The New and Evolving Science of Polymyalgia Rheumatica

Glucocorticoids in Rheumatic Disorders: Understanding and Assessing Toxicity With the Glucocorticoid Toxicity Index

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Dear Colleagues,

This is a very exciting time in the field of polymyalgia rheumatica (PMR). With an increased focus on basic and clinical research regarding the pathogenesis of PMR, we now understand more about this disease than ever before. We know that cytokines play many key roles in the inflammation that drives PMR. One such example is interleukin-6 (IL-6), a multifunctional cytokine that contributes to local and systemic inflammation in patients with PMR.

Sanofi and Regeneron Pharmaceuticals are excited to bring you additional educational materials describing some of the fundamental aspects of PMR through a series of scientific monographs entitled *The New and Evolving Science of Polymyalgia Rheumatica*. In the first installment, we discussed the pathophysiology of PMR and the role IL-6 plays as a key factor in the disease. In this second installment, we will focus on how glucocorticoids have shaped the treatment landscape in a range of rheumatic disease, and how we can refine their use through the Glucocorticoid Toxicity Index (GTI) and its related clinical outcome assessments.

We hope you find this installment informative and engaging.

Sincerely,

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I. Introduction

Glucocorticoids in the management of rheumatic diseases

Glucocorticoids (GC) are widely used in the management of rheumatic diseases and are the most frequently used class of immunosuppressive drugs in the world.[1] In the 1930s, the biochemist Edward Kendall isolated compound E, now known as cortisone, from bovine adrenal glands.[2] A milestone in glucocorticoid use occurred in September 1948 when Philip Hench and colleagues used compound E for the first time to successfully treat 14 patients with rheumatoid arthritis (RA).[3] This success paved the way for the approval of prednisone and prednisolone in 1955 as the first synthetic glucocorticoids. Shortly thereafter, methylprednisolone and dexamethasone also gained approval (Figure 1).[1] Since then, glucocorticoids have played a crucial part in the treatment of many dermatologic, pulmonary, ophthalmologic, hematologic, and gastrointestinal disorders, as well as multiple rheumatic diseases.[1,4,5]

However, even in the years before approval, it was becoming clear that GC use was associated with adverse effects, especially when used long term.[1] For this reason, while GCs are still widely used to treat a range of diseases, guidelines for their use are often re-evaluated and updated as we learn more about GC-related adverse events (Figure 1).[1] As an example, the most recent EULAR guidelines for RA were updated in 2022 and recommend that short-term glucocorticoid treatment should be tapered and stopped as rapidly as possible.[6]

In the context of normal physiologic functioning, glucocorticoids are involved predominantly in metabolism of carbohydrate, protein and fat. They also have anti-inflammatory and immunosuppressive properties, as well as antiproliferative and vasoconstrictive effects (Table 1).[4] This makes them effective in mitigating symptoms related to heightened immune activity and suppressing disease progression.[5] Yet the use of glucocorticoids is linked to a variety of adverse effects affecting many major organ systems[1]; therefore, when administering glucocorticoid therapy, the benefits should always be weighed against the risks.[1]

Table 1: Primary effects of glucocorticoids[4]

Anti-inflammatory	GCs can inhibit inflammation by blocking the action of inflammatory mediators (transrepression) or by inducing anti-inflammatory mediators (transactivation)
Immunosuppressive	By directly affecting T lymphocytes, GCs can suppress delayed hypersensitivity reactions
Antiproliferative	GCs exert an antiproliferative effect by inhibiting DNA synthesis and turnover of epidermal cells
Vasoconstrictive	GCs inhibit the action of vasodilatory mediators such as histamine

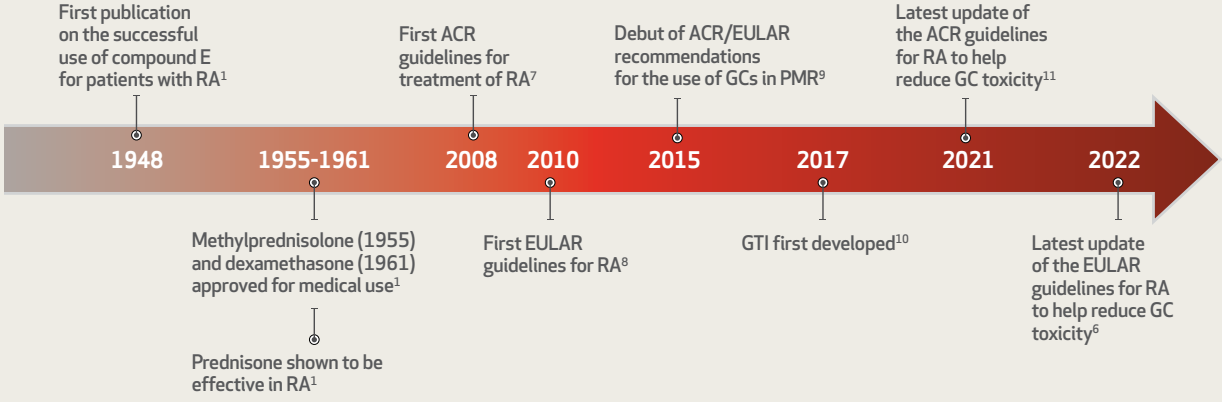

Figure 1: Guidelines for the utilization of glucocorticoids in rheumatologic diseases such as rheumatoid arthritis (RA) and polymyalgia rheumatica (PMR) are evolving and undergoing regular updates as more information about GC-related adverse events becomes available.[1,6-11]

