Assessing glucocorticoid toxicity: are the measures sensitive enough?

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The Glucocorticoid Toxicity Index (GTI) is a composite instrument designed to capture change in glucocorticoid-related morbidity over time.[1] It was developed through consensus methods and multi-criteria decisions among 19 medical specialists, with relative domain weights decided via clinician consensus.[2] The GTI has now been used in more than 45 studies, including 12 phase 3 clinical trials.[1]

The GTI comprises eight domains: body mass index, blood pressure, glucose tolerance, lipid metabolism, glucocorticoid myopathy, skin toxicity, neuropsychiatric effects and infections. Two overall scores are calculated: the cumulative worsening score (CWS), which includes transient and permanent GC toxicity from baseline to specific time points, and the Aggregate Improvement Score (AIS), which accounts for improvement as well as worsening GC-toxicity.[1]

In *The Lancet Rheumatology,* Naomi Patel and colleagues[3] present an analysis of domain scores of the GTI using data from the phase 3 ADVOCATE trial.[4] In a clinical trial context where the GTI is used to produce repeated measures to demonstrate differences between (and within) groups of patients taking different dosages of glucocorticoids, and to measure the impact of steroid sparing agents, it is expected to have a high level of measurement validity and reliability.

ADVOCATE is a randomised controlled trial assessing whether avacopan could replace a standard glucocorticoid tapering regimen in patients with anti-neutrophilic cytoplasmic autoantigen (ANCA)-associated vasculitis; the primary outcomes of the trial were clinical remission and sustained remission at week 26.[4] In ADVOCATE, a double-dummy design was used in which patients received avacopan (30 mg twice daily) or matching placebo for 52 weeks, and prednisone or a matched placebo on a tapering schedule for the first 20 weeks. The GTI was completed for all 331 trial participants, and total CWS and AIS were included as secondary trial outcomes.[4] Patients in the avacopan group received approximately one third of the prednisolone equivalent of glucocorticoids (mean 1,073 mg; median 400 mg) compared with the standard glucocorticoid taper group (mean 3,192 mg; median 2,847 mg).[3]

A key consideration in outcome measurement is discriminant (known groups) validity, whereby scores are compared between groups that are expected to differ significantly.[5] In the study by Patel and colleagues,[3] which included data from 307 of the participants in ADVOCATE, the domains that demonstrated a significant between-group difference (favouring the avacopan group) at week 13 were glucose tolerance, body mass index, lipids, and skin toxicity (for both the CWS and AIS); differences remained significant at week 26 for all except the glucose tolerance domain. No differences were seen in the blood pressure, glucocorticoid myopathy, neuropsychiatric, or infection domains.

When analysed by sex, only one domain (body mass index) showed a significant between groups difference in CWS and AIS scores for females at week 26. In males, CWS and AIS scores demonstrated a significant between groups difference in two domains (lipids, skin toxicity) at 26 weeks.

Overall, there was no difference between the avacopan and standard glucocorticoid taper group in four (50%) of the eight domain scores overall. In females there was no difference in seven (87.5%) of the domain scores. The lack of difference in these domains might be because there was not a great enough

difference in the two arms in terms of glucocorticoid dose, which was 3-fold in this trial, or perhaps those domains do not truly differentiate between higher and lower doses of glucocorticoids.

In the development of the GTI, face/content validity (the degree to which the tool accurately reflects the topics of importance, relevance, and acceptability to user groups) was tested with clinicians but not with patients. A combination of face/content validity, excellent internal consistency, and test-retest reliability is a good indicator that a tool will be sensitive to change (i.e., responsive) when used in a longitudinal study, following an intervention.[2]

The glucocorticoid myopathy domain requires clinicians to "assess muscle strength and impact on day-to-day function," whereas the neuropsychiatric domain requires the clinician to "assess the degree to which patient's lives and day to day functioning are impacted by insomnia, depression, and steroid-induced violence".[1] These complex concepts might be better captured directly from the patients themselves. Published literature on patients' perspectives was considered during the development of the GTI, but no patients were involved in the development of GTI items, domains, or weightings.[2]

To fill this gap, a dual-measure approach may be required, with the GTI capturing the clinician perspective of glucocorticoid impact, plus a novel patient reported outcome measure (developed and validated with patient input) to capture patient's perspective of the impact of glucocorticoids on health-related quality of life.

We commend the developers of the GTI for painstaking work in developing this important measure of glucocorticoid impact. We would suggest that further validity and reliability testing for domain scores and total CWS and AIS scores is indicated to ensure that the GTI is psychometrically robust for use as a repeated measure in future clinical trials, which requires a (demonstrated) high level of precision.

Conflict of interest.

MN, JD and JR are all inventors of a treatment focused Patient Reported Outcome to measure the impact of glucocorticoids in patients with rheumatic diseases (the Steroid PRO) and have received Steroid PRO research grant from Vifor Pharma; GCA PRO funding from NIHR RfPB; Steroid PRO cross-condition validation study research grant from Sanofi.

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