smkaymaz@gmail.com
This manuscript was peer-reviewed by Dr. Emine Sarıyıldız

ABSTRACT

The Glucocorticoid Toxicity Index (GTI) is a glucocorticoid-related toxicity measurement tool which was recently developed by an international expert panel. GTI can be calculated with two different methods: Cumulative Worsening Score (CWS) and Aggregate Improvement Score (AIS). The total glucocorticoid-related toxicity during follow-up can be calculated with CWS. All parameters that develop over time continue to be included, and a decrease in the CWS is not possible. On the contrary, both increase and decrease in toxicity can be assessed in scoring with the AIS method. A drug that reduces glucocorticoid toxicity should be able to reduce the AIS score. Cumulative glucocorticoid dose was found to be associated with higher GTI scores in studies. Although not all glucocorticoid-related toxicities can be covered, parameters that are common, dynamic, and more likely to be glucocorticoid-related are included in GTI. GTI has some limitations such as the possibility of not detecting chronic damage, the difficulty in interpreting the score in the patients who have already sterted the glucocorticoid treatment, some parameters requiring direct interaction with the patient, and difficulty in calculation.

Keywords: glucocorticoid toxicity index, cumulative dose, glucocorticoid toxicity, inflammatory diseases.

Introduction

Glucocorticoids (GCs) has been the mainstay of the treatment in inflammatory diseases. However, the toxicity risk and comorbidities related to GC use remains a concern, especially in long-term and high dose GC treatment. Therefore, additional immunosuppressive (IS) agents aim to reduce the GC dose and thus GC-related adverse events. An effective IS should have a GC sparing effect and reduce GC-related toxicity [1].

To date, GC toxicity has been defined in many different ways. In a study comparing budesonide and prednisolone in Crohn Disease, GC-related main side effects were listed as moon face, acne, swollen ankles, easy bruising, hirsutism, buffalo hump and skin striae [2]. In another study evaluating the effectiveness of low-dose steroids in rheumatoid arthritis (RA), toxicity assessment was based on blood pressure, body mass index (BMI) and DEXA [3]. Weight, blood pressure, glucose levels, depression, osteoporotic fractures, glaucoma, cataract were recorded in every visit for adverse event evaluation in the study which involved early RA patients with very low dose prednisolone treatment [4].

Glucocorticoid Toxicity Index (GTI), which was developed by an international group of experts is an instrument which aims to assess GC related toxicity and the change in toxicity over time [5]. The index was developed and initially validated in 2017 and revised in 2022 (GTI 2.0) defining two analytic approaches: Cumulative Worsening Score (CWS) and Aggregate Improvement Score (AIS). The principles adopted in selecting items were choosing the most frequent items which have the likelihood of occurrence >%5 over 6 months to 3 years duration,

importance of the items for both clinician and the patient, choosing independent items and dynamic items that can reflect the change over time. After the selection of the parameters, the items were voted by experts for weighting [6]. To evaluate changes in glucocorticoid toxicity, measurements should be taken at least at two different time points. The first measurement establishes a baseline GTI score to assess the patient's current condition. The second measurement evaluates any improvement or worsening compared to baseline. These measurements can be performed for both newly initiated GC patients and those with a history of GC use. It is recommended that GTI be applied at 3-month intervals during GC therapy.

Glucocorticoid Toxicity Index Scoring

Cumulative worsening score

CWS was developed to assess the total toxicity over time. Every damage item that develops after the initial visit continues to be counted, even if it is temporary and resolves during follow-up. Therefore, the CWS can increase or remain the same during time, but cannot decrease. An effective GC sparing agent will provide lower CWS compared to the standard therapy. This score ranges between 0 and 439 [6].

Aggregate improvement score

In clinical trials, patients may have been exposed to GCs before the trial and some GC-related toxicity parameters may have developed at initial visit. AIS allows to evaluate the decrease in toxicity which is already present at the baseline visit. If a damage item improves during follow-up, that item provides a corresponding point reduction in the AIS. Therefore, reduction in GC toxicity can be measured with AIS. On the contrary, in case of worsening in the relevant toxicity, the score increases. Corresponding improvement and worsening in the same item cause an equal increase or decrease in the AIS (Table 1). If a drug is effective in reducing GC toxicity, AIS should decrease over time in the treatment arm. This score ranges between -346 and 439 [6].