Glucocorticoids offer effective symptomatic relief in various inflammatory and autoimmune diseases, making them valuable for short-term interventions. However, extended use of glucocorticoids can cause severe adverse events that often may lead to comorbidities, and therefore a careful risk-benefit assessment must be considered when using GCs long term.[12] Traditionally, GCs have been widely used in RA to rapidly alleviate joint pain, swelling, and morning stiffness.[13,14] They are particularly effective when initiating disease-modifying antirheumatic drugs (DMARDs), since GCs provide immediate relief while waiting for the slower-acting DMARDs to take effect.[15] Glucocorticoids are also beneficial in other forms of rheumatic diseases, such as polymyalgia rheumatica (PMR), giant cell arteritis (GCA), systemic vasculitis, Sjögren's syndrome, and systemic lupus erythematosus (SLE) (Table 2).[1,9,16,17] The potential for minimizing glucocorticoid toxicity while preserving or even enhancing therapeutic efficacy is now within reach for clinicians, thanks to the advent of novel immunomodulatory agents. This underscores the ongoing shift in the field towards exploration and development of innovative treatment approaches.[18]

Table 2: Use of glucocorticoids in selected rheumatic diseases[9,15-17,19-22]

Rheumatic Disease	Symptoms	Glucocorticoid Use	Dose and Duration
Rheumatoid arthritis[15]	Joint pain, swelling, stiffness	GCs are used to reduce inflammation, control symptoms, and bridge therapy during DMARD initiation	Typically, short-term use during acute flare-ups; long-term use is minimized due to potential side effects. The duration of use is often determined based on the individual patient's response and the need for other disease-modifying medications such as DMARDs
Polymyalgia rheumatica[9]	Pain and stiffness in the shoulders, neck, and hip girdles[19]	GCs are the first line of treatment and may rapidly alleviate symptoms, but many patients may need to stay on GCs for extended periods of time	Typically, a higher dose initially, gradually tapered over weeks to months; long-term use has been necessary due to a historic lack of steroid-sparing alternative treatments
GCA[20]	Persistent localized headache, often in the temporal area, jaw claudication, visual symptoms/visual loss	High-dose GC therapy (40-60 mg) is the first-line therapy, which should be initiated immediately	Treatment with high-dose GC (40-60 mg/daily) leads to reduction of symptoms; once disease is controlled, gradual taper over a few months to a year is recommended. Long-term use has been necessary due to a historic lack of steroid-sparing alternative treatments.
Systemic vasculitis[17]	Inflammation of blood vessels	GCs are used in combination with other immunosuppressive agents to avoid GC-related adverse events	Initial high doses for induction, followed by gradual tapering over several months to years, depending on disease control. Long-term use has been necessary due to a historic lack of steroid-sparing alternative treatments.
Sjögren's syndrome[21]	Dry eyes, dry mouth, fatigue	GCs may be used topically as well as systemically to alleviate symptoms	Use of GC at the minimum dose and length of time necessary to control active systemic disease, only when required
Systemic lupus erythematosus (SLE)[16]	Joint pain, skin rashes, kidney involvement, fatigue, etc[22]	GCs are used at the lowest possible dose to control inflammation, manage organ involvement, and suppress disease activity	Variable, with the goal of minimizing long-term use; treatment duration is often individualized based on disease activity and response to other medications. For maintenance treatment, dosage should be decreased to a dose of ≤5 mg/day (prednisone equivalent), and, whenever feasible, GCs should be discontinued altogether.

Mechanism of action of glucocorticoids

The physiologic and pharmacologic activity of glucocorticoids is mediated by the glucocorticoid receptor (GR).[23] Glucocorticoid-activated GR can regulate gene expression in 3 ways: (a) binding to DNA directly, (b) tethering itself to other DNA-bound transcription factors, or (c) both. In addition, GR can also signal in a nongenomic manner through alterations in the activity of various kinases.[23]

Most of the anti-inflammatory and immunosuppressive actions of GCs are attributable to their interaction with the cytosolic GC receptor, which translocates to the nucleus upon GC binding. The GC receptor acts in both inflammatory leukocytes and in structural cells, such as the epithelium, to alter gene transcription. The impact of this is both the upregulation of anti-inflammatory genes and the downregulation of inflammatory genes. Consequently, GCs affect the downstream production of cell adhesion molecules, as well as pro-inflammatory cytokines, chemokines, and key enzymes involved in the initiation and/or maintenance of the host inflammatory response.[4]

Glucocorticoids can suppress inflammation by multiple mechanisms at both the cellular and transcriptional level, affecting both the innate and the adaptive immune system.[24] Glucocorticoids activate the innate immune system via receptors expressed on macrophages and dendritic cells, among others. These cells stimulate the production of cytokines and chemokines and ultimately activate the adaptive immune system, mediated by T and B lymphocytes.[24] At the cellular level, they can induce apoptosis of immune cells to reduce inflammation, such as T lymphocytes, neutrophils, basophils, and eosinophils.[24] At the transcriptional level, glucocorticoids exert their therapeutic effects by modulating gene expression and suppressing the production of pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNFα).

Glucocorticoids also inhibit the migration of inflammatory cells, including neutrophils and monocytes, to sites of inflammation.[24] In addition to these hematopoietic cells, glucocorticoids also act on stromal cells such as synovial fibroblasts, chondrocytes, and osteoblasts to reduce signaling via cytokines such as IL-6 and TNF and dampen the immune response (Figure 2).[25] These inflammation effects, however, are not long term. For example, in polymyalgia rheumatica (PMR), glucocorticoids can rapidly suppress IL-6 production and provide immediate disease control. However, since they do not address the underlying mechanism of IL-6 production, IL-6 levels may become elevated again after a few months of treatment, leading to relapse.[26] While chronic GC therapy could lead to persistent IL-6 suppression, it is also associated with the adverse effects described above.[12,27] In line with findings from other rheumatic diseases, GCs should generally not be considered a long-term solution to manage chronic inflammation.[15,16,21]

Glucocorticoid dosing

The dose, duration, and administration of glucocorticoids depend on the diagnosis, indications for glucocorticoid therapy, and the goal of treatment.[5] For some rheumatic diseases, such as myositis, systemic vasculitis, and PMR, glucocorticoids remain cornerstones of treatment. For others, they are employed primarily as adjunctive therapy (albeit often in high doses such as in systemic lupus erythematosus).[5] Some conditions now require relatively little GC therapy, assuming access to effective GC-sparing therapies.[18]

