Viewpoint
How to Make Glucocorticoids Safer

Glucocorticoids (GCs) are among the most prescribed medications and are used to treat myriad autoimmune and inflammation disorders either systemically (systemic lupus erythematosus (SLE), multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, psoriasis) or locally (skin allergies, asthma, allergic rhinitis). In 2019, approximately 20 million individuals in the United States were prescribed glucocorticoids, representing ~6% of the population (https://clincalc.com/DrugStats/). This number represents patients prescribed either oral (systemic) or local (topical or inhalation) but not over-the-counter topical glucocorticoids, which suggests total usage is well above 6% of the population. GCs have been the mainstay for clinical immunosuppression for over 70 years, beginning with the pioneering work at the Mayo Clinic, where the adrenal cortical hormone cortisol was discovered to effectively reverse the debilitating effects of rheumatoid arthritis in patients (Hench, 1964). Philip Hench, Edward Kendall, and Tadeus Reichstein were awarded the Nobel Prize in Physiology or Medicine in 1950 “for their discoveries relating to the hormones of the adrenal cortex, their structure, and biological effects.” Major side effects of systemic GC therapy were quickly identified and even discussed by Hench in his 1950 Nobel lecture less than two years after the first report of cortisol’s efficacy (Hench, 1964). The detrimental effects of systemic GC treatment are quite extensive and include osteoporosis and increased risk of fractures, hyperglycemia, muscle atrophy, and neuropsychiatric disorders (Cain and Cidlowski, 2017). The doses of GCs required to drive immunosuppressive efficacy in many disorders are typically supraphysiological and drive severe side effects. Even considering these significant side effects, GCs remain the standard of care for many autoimmune and inflammatory disorders today. Oral GCs, which are associated with more severe side effects, are still widely used by 1.2% of the U.S. population over 20 years of age (Overman et al., 2013). Concomitant use of additional drugs to reduce or prevent side effects is common, such as utilizing antosteoporosis agents to reduce the increased risk of bone fractures.

Other approaches have been employed to avoid the side effects of GCs while still maintaining their immunosuppressive effects. GCs exert their function via agonizing the GC receptor (GR), a member of the steroid receptor superfamily (Burris et al., 2023). Several pharmaceutical companies have attempted to develop selective GR “modulators” analogous to selective estrogen receptor “modulators” that are engineered to maintain beneficial effects while eliminating or reducing unwanted detrimental side effects. Multiple strategies have been employed to identify and optimize these dissociated or selective GR modulators. GRs exhibit the ability to both transactivate and transrepress various target genes and regulate target genes by both direct recognition of DNA-response elements (glucocorticoid response elements) and indirectly via interfering with the function of other transcription factors. In general, the transrepression activity has been associated with indirect regulation and anti-inflammatory activity, whereas the transactivation activity is associated with direct recognition of glucocorticoid response elements and the undesirable side effects of GR agonists (Schäcke et al., 2004). GR ligands that display unique or biased activity in the manner in which they modulate these activities provide for the SEGRM pharmacological profile that has been the focus of developing safer drugs that target GR (Clark and Belvisi, 2012; Vandewalle et al., 2018; Van Moortel et al., 2020; Mao et al., 2023). Although selective estrogen receptor “modulators” such as raloxifene have been FDA-approved, the development of GR modulators with the appropriate pharmacological profile has been very challenging, and none have progressed to registration so far.

Deshmukh et al. took a different approach to potentially reducing the side effects of GCs (Deshmukh et al., 2024). These authors used key information about how anomalous toll-like receptor (TLR) 7 signaling underlies the pathogenesis of SLE, and that activation of TLRs drives GC resistance to hypothesize that targeting both these classes of receptor simultaneously may impart enhanced efficacy of GCs allowing reduction of their side effects. Interestingly, other key components of the immune system have also been shown to drive GC resistance, including TNFα, suggesting a potential wider use of such an approach to reducing the side effects of GCs (Dendoncker et al., 2019).

