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The Risk Benefit Ratio of Glucocorticoids in SLE: Have Things Changed over the Past 40 years?

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Opinion statement

Purpose of review Glucocorticoids have been the mainstay of treatment in systemic lupus erythematosus for more than half a century. Despite advancements in knowledge concerning the pathophysiology of systemic lupus, the genomic/non-genomic actions of glucocorticoids, and the use of novel therapeutic agents in SLE, the burden of toxicity from glucocorticoid use remains unchanged.
Recent findings SLE patients receiving long-term prednisone therapy are at significant risk of morbidity due to permanent organ damage, and prednisone daily dosages above 6 mg have been shown to increase the risk of future organ damage by 50%. Glucocorticoid use carries a higher risk of opportunistic infections, iatrogenic osteoporosis, and avascular necrosis, an increase in risk of cardiovascular events, cataracts, and glaucoma, as well as psychiatric adverse effects like psychosis and manic episodes. There are limited data regarding the relative efficacy of the different glucocorticoid formulations or dosing regimens.
Summary The use and dosing of glucocorticoids in SLE remains more art than science, although our knowledge regarding their complex genomic and non-genomic effects, as well as the resultant adverse effects, has greatly expanded over the past half a century.

Introduction

The discovery of compound E (hydrocortisone) by Kendall and Reichstein in 1936 would prove to be a monumental point in the history of medicine; however, the first few attempts at therapeutic use of isolated glucocorticoids were disappointing. The first clinical study by George W. Thorn on 30 cases of Addison's disease showed that deoxycortisone acetate did not alter hypoglycemia, but did normalize electrolyte balance [1]. A double-blind study of deoxycortisone acetate in five patients with rheumatoid arthritis in 1950 was disappointing [2]. The first clinical use of cortisone was announced in the Proceedings of the Staff Meetings of the Mayo Clinic on April 13, 1949 [3], by Philip S. Hench, chief of the Mayo Clinic rheumatology section, who reported the case of a 29-year-old woman with refractory rheumatoid arthritis. On September 21, 1948, she received twice daily intramuscular injections of 50 mg cortisone with improvement after the second dose. This was followed by the first report of 33 patients treated with cortisone published in 1950 which included a single patient with SLE—the first documented use of glucocorticoids in SLE [4].

Glucocorticoid use rapidly expanded and became the mainstay of treatment for most rheumatological diseases. With the expansion of their use, the first reports of steroid adverse effects appeared. In 1951, Freyberg described edema, rounded facies, tachycardia, hypertension, and insomnia in a series of patients with rheumatoid arthritis. His quote: "The longer the treatment was continued, the greater was the chance for trouble!" reflects the experience of every physician who has prescribed corticosteroids over the past six decades [5]. The scope of this review is to describe the experience with glucocorticoid therapy in systemic lupus as well as to address many of the controversies regarding appropriate dosing, duration of therapy, and long-term adverse effects.

Glucocorticoid mechanisms of action and resistance

Glucocorticoids mediate their effect through intracellular glucocorticoid receptors, which belong to a large family of transcription factors known as nuclear hormone receptors. The human glucocorticoid receptor is the product of one gene that is located in chromosome 5q31–32 [6]. Glucocorticoids signal through genomic and non-genomic pathways. Anti-inflammatory effects of glucocorticoid treatment are carried out by classic genomic pathways. Glucocorticoids bind to the cytosolic glucocorticoid receptor, which leads to transactivation (induction of gene transcription of certain genes like lipocortin1 and genes involved in metabolism) or transrepression (inhibition of transcription of target genes like Il-2). Rapid, non-genomic glucocorticoid actions are mediated through physical and biochemical interactions with cytosolic and membrane-bound glucocorticoid receptors. Unlike genomic effects, non-genomic effects of glucocorticoids do not require protein synthesis and occur rapidly within seconds to minutes of receptors activation. The non-genomic effects of glucocorticoid receptors utilize the activity of various kinases, like phosphoinositide 3-kinase, AKT, and mitogen-activated protein kinases [7]. Membrane-bound glucocorticoid receptors are up-regulated in patients with systemic lupus erythematosus and by inflammatory stimuli and down regulated by glucocorticoids, suggesting a negative feedback loop to control glucocorticoid action [8].