High doses are usually used for systemic vasculitis as induction therapy or for flares, or in other occurrences such as gout attacks. Low-dose glucocorticoid therapy is effective for RA in relieving symptoms in the short and medium term. Glucocorticoids can also be used locally in the form of intraarticular injections in persistent non-infectious arthritis.[5]

The therapeutic benefits of glucocorticoids span from alleviating pain in arthritic conditions to exerting disease-modifying effects in early rheumatoid arthritis, as well as demonstrating potent immunosuppressive actions in vasculitis and systemic lupus erythematosus.[5]

Many factors must be taken into consideration when deciding on GC dosages, including different GC preparations, potential drug interactions with concurrent administered agents, underlying conditions, patient comorbidities, and an individual's response to GC treatment.[5] In order to optimize patient outcomes, treatment plans involving GCs should be individualized, taking into account the specific disease, patient characteristics, and overall treatment goals to optimize patient outcomes.[5] Thus, determining the appropriate dosage of GCs for a child with asthma involves a different set of considerations compared to those used for an elderly individual with PMR.

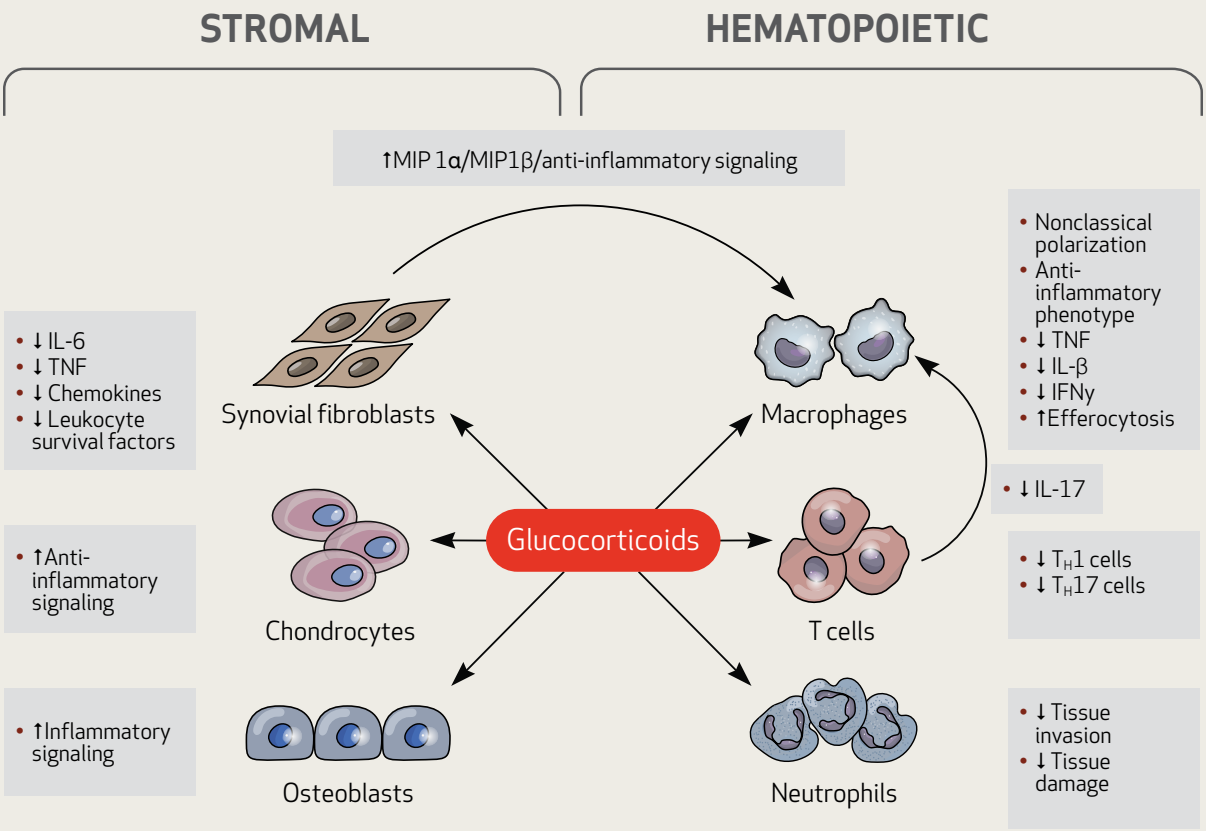

Figure 2: Glucocorticoids act on cells of the hematopoietic and stromal lineages to exert a multifaceted anti-inflammatory effect.[25]

II. Challenges in Using Glucocorticoids for Disease Management

Although GCs offer significant therapeutic benefits, their long-term use is associated with adverse effects, including osteoporosis, diabetes, weight gain, cataracts, and increased susceptibility to infections (Figure 3, Table 3).[5] Therefore, a goal of treatment in rheumatic diseases is to minimize the dose and duration of glucocorticoid therapy while achieving optimal disease control.[5] This is sometimes attempted through a combination of GCs with other immunosuppressive medications, such as DMARDs or biologic agents to reduce the reliance on GCs over time.[5] The use of GCs should be carefully monitored from the start of treatment to ensure that the benefits of GCs are balanced with the potential risks associated with long-term therapy.[5]

Monitoring GC toxicity

Traditionally, GC toxicity has been managed by individual monitoring of various organ systems, which is cumbersome and does not provide standardized outcomes (Table 3).[28] Thus, there has been a significant need for a convenient and dependable tool to measure glucocorticoid toxicity for the effective management of a spectrum of diseases relying on GCs for treatment.[18]