Glucocorticoid toxicity index studies

The GTI has been used in several real-life studies and clinical trials. In a retrospective study which assessed GTI in patients with ANCA associated vasculitis, GTI score was associated with cumulative GC dose. In this study, the most common toxicity parameter was infections which were mostly mild, such as oral candidiasis and varicella zoster [7].

In a post hoc analysis of the Tocilizumab in Giant Cell Arteritis (GIACTA) trial, baseline GTI scores of the giant cell arteritis (GCA) patients was evaluated. The mean GTI score was 111.3 ± 53.2 in the overall group. The domains that caused the greatest increase in GTI score were blood pressure (24.0%), glucose tolerance (22.6%) and neuropsychiatric effects (15.9% of the overall score). Patients with a relapsing disease had higher GTI scores compared to newly-diagnosed GCA patients (GTI relapsing vs newly-diagnosed: 122.5 vs. 98.9; $P < 0.001$) [8].

In the ADVOCATE trial, the RCT investigating the efficacy and safety of avacopan in ANCA associated vasculitis, GTI was designated as a secondary outcome. CWS and AIS were lower in the avacopan group than prednisone group (CWS avacopan vs prednisone: 39.7 vs 56.6 points), (AIS avacopan vs prednisone: 11.2 vs 23.4 points) at 26th week of the study [9].

GC-related toxicity was assessed in lupus nephritis patients using GTI, in a retrospective study. Higher cumulative GC dose was associated with higher CWS and AIS in lupus nephritis patients at 5 years of follow-up [10].

In a Turkish Takayasu arteritis cohort, mean baseline GTI score was 51.5 ± 52.4 and GTI score was correlated with age ($r=0.32$, $p=0.014$), cumulative GC dose ($r=0.34$, $p=0.017$) and the duration of the GC exposure ($r=0.27$, $p=0.041$) [11].

In a study conducted in a rheumatology outpatient clinic, the median (min-max) GTI-AIS score at 6 months was 29 (-42 to 190) in the GC-naive patients and 0 (-82 to 40) in the GC-experienced patients (GC treatment for ≤2 years). Higher cumulative GC dose was associated with higher GTI scores in both groups ($p< 0.001$). In addition, in the GC-naive group, patients with vasculitis had higher GTI scores than inflammatory arthritis ($p< 0.001$) [12].

Table 1. Glucocorticoid toxicity index 2.0 domains and weights of the items [6]

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	
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 3%)	-29
No significant change in BMD (+/- 3%)	0
Decrease in BMD (loss of more than 3%)	29
6. Steroid 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
None to Moderate weakness (with functional limitation)	63
7. Skin steroid-related Toxicity	
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
Increase in Skin Toxicity - None to Moderate	26
8. Neuropsychiatric - steroid related symptoms	
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	
Increase in NP Toxicity - None to Mild	11
Increase in NP Toxicity - Mild to Moderate	63
Increase in NP Toxicity - None to Moderate	71
9. Infection	
No infection	0
Oral or vaginal candidiasis or non-complicated zoster (<Grade3)	19
Grade 3, 4, or 5 infection	93

Limitations and Strengths of Glucocorticoid Toxicity Index

GTI has several weaknesses and limitations as well as strengths. Glucocorticoids have approximately 70 toxicities. Not all of these toxicities are included in the GTI. Toxicities that were common, easy to measure, are of a dynamic nature that may show improvement or worsening of toxicity over time and are more likely to be due to the effect of GC treatment were included in the GTI. Toxicities that were difficult to separate from co-morbidities or the effects of the underlying disease were also excluded. For example, toxicities such as atherosclerosis, myocardial infarction, and stroke were not included in the GTI because all these toxicities are often confounded with either co-morbidities (e.g. smoking) or the effects of the disease under treatment (e.g. systemic lupus erythematosus). Additionally, some GC toxicities occur acutely (within hours to days), others subacutely (weeks to months), and others chronically (months to years). Chronic toxicity may not be captured during GTI assessment [6].

Another limitation is that the toxicities may not be attributed to glucocorticoids alone. Drugs frequently used with GCs may have a synergistic effect with certain GC toxicities. For example, immunomodulatory agents may increase the risk of infection, and this effect may be difficult to distinguish from GCs. Patients may have comorbidities (e.g. obesity, hypertension, etc.) that precede GC treatment and vary across patient populations and disease states [6,13].