Through their genomic and non-genomic actions, glucocorticoids induce a range of anti-inflammatory effects, among which the most prominent ones are as follows: (1) the reduction of T-lymphocyte proliferation and activation, (2) inhibition of B-lymphocyte proliferation and immunoglobulin production, particularly IgG, (3) inhibition of mononuclear cell and neutrophil leucocyte

migration and their adhesion to inflamed capillary endothelium, (4) reduction of the synthesis of inflammatory prostaglandins by inhibition of phospholipase A2 activity (via induction of annexin-1), and (5) by suppression of cyclo-oxygenase expression, as well as by impairment of fibroblast activity with reduced collagen synthesis and inhibition of matrix metalloproteinases [9].

Up to a third of SLE patients have an insufficient response to glucocorticoids [10]. Several mechanisms of glucocorticoid resistance have been described. The glucocorticoid receptor occurs in two alternative splice variants encoding GRalpha and GRbeta. The GRbeta variant does not contain a glucocorticoid binding domain and cannot mediate anti-inflammatory glucocorticoid effects. SLE patients with high disease activity exhibit significantly elevated GRbeta transcript levels and corresponding protein levels in PBMCs (peripheral blood mononuclear cells) suggesting that increased expression of GRbeta isoform may be associated with a more severe clinical presentation of SLE [11]. Another issue in glucocorticoid resistance is the modification (e.g., phosphorylation, nitrosylation, ubiquitination) of the glucocorticoid receptor [10], which can potentially affect the binding of glucocorticoids to the receptors and the receptor function.

Another method of glucocorticoid resistance in SLE patients occurs through the triggering of plasmacytoid dendritic cells through Toll-like receptors 7 and 9 by nucleic acid-containing immune complexes leading to activation of the NF-kappa B pathway which is essential for the survival of plasmacytoid dendritic cells. Glucocorticoids do not affect NF-kappa B activation which prevents glucocorticoid induction of plasmacytoid dendritic cell death in SLE resulting in their constant activation, continuous interferon-α secretion, and high SLE activity [12].

Pharmacokinetics and modes of administration

Various routes of administration have been developed, some of them specifically with the goal of avoiding systemic adverse reactions. The most commonly used routes include oral, intravenous, intraarticular, intralesional, intranasal, inhalation, and topical administration to the eyes or skin.

Prednisone, prednisolone, methylprednisolone, and triamcinolone are the most commonly used formulations. The pharmacokinetics depends on the route of administration and formulation used. Data do not clearly support a difference in efficacy for once daily or divided doses, although, there is emerging evidence of the role of the circadian rhythms in the control of the immune response and once daily morning regimens are preferred due to a lower risk of adrenal suppression and systemic side effects [13].

There are limited data regarding the relative efficacy of the different glucocorticoid formulations. A randomized study found that intramuscular triamcinolone was equally effective and more rapid in onset than an oral 6-day methylprednisolone taper for mild to moderate flares [14].

Intravenous pulse steroid therapy remains the standard of care for life threatening lupus manifestations. The rationale behind the use of high-dose steroids is based on a more rapid, longer lasting, and stronger immunosuppressive effect via genomic effects mediated by 100% saturation of glucocorticoid receptors, but more importantly by more pronounced non-genomic effects compared to lower oral prednisone dosages [10]. Pulse methylprednisolone has been shown to normalize the aberrant expression of MHC class II and to decrease the secretion

of interferon gamma [15]. In pediatric lupus patients, pulse dose methylprednisolone was shown to fully inhibit the interferon alpha signature in PBMC's, unlike oral prednisone [12]. The dosage used for pulse doses remains controversial. In a double-blinded randomized control trial including 21 patients with lupus including CNS, renal manifestations, and fevers, Isenberg et al. [16] compared three daily infusions of either 100 mg or 1 g of methylprednisolone with no difference in outcomes between the doses. Moreover, in a retrospective study, Badsha et al. compared the effects of 1–1.5 g methylprednisolone vs. 3–5 g methylprednisolone total dosage over 3 days in SLE patients with flares in different organs. Both dosages were equally effective with a higher rate of infections noted in patients who received 3–5 g of methylprednisolone [17, 18].