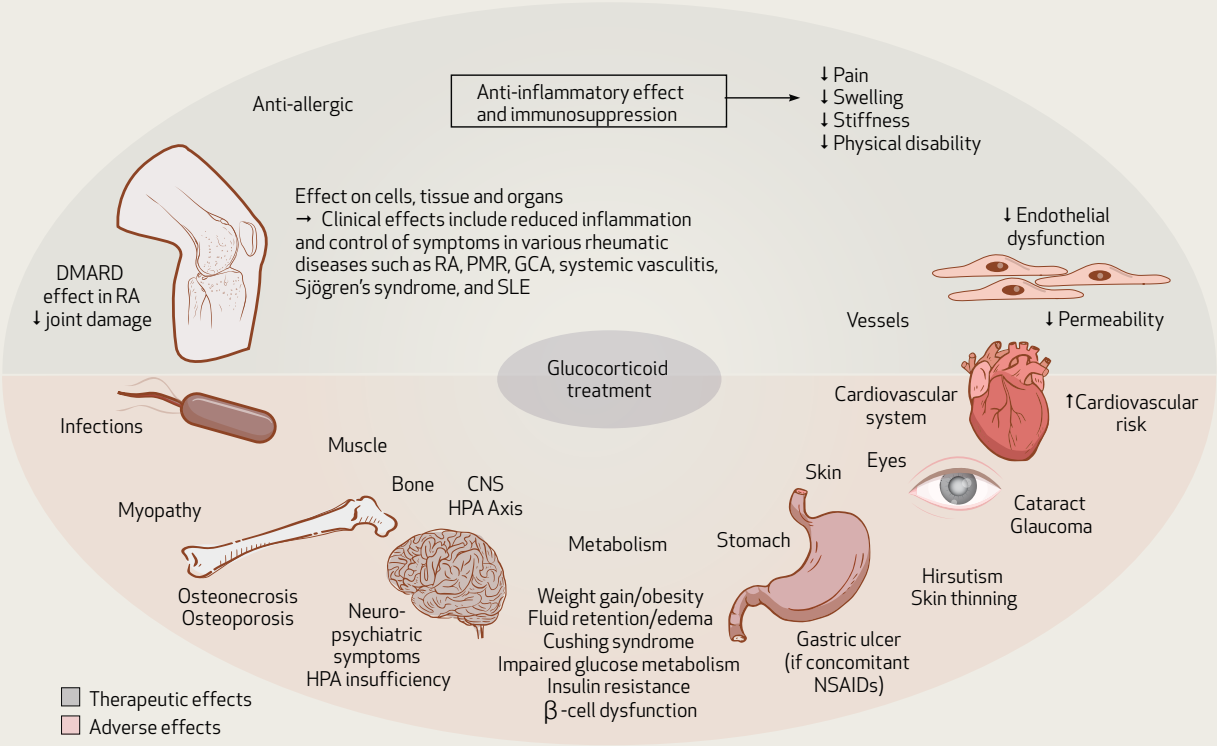

Figure 3: Glucocorticoids can exert positive effects (gray) which could help achieve disease control, but they also can lead to negative effects (pink) that manifest as adverse events of glucocorticoid treatment.[5]

Table 3: Conventional approaches to assessing glucocorticoid toxicity: individual organ system monitoring without unified readout[28]

GC-related adverse effects: organ system	Effects	Risk factors	Possible monitoring test or intervention
Skin	• Thinning • Bruising • Impaired healing	• Age (older) • Comorbidities (diabetes or diseases where skin integrity is compromised) • High cumulative dose of GC	• Confocal laser microscopy • Ultrasound • Evaporimetry • Optical coherence tomography • Dermaphot® imaging
Gastrointestinal	• Ulceration • Impaired healing	• Age (older) • Concomitant treatment with NSAIDs • GC dose (high daily and cumulative)	• Hemoglobin levels • Prophylactic gastroprotective treatment (if clinically indicated)
Eye	• Cataract • Glaucoma	• Age (older) • GC dose (high cumulative)	• Eye examination including tonometry
Skeletal muscle	• Myopathy	• Age (older) • Not physically active • GC dose (high cumulative)	• Muscle strength testing • Muscle biopsy • CT/MRI scan for muscle cross-sectional area • Patient questioning
Bone	• Osteoporosis • Osteonecrosis	• Age (older)	• Bone mineral density • Bone protection therapy
Adrenal	• Suppression of endogenous GC production	• Basal cortisol levels <386 nmol/L • Total GC dose >8.5 g • GC treatment duration >19 months	• Slow reduction in GC dose • ACTH stimulation test
Metabolic	• Diabetes • Weight gain • Hyperglycemia	• Age (older) • Cumulative dose of GC ≥1.8 g • Sex (female) • Family history	• Blood glucose test (while fasting) • Glucose tolerance test (oral) • Weight and height
Cardiovascular disease	• Accelerated atherosclerosis • Hypertension • Hypercholesterolemia	• High cumulative GC dose • Hypertension • CVD risk factors before GC therapy	• Hypertension screening before GC treatment • Blood pressure • Lipid profile
Neuropsychiatric	• Anxiety • Depression • Psychosis	• Female • Alcoholism • Family history of depression • GC dose (high)	• Patient questionnaires • Pharmacotherapy
Infection	• Lymphopenia • Impaired neutrophil function • Hypogammaglobulinemia	• Concomitant immunosuppressive treatments	• Lower threshold for suspecting and investigating sepsis

There are several challenges, including those associated with measurement and disease activity, when it comes to assessing GC toxicity as shown in Figure 4.[18]

Thus, despite the well-recognized phenomenon of GC toxicity, there has been no practical and reliable means of calculating whether GC toxicity has worsened or improved and to what degree such changes have occurred.[18] This led to the development of the Glucocorticoid Toxicity Index (GTI) score, whose purpose is to measure change in GC toxicity between 2 points in time.[18] The GTI score can quantify both worsening and improvement in GC toxicity.[18]