Address correspondence to: Dr. Thomas P. Burris, University of Florida, 2033 Mowry Rd, Gainesville, FL 32610. E-mail: burris.thomas@ufl.edu

No author has an actual or perceived conflict of interest with the contents of this article.

dx.doi.org/10.1124/jpet.123.001931

ABBREVIATIONS: GC, glucocorticoid; GR, glucocorticoid receptor; SLE, systemic lupus erythematosus; TLR, toll-like receptor.
TLRs play a key role in the innate immune system, recognizing a range of pathogen- or damage-associated molecular pattern-containing molecules and mediating induction of an innate immune response, such as induction of inflammatory cytokines or type I interferon production. Ten TLRs exist in humans, and each responds to specific (but sometimes overlapping) classes of pathogen-associated molecular pattern-containing molecules and damage-associated molecular pattern-containing molecules. Various TLRs are expressed either on the cell surface or intracellularly (on endosomes) and respond to either extracellular or intracellular ligands, respectively. Of particular interest for the purposes of this study are TLR 7 and 8, which are endosomal TLRs that function as receptors for single-stranded RNA, induce interferon, and function normally in anti-viral defense (Fitzgerald and Kagan, 2020). TLRs can also play a role in pathophysiology. For example, gain-of-function genetic variation of TLR7 leads to SLE in humans (Brown et al., 2022). These data are consistent with the observation that knockout of tlr7 or treatment of mice with lupus with TLR7/8 inhibitors (TLR7/8i) reduces the severity of the disease (Christensen et al., 2006; Vlach et al., 2021). Interestingly, either activation of TLR7 or enhanced interferon production has been shown to mediate resistance to GCs (Guiducci et al., 2010; Dankers et al., 2022).

These observations led Deshmukh et al. to examine whether a combination of a TLR7/8i with a GC may allow for enhancement of the efficacy of GCs, affording a lower dose of GCs and, thus, reduced side effects. The synergistic suppression of the proinflammatory response in activated monocytes (interleukin 6 and TNFα response to resiquimod (R848), a dual TLR7/8 agonist) was particularly robust when a combination of a TLR7/8i (CMPD2 — a close analog of the clinical candidate enpatoran) and dexamethasone (DEX; the GC used throughout these studies) was employed. Interestingly, the combination (CMPD2 and DEX) was not as effective in dendritic cells or B cells. At least some of the differential sensitivity may be due to different patterns of expression of TLR 7 and 8 in these cell types, but the mechanism is probably much more complex. However, the ability to reduce the GC dose required for efficient immunosuppression by the addition of a TLR7/8i suggests that such a combination may have “glucocorticoid sparing” potential with regard to the debilitating side effects of use of GC treatment alone. It would be interesting to assess the expression of a larger array of GR-regulated anti-inflammatory genes under these conditions to better understand the full potential of this particular pharmacological approach.

The critical next step was to test their hypothesis in an in vivo disease model, and the authors employed the MRLlpr spontaneous mouse model of lupus. Importantly, disease in this model is driven by loss of tolerance in T cells and is believed to be independent of TLR activation. The lupus-like phenotype in this model is characterized by the development of proteinuria and anti-dsDNA antibodies and has been previously demonstrated to be responsive to either GCs or CMPD2 alone. Here, the investigators were able to show that the combination of suboptimal doses of GCs and the TLR7/8i led to near-complete suppression of proteinuria and eliminated mortality. Interestingly, in terms of the effects on anti-dsDNA Ab levels, the efficacy of the drug combination was no better than the low-dose DEX alone. This was likely because the low-dose DEX was quite effective alone on this endpoint, and there was no window for improvement. However, it also suggests that various pharmacological endpoints are likely to have differing levels of sensitivity to the combinations, and this may include the drivers of various side effects that the GCs induce. The current studies did not assess how low-dose DEX/TLR 7/8i combinations might reduce side effects (e.g., osteoporosis, hyperinsulinemia, hyperglycemia, and muscle atrophy) while maintaining immunosuppressive activity in an in vivo model, and this is clearly the next and most essential step to test their hypothesis. The fact that the TLR7/8i used by Deshmukh et al. is a close analog of enpatoran, a compound in phase 2 clinical trials for the treatment of SLE and cutaneous lupus erythematosus (NCT0516286), suggests that clinical evaluation of low dose GC/TLR7/8i combinations is at hand. The potential to substantially improve the quality of life of patients treated with GCs is significant.

Thomas P. Burris

Department of Pharmacodynamics, College of Pharmacy, Genetics Institute, University of Florida

References
Burris TP, de Vera IMS, Cote I, Flaveny CA, Wanninayake US, Zhang J, Coons LA et al. (2023) Interna-


Hench PS (1964) The Reversibility of Certain Rheumatic and Non-Rheumatic Conditions by the Use of Cortisone or of the Pituitary Adrenocortical Hormone, Elsevier Publishing Company Amsterdam.