Glucocorticoids can alter the response to anticoagulants, and close monitoring of coagulation parameters should be employed. Itraconazole inhibits CYP3A4 (cytochrome P450 3A4) and inhibits the clearance of synthetic glucocorticoids potentially leading to rapid development of Cushing's syndrome [19]. Diltiazem is another CYP3A4 inhibitor that has been shown to increase methylprednisolone concentrations 2.6-fold [20], and this combination should be avoided. Combined oral contraceptives have been shown to increase prednisolone concentrations by 131% suggesting a potentially important clinical interaction [21].

Adverse effects

Skeletal system

Harvey Cushing in 1932 described skeletal decalcification as a clinical feature of adrenal hyperplasia secondary to ACTH-secreting pituitary adenomas, the first publication recognizing the negative effects of glucocorticoids on the bone [22]. Glucocorticoid-induced osteoporosis is the most common cause of iatrogenic osteoporosis and the most common cause of osteoporosis for all causes in adults 20 to 45 years old [23]. Rapid bone loss (up to 12%) occurs during the first 6 to 12 months of corticosteroid therapy [24]. Fractures are among the most frequently reported adverse effects. In general, the risk ratio for any fracture in patients using systemic corticosteroids ranges from 1.60 to 1.75 [25]. The risk for vertebral fracture with corticosteroid use is greater than that for fractures at other sites, namely threefold higher than in patients who do not use corticosteroids [26].

A study of 45 patients with newly diagnosed SLE who required 40 mg/day or more prednisolone showed that 15 (33%) developed silent osteonecrosis of the femur and five (11%) symptomatic osteonecrosis of the femur. The only significant difference between the groups was the more frequent use of pulse therapy with 1000 mg/day methylprednisolone in the silent osteonecrosis group [27]. Seventy-two patients with active SLE, who received high-dose corticosteroid for the first time, were monitored by magnetic resonance imaging for at least 12 months for the development of osteonecrosis at hips and knees [28]. Osteonecrosis was detected in 32/72 patients (44%) between 1 and 5 months (3.1 months on average) after starting high-dose corticosteroid treatment. No events were detected after 6 months. One of the most significant risk factors for the development of avascular necrosis was the daily dose of oral corticosteroids and the development of cushingoid appearance in response to steroids (74% with vs 42% without, $P < 0.002$) [29]. In a retrospective study of patients with SLE, the total dosage of prednisolone did not differ between those with avascular necrosis and controls (17.7 vs 14.1 g, $P = 0.22$) but differed significantly in highest cumulative dosage at

1 month (1.78 vs 1.14 g, $P = 0.0001$) and 4 months (4.5 vs 2.75 g, $P = 0.001$). In this study, the mean daily steroid dosage was 15.6 mg of prednisolone for those with avascular necrosis vs 9.3 mg without avascular necrosis ($P = 0.0001$). The development of a cushingoid body habitus while taking corticosteroids was highly correlated with the occurrence of avascular necrosis (79 vs 53%, $P = 0.004$) [30].