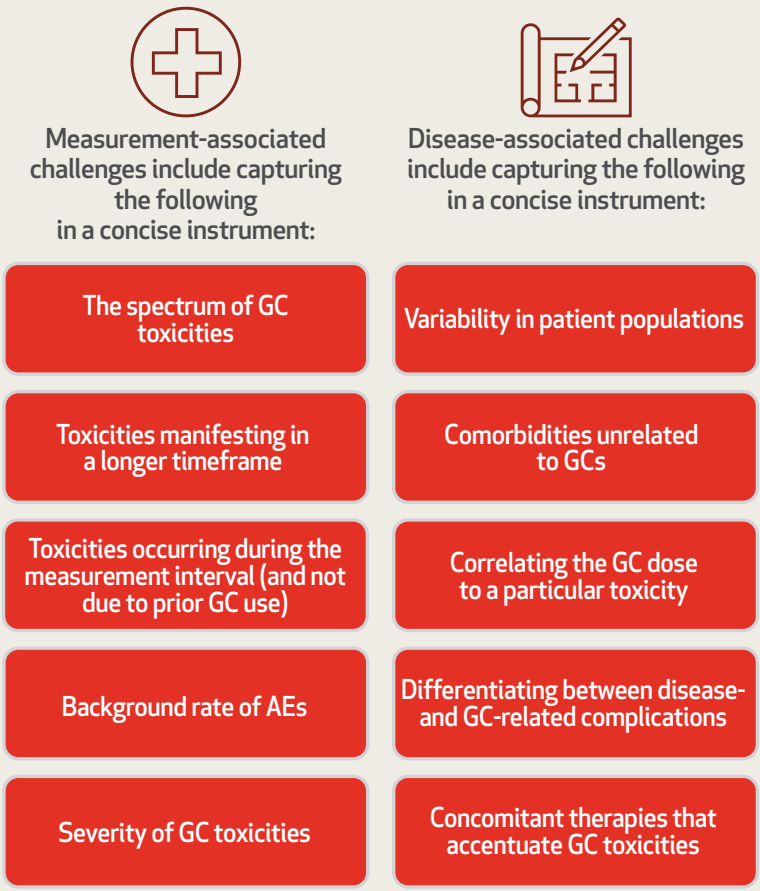

Figure 4: Capturing glucocorticoid toxicity in a concise and user-friendly tool presents measurement- and disease-associated challenges.[18]

III. Development of the Glucocorticoid Toxicity Index (GTI) and GTI-Metabolic Domains (GTI-MD)

The GTI was developed by a group of 17 international physician-investigators from the United States, Europe, Canada, Australia, and New Zealand. The group had expertise across the spectrum of inflammatory disease, representing 11 different subspecialties including rheumatology, pulmonology, nephrology, neurology, ophthalmology, dermatology, infectious disease, and psychiatry.[18] The GTI is a composite of nine weighted domains: body mass index, blood pressure, glucose metabolism, lipid metabolism, bone mineral density, GC-induced myopathy, skin toxicity, neuropsychiatric effects, and infection (Table 5).[18]

The GTI has now been licensed for use in nearly 30 indications, across a range of diseases (Figure 5).[18] A pediatric version of the instrument, developed by a separate second group of investigators, has been licensed for use in Kawasaki's disease, pediatric lupus, pediatric lupus nephritis, and juvenile idiopathic arthritis.[29]

The algorithms for calculating the GTI and its sibling clinical outcome assessments of GC toxicity are accessed via a digital platform that complies with regulatory standards and ensures uniformity and rigor in the assessment of GC toxicity.[30] The clinical team records the relevant clinical observations and laboratory values in the case report form and the platform calculates the scores automatically.[30]

An abridged version of the instrument known as the GTI-Metabolic Domains (GTI-MD) is described further below.

Table 4: Key Terms

GTI: Glucocorticoid Toxicity Index
GTI-MD: Glucocorticoid Toxicity Index – Metabolic Domains
CWS: Cumulative Worsening Score
AIS: Aggregate Improvement Score

Table 5: The domains of GTI examined through simple clinical measures or laboratory tests[18]

Domain	Description
Body mass index	Height and weight
Blood pressure*	Systolic and diastolic blood pressure
Glucose metabolism*	Hemoglobin A1c
Lipid metabolism*	Low-density lipoprotein
Bone mineral density	DEXA (dual X-ray absorptiometry) scan
Glucocorticoid myopathy	Testing for proximal muscle weakness through physical examination
Skin toxicity	Physical examination
Neuropsychiatric effects	Interview with patient
Infection	Reporting of adverse event

*Increases and decreases in medications for hypertension, glucose metabolism, and hyperlipidemia are considered in the GTI scoring algorithm.

The domains of the GTI score that were chosen for inclusion share 4 main attributes[18]:

1. Frequency of occurrence (i.e., likelihood of occurrence greater than 5% over the course of 6 months to 3 years)
2. Importance to both providers and patients
3. Independence from other items
4. Dynamic in nature (i.e., they can change by either improving or getting worse over time with varying GC dosing)

Toxicities were excluded if they were difficult to separate from either concurrent comorbidities or effects of the underlying disease. For example, toxicities excluded from the GTI such as atherosclerosis, myocardial infarction, and stroke are frequently confounded by either comorbid conditions (e.g., smoking) or the effects of the disease under treatment (eg, systemic lupus erythematosus). Toxicities that cannot be evaluated objectively without a requirement for invasive testing or subspecialty consultation are also excluded.[18]

The GTI is a clinician-facing instrument that measures change in GC toxicity.[18] In order to calculate a GTI score, measurements taken at two timepoints—e.g., baseline and 3, 6, or 12 months—are required. Serial measurements at several timepoints, such as baseline, 6 months, and 12 months, are also possible.