Baseline GTI scoring is different from the scoring performed at later follow-up. In the baseline GTI

score, the minimum score is 0 and assesses the patient's current condition. However, subsequent scoring may be negative or positive according to the improvement or worsening of GC toxicity compared to baseline. Therefore, in order to assess the GTI, it is first necessary to calculate the patient's baseline GTI score [5,13]. In patients who have already started glucocorticoid therapy, baseline GTI is calculated at the time point at which GTI is first assessed, not at the time glucocorticoid is first started. It is therefore difficult to interpret the GTI in patients who have already started glucocorticoid therapy and to relate it to cumulative glucocorticoid exposure. On the contrary, it would be more rational to assess the GTI from the time glucocorticoid therapy is initiated.

Several domains in the GTI (such as skin toxicity or neuropsychiatric effects) require direct patient interaction. These domains require careful objective consideration of GC toxicity. Assessing by the same person ensures standardization in these domains and provides more accurate results [6,13].

Finally, GTI scores are difficult to calculate. A digital platform has been developed to facilitate the use and scoring of the GTI but there is a need for a charge for use. The application records the data from the patient visit required for GTI and analyses, tabulates, and scores it in 2-3 minutes. Thus, it provides accurate results in a short time by eliminating the user error. The manual calculation on the other hand can be complicated and lead to errors during calculation and is time-consuming [6,13].

Author contribution

Study conception and design: SKT, MBK; draft manuscript preparation: SKT, MBK. All authors reviewed the results and approved the final version of the manuscript.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] McDonough AK, Curtis JR, Saag KG. The epidemiology of glucocorticoid-associated adverse events. Curr Opin Rheumatol 2008;20(2):131-7. https://doi.org/10.1097/BOR.0b013e3282f51031

[2] Rutgeerts P, Löfberg R, Malchow H, et al. A comparison of budesonide with prednisolone for active Crohn's disease. N Engl J Med 1994;331(13):842-5. https://doi.org/10.1056/NEJM199409293311304

[3] Capell HA, Madhok R, Hunter JA, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: Results of a randomised controlled trial. Ann Rheum Dis 2004;63(7):797-803. https://doi.org/10.1136/ard.2003.014050

[4] Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: A multicenter, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52(11):3371-80. https://doi.org/10.1002/art.21421

[5] Miloslavsky EM, Naden RP, Bijlsma JWJ, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis 2017;76(3):543-6. https://doi.org/10.1136/annrheumdis-2016-210002

[6] Stone JH, McDowell PJ, Jayne DRW, et al. The glucocorticoid toxicity index: Measuring change in glucocorticoid toxicity over time. Semin Arthritis Rheum 2022;55:152010. https://doi.org/10.1016/j.semarthrit.2022.152010

[7] Floyd L, Morris A, Joshi M, Dhaygude A. Glucocorticoid Therapy in ANCA Vasculitis: Using the Glucocorticoid Toxicity Index as an Outcome Measure. Kidney360 2021;2(6):1002-10. https://doi.org/10.34067/KID.0000502021

[8] Patel NJ, Fu X, Zhang Y, Stone JH. Baseline Glucocorticoid-Related Toxicity Scores in Giant Cell Arteritis: A Post Hoc Analysis of the GiACTA Trial. ACR Open Rheumatol 2023;5(1):51-8. https://doi.org/10.1002/acr2.11520

[9] Jayne DRW, Merkel PA, Schall TJ, Bekker P, ADVOCATE Study Group. Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med 2021;384(7):599-609. https://doi.org/10.1056/NEJMoa2023386

[10] Usiskin IM, Kyttaris VC. Estimating glucocorticoid-related morbidity in lupus nephritis using the glucocorticoid toxicity index. Lupus 2023;32(4):565-70. https://doi.org/10.1177/09612033231160969

[11] Kaymaz Tahra S, Alibaz Oner F, Direskeneli H. Glucocorticoid related damage assessed with glucocorticoid toxicity index (GTI) in patients with Takayasu's arteritis. 20th International Vasculitis & ANCA Workshop, 2022.

[12] Bahap-Kara M, Sariyildiz E, Zengin HY, Karadag O, Bayraktar-Ekincioglu A. Prospective Assessment of Glucocorticoid Toxicity in Rheumatology Practice: A Focus on the Glucocorticoid Toxicity Index. Rheumatology (Oxford) 2024;keae288. https://doi.org/10.1093/rheumatology/keae288

[13] McDowell PJ, Stone JH, Zhang Y, et al. Quantification of Glucocorticoid-Associated Morbidity in Severe Asthma Using the Glucocorticoid Toxicity Index. J Allergy Clin Immunol Pract 2021;9(1):365-72. https://doi.org/10.1016/j.jaip.2020.08.032