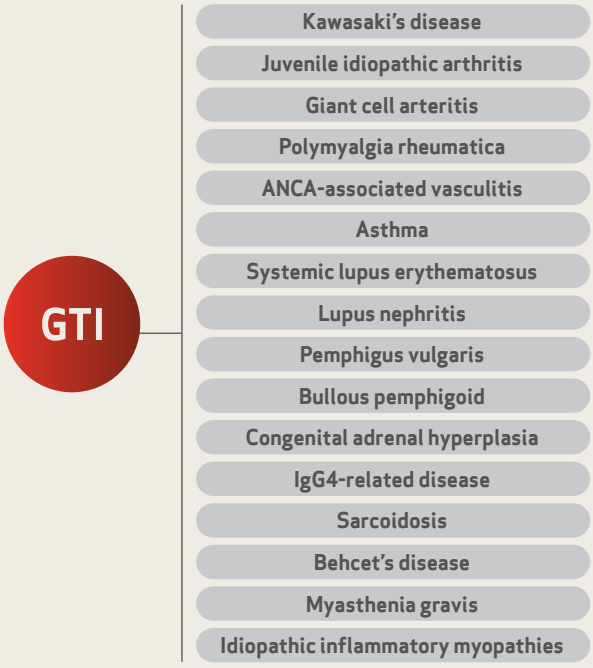

Figure 5: The GTI has been used to measure glucocorticoid toxicity in a wide range of diseases.[18]

The data calculated by the GTI platform are presented as two separate measures known as Cumulative Worsening Score (CWS) and Aggregate Improvement Score (AIS). Together they capture the nuances of GC toxicity worsening and improvement[18]:

- Cumulative Worsening Score (CWS): The CWS is an assessment of the total GC toxicity that has occurred since baseline. New toxicities that occur are added to the CWS. Toxicities that resolve remain in the score so that the CWS is a running total of any toxicity that appears during the period of observation.[18]
- Aggregate Improvement Score (AIS): The AIS is designed to demonstrate whether new therapies are effective at lowering any baseline GC toxicity over the course of treatment. Therefore, toxicities that resolve during follow-up are dropped from the AIS.[18]

Higher GTI scores indicate higher toxicity (worsening); lower scores indicate lower toxicity (improvement). If an investigational treatment is effective in lowering steroid toxicity, GTI scores will be lower in the investigational arm of the trial over time.[18,31] The minimum clinically important difference (MCID) for GTI scores is ≥10 points.[18]

Validation procedures for the GTI were conducted over several years. The Scientific Committee assessed the GTI for clarity, format, visual design, organization, and navigation. They also assessed 15 cases of real-world patients who had experienced changes in GC toxicity during treatment.[18]

Subsequently, GTI scores were first validated in a real-world cohort of 101 patients with severe asthma starting an IL-5 inhibitor treatment.[18] Later, the GTI score was also assessed in the ADVOCATE trial, a phase 3,

randomized, double-blind, controlled trial conducted in 330 patients, which evaluated the efficacy and safety of avacopan in patients with ANCA-associated vasculitis.[18]

GTI-Metabolic Domains (GTI-MD)

The GTI was originally developed for use in clinical trials to capture the full sweep of GC toxicity to test the efficacy of investigational treatments that are intended as alternatives or addition to GCs.[18,31] In contrast, in clinical practice, an abridged version of the GTI might be a more appropriate and feasible approach. The GTI-Metabolic Domains (GTI-MD) was developed for this purpose.[31]

The GTI-MD, which correlates highly with the full GTI, was created for point-of-care applications. The 4 GTI domains that comprise the GTI-MD are collected easily in the clinic, are purely quantitative, and require no additional clinician assessment.[31] In fact, BMI, glucose tolerance, blood pressure, and lipid metabolism are parameters recorded at most visits, and therefore can be imported from electronic health records (EHRs).[31] This opens up the possibility that GTI-MD scores can be calculated in the background of the clinical visit, alerting clinicians to emerging GC toxicity for patients whose GTI scores warrant closer monitoring or treatment changes.[31] The GTI-MD also has powerful implications for health economics and outcomes research, enabling investigators to address questions related to GC toxicity through large datasets.[31]

Use of the GTI-MD in practice: a hypothetical case study

BASELINE VISIT

- Alexandra is a 70-year-old woman who developed severe pain in her shoulders and hips about a year ago. Her treatment journey is shown in Figure 7.
- Her rheumatologist diagnosed her with PMR and started Alexandra on prednisone (20 mg/day).
- At the baseline visit, the rheumatologist also collected the information required to calculate the GTI-MD, an abridged assessment that correlates highly with the GTI.[31]
- Data required to assess the GTI are usually collected at routine visits: the patient's BMI, blood pressure, and medications, as well as measurements of a hemoglobin A1c and lipid profile.[31] Alexandra's data are shown in Figure 8, below.
- The GTI-MD can be calculated using information from the EHR.[31]
- The rheumatologist planned to assess the GTI-MD approximately every six months, but saw Alexandra more frequently to monitor her PMR and the GC taper.

Figure 7: Timeline of Alexandra's treatment journey.

Baseline Data Needed for GTI-MD

Module	Baseline	
BMI	27	
Blood pressure	139/90	
Hemoglobin HbA1c (%)	6.2	
LDL (mg/dL)	180	
Medications:	Glucose control Blood pressure Lipid control	None Lisinopril 10 mg Simvastatin 10 mg

Figure 8: Alexandra's Baseline data.

GTI-MD FOLLOW-UP VISIT #1 (6 months after baseline)

- Alexandra's prednisone dose had been tapered.
- Her disease still required a maintenance dose of 5 mg.
- The GTI-MD assessment confirmed the emergence of GC toxicity (Figure 9).

GTI-MD Scores at 6 Months

GTI-MD	Clinical inputs		GTI-MD Domain scores #1	
Module	Baseline	Follow-Up Visit 1 (6 months)	Cumulative Worsening Scores Visit 1	Aggregate Improvement Scores Visit 1
BMI	27	30	+21	+21
Blood pressure	139/90	155/96	+44	+44
BP medication (mg)	Lisinopril 10	Lisinopril 40		
Hemoglobin HbA1c (%)	6.2	6.9	+44	+44
Glucose medication (mg)	None	Metformin 500		
LDL (mg/dL)	180	185	0	0
Lipid medication (mg)	Simvastatin 10	Simvastatin 10		
	GTI Scores between Baseline and Follow-Up Visit 1		109	+109

Figure 9: Alexandra's change in toxicity between Baseline and Follow-Up GTI visit 1.

Interpretation of the GTI-MD between Baseline and Follow-Up Visit 1:

- With the GTI-MD, higher scores equate to higher toxicity.
- At Follow-Up Visit #1, Alexandra's BMI has increased from 27 to 30.
- Her BP and HbA1c levels have increased.
- Her medications for BP and glucose control have also been increased.
- Her lipid metabolism did not change because her LDL did not reach the level of a clinically significant change (10%) and there is no change in lipid medications.
- GC toxicity has occurred in 3 of the 4 GTI-MD domains (+21 for BMI, +44 for BP, and +44 for glucose tolerance).
- There has been no decrease in GC toxicity in any of the 4 domains, so her CWS and AIS values are the same at +109
- The minimum clinically important difference (MCID) for the GTI-MD is 10 points.[18] As +109 is more than 10 times the minimum clinically important difference, this represents substantial GC toxicity.

Given the poor disease control and the presence of GC toxicity, Alexandra's rheumatologist introduces an alternative steroid-sparing treatment.

Because of the GC toxicity reflected in the GTI-MD scores, her rheumatologist is concerned about other hidden GC toxicities, orders a bone mineral density study, and starts Alexandra on prophylactic treatment against osteoporosis.

FOLLOW-UP VISIT #2

- Alexandra remains on the alternative steroid-sparing treatment which is controlling her disease.
- She has tapered off GCs entirely.
- Her GTI-MD scores at this visit are shown below, in Figure 10.

Change in Toxicity Between Follow-Up GTI Visits 1 & 2				
GTI-MD	Clinical inputs		GTI-MD Domain scores #2	
Module	Follow-Up Visit 1	Follow-Up Visit 2	Change in Cumulative Worsening Scores, by Domain	Change in Aggregate Improvement Scores, by Domain
BMI	30	26	0	-21
Blood pressure	155/96	135/88	0	-44
BP medication (mg)	Lisinopril 40	Lisinopril 20		
Hemoglobin HbA1c (%)	6.9	6.0	0	-32
Glucose medication (mg)	Metformin 500	Metformin 500		
LDL (mg/dL)	185	162	0	-19
Lipid medication (mg)	Simvastatin 10	None		
	GTI Scores between Follow-Up Visits 1 & 2		0	-116

Figure 10: Alexandra's change in toxicity between Baseline and Follow up GTI visit.

Interpretation of the GTI-MD scores at Follow-Up Visit 2:

There has been no increase in GC toxicity in any domain compared to Follow-Up Visit 1, and this is reflected in the CWS and AIS as explained below:

WORSENING:

- Because the CWS is a running total of ALL GC toxicity, the value can only increase or stay the same.
- The CWS value between Follow-Up Visit 1 and 2 is 0, reflecting no additional GC toxicity in this interval

IMPROVEMENT:

- However, GC toxicity has IMPROVED in all 4 domains for this interval. This is reflected in lower (negative) scores in the BMI, BP, glucose tolerance, and lipid metabolism domains (-21, -44, -32, and -19, respectively).
- The total AIS value for Follow-Up Visit 2 is -116 (lower scores = lower GC toxicity).

The GTI scores over the full year of follow-up are summarized in Figure 11.

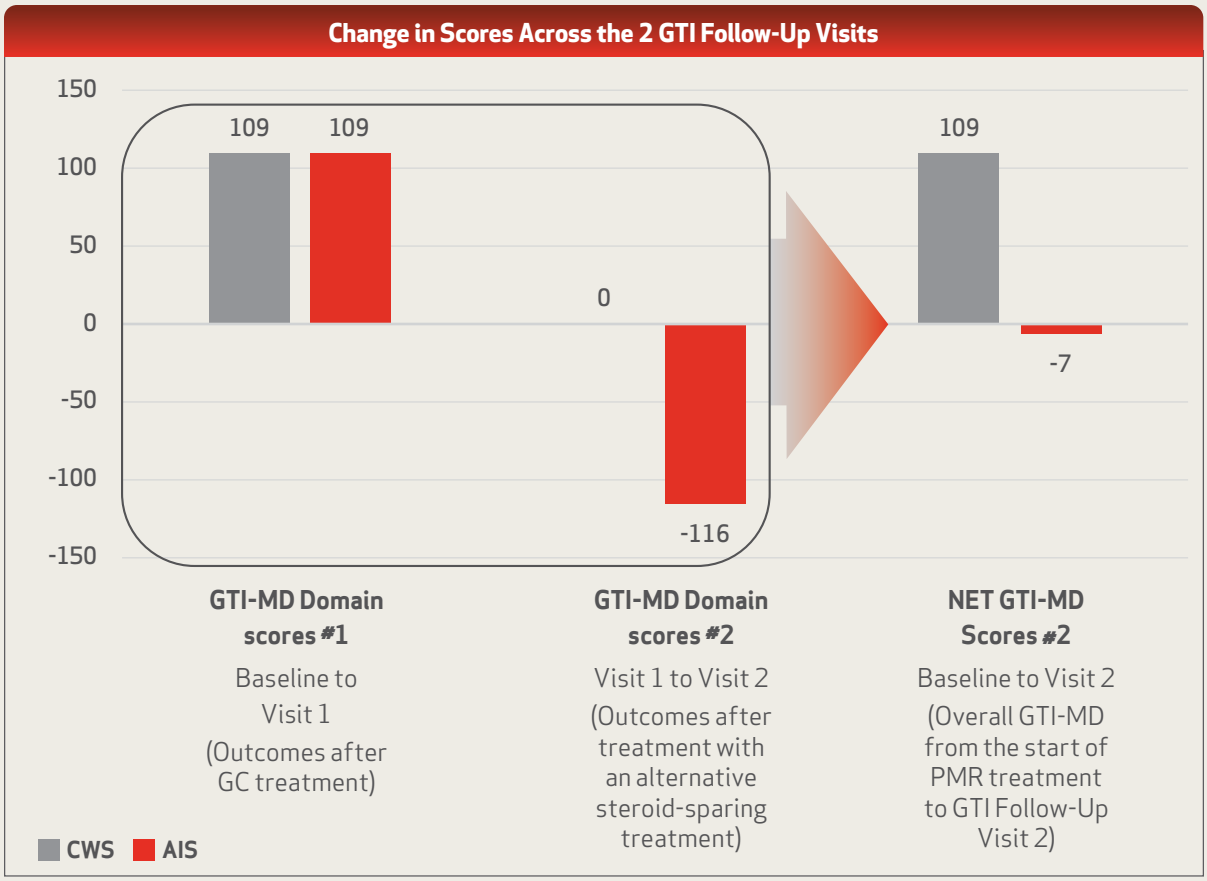

Figure 11: Changes in GTI scores during Alexandra's treatment journey.

Figure 11 illustrates that the patient incurred GC toxicity over the course of the one-year follow-up period. This is reflected by the overall CWS of +109 at the end of the year (+109 +0 = +109). A score of +109 represents significant GC toxicity in the context of an MCID of 10 points. The encouraging feature of Alexandra's course, however, is that, even though she developed GC toxicity while on prednisone, this toxicity resolved over time, corresponding to her successful prednisone taper mediated by the alternative steroid-sparing agent that proved effective in controlling her PMR symptoms. In fact, the overall AIS value of -7 (+109 -116 = -7) indicates that Alexandra's GTI-MD score is lower following the end of 1 year of treatment than it was at baseline. Keep in mind, Alexandra is a hypothetical patient, and the clinical results described here are not necessarily predictive of results in real-world scenarios.

This case study demonstrates that the GTI-MD can be a valuable tool for assessing GC toxicity efficiently in the clinic and monitoring the potential for toxicity to emerge over longitudinal follow-up. The GTI-MD score allows for monitoring GC toxicity over time, optimizing care for patients currently on GC or transitioning to GC-sparing agents.[18]

GTI-MD scores can also be calculated in the background from EHR data, for early detection of emerging GC toxicity. There is a great potential for integrating the GTI-MD into the current EHR system to help physicians with longitudinal monitoring, preventing treatment-related complications, and reducing long-term healthcare costs.[31]

IV. Implications of Using GTI to Evaluate Steroid-Sparing Therapies

As use of the GTI and GTI-MD broadens, the measurement of change in GC toxicity has multiple implications for evaluating the effectiveness of GC-sparing therapies.

- **Treatment Decision Support**: The GTI and GTI-MD provide standardized, objective approaches to assessing the toxicity associated with GC use. This aids clinicians in making informed decisions when choosing steroid-sparing drugs. Healthcare providers at point of care can consider not only the efficacy of a drug in managing the condition but also the potential use of the GTI-MD to minimize GC-related side effects.
- **Individualized Treatment Plans:** The GTI assesses GC toxicity directly, with scores derived from the domains data of each individual. This allows a more patient-centered approach to treatment. By considering the specific toxicity profile of each steroid-sparing drug, healthcare professionals can tailor treatment plans to the individual patient, taking into account factors such as age, comorbidities, and overall health.
- **Risk-Benefit Assessment:** The GTI facilitates a comprehensive risk-benefit assessment. It helps clinicians weigh the potential benefits of using a steroid-sparing drug against the known toxicities associated with GC use, facilitating informed and intentional selection of the most suitable treatment option for a given patient.
- **Monitoring and Adjustment:** The GTI-MD can be useful for monitoring patients in routine care over time. It enables healthcare providers to assess the cumulative toxicity of GCs and adjust treatment plans accordingly, optimizing the balance between achieving effective disease control and the avoidance of side effects.
- **Research and Development:** In the context of clinical research and drug development, the GTI provides a quantitative measure for comparing the safety profiles of different steroid-sparing agents. This can guide researchers in identifying and developing new drugs with improved safety profiles.

V. GTI Score Strengths and Weaknesses

The GTI and GTI-MD scores present both strengths and potential weaknesses. Notable strengths of these instruments are their scientifically rigorous development by an international panel of subspecialty experts; the derivation of weights for each item of GC toxicity; deployment of a composite of relevant GC domains; validation in both real-world clinical experiences, and phase 3 clinical trials; and correspondence with patient-reported quality-of-life outcomes.[18] Furthermore, the GTI score uses data already collected in the clinical setting or trials, such as body mass index, blood pressure, hemoglobin A1c, low-density lipoprotein concentrations, medication changes, occurrences of infections, and other data that are simple to collect. This minimizes the need to collect extra data, as much of the data included in the GTI and GTI-MD are collected routinely in their respective settings.[18]

One potential weakness of the GTI is that it does not capture all GC toxicities. However, the toxicities that comprise the GTI were chosen because they are more common, have clinical impact, and are likely to change with varying GC doses.[18] Another potential concern is that users might find calculating the GTI score challenging.[18] The digital platform, however, facilitates accuracy, speed and scientific rigor. The clinician need not be burdened with weights and scoring logic.[30] Calculations are derived in seconds in the background, requiring no computation by the user.[30]

VI. Conclusions

While glucocorticoids have been in use for more than 75 years as an effective treatment in the short term for a variety of inflammatory disorders, their long-term use is associated with multiple potential toxicities that warrant continuous monitoring and caution in use, and an exit strategy from GC regimens that should be considered from the start of treatment.[12,18] Innovative immunomodulatory agents provide clinicians with treatment options to potentially reduce GC toxicity while potentially maintaining or enhancing therapeutic effectiveness.[18] The GTI has emerged as a valuable tool with great potential to enhance clinical practices in assessing new steroid-sparing agents by means of a systematic and quantifiable approach to compare the potential toxicities associated with glucocorticoid therapy.[18] The integration of the GTI score in evaluating steroid-sparing therapies can offer several advantages such as informed treatment decision support, individualized treatment plans, risk-benefit assessments, and longitudinal monitoring capacity. Additionally, the GTI-Metabolic Domains (GTI-MD), an abridged version of the GTI, incorporates domains routinely assessed during a standard clinic visit and might be more accessible and widely utilized in clinical practice as well as in health economics and outcomes research.[31]

Through its application in both clinical trials and the real world, the GTI has shown great potential to contribute to research and development, minimize complications from GC treatment, and be a valuable tool moving forward to optimize patient care in the coming years.[31]

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