Cardiovascular system

Glucocorticoid use has been associated with atherosclerosis in SLE [31•], at least partly through a dramatic increase in the risk of multiple traditional cardiovascular risk factors. In a meta-analysis of 93 studies, patients treated with steroids were four times more likely to have hypertension of diabetes compared with controls [32]. In an observational population-based study, the rate of cardiovascular events was 23.9 per 1000 person-years among glucocorticoid users vs. 17 per 1000 person-years among nonusers. A dose of prednisone of 7.5 mg or more was associated with a 2.56-fold increased risk of cardiovascular events [33]. In patients with SLE, a change in prednisone dose of 10 mg was associated with an increase in cholesterol levels of 7.5 ± 1.46 (SE) mg%, an increase in mean arterial blood pressure of 1.1 mmHg, and an increase in mean weight of 5.50 ± 1.23 lb (SE) (2.5 ± 0.55 kg) [34]. In the Hopkins Lupus Cohort, the effect of corticosteroids on cardiovascular risk is independent of disease activity and traditional cardiovascular risk factors [31•]. Patients currently taking corticosteroids at a dose of 10 mg/day or more had significantly higher rates of cardiovascular events. Those on 20 mg/day or more had a fivefold increased rate after adjustment for age, and current use had a stronger association with cardiovascular events than did cumulative past use [31•].

Ophthalmologic

In the Hopkins Lupus Cohort, the incidence of cataract was 13.2/1000 persons-years. The strongest predictor for cataract development was a cumulative prednisone dose equivalent to 10 mg/day for 10 years (RR = 2.9, $P = 0.0010$) [35]. Some studies in patients with systemic glucocorticoid exposure have shown that this dose level does not exist, and that cataracts would develop regardless of the dose, duration of corticosteroid therapy, or patient age [36]. The more potent corticosteroids, dexamethasone and betamethasone administered topically or systemically, induce more cataract and glaucoma compared to less potent steroid formulations like prednisolone [37].

Psychiatric

Nishimura et al. [38] observed 14 cases of new-onset DSM-IV disorders, primarily manic episodes, among 135 patients with SLE who had no evidence of CNS lupus and were treated with glucocorticoids. Symptoms occurred after a mean of 12.5 days post treatment initiation, and all symptomatic patients were receiving prednisone at doses over 40 mg daily. Appenzeller et al. [39] reported episodes of acute psychosis meeting DSM-IV criteria in 89 out of 520 SLE patients, among which corticosteroid-induced psychoses accounted for a third of cases. All patients with corticosteroid-induced psychosis were taking prednisone 0.75–1.0 mg/kg/day. In a prospective cohort of 92 SLE patients [40], corticosteroid-induced psychosis occurred in 5% of patients. Factors predictive of psychosis

were low serum levels of albumin, complement, and creatinine; history of anxiety disorders; and a family history of psychiatric illnesses. After multivariate adjustment, only hypoalbuminemia remained a significant predictor. In the Hopkins Lupus cohort, the major predictors of depression were prednisone at a dose >20 mg daily, longitudinal myelitis, and cutaneous activity [41].

Infection risk

Glucocorticoid use increases the risk of bacterial, fungal, and viral infections, as well as the risk of tuberculosis reactivation. In a community-based study of 3030 patients with SLE, a six to sevenfold increased risk of serious infections was observed in patients with SLE. Patients starting prednisone doses ≤15 mg/day without antimalarials had a fourfold greater risk of serious infection than did patients with SLE starting antimalarials only [42].

Glucocorticoids and risk of organ damage in SLE

SLE patients receiving long-term prednisone therapy are at significant risk of morbidity due to permanent organ damage. Zonana-Nacach et al. [43] showed that the cumulative prednisone dose was significantly associated with the development of osteoporotic fracture, cataracts, coronary artery disease, avascular necrosis, and diabetes mellitus. In the Lumina cohort, the time to damage accrual was shown to be shorter in patients exposed to corticosteroids [44]. In the Hopkins Lupus Cohort [45•], it was estimated that a 1 mg/day increase in prior prednisone dose during follow-up was associated with a 2.8% increase in the risk of developing new organ damage. Exposure to a mean prior prednisone dose of ≥7.5 vs. <7.5 mg/day significantly increased the risk of developing cataracts, osteoporotic fractures and cardiovascular damage. Gladman et al. [46] showed that a significant proportion of the damage in SLE both early and late could be attributed to corticosteroid therapy, and that this damage accumulated over time so that it constituted most of the damage at 15 years.

Is there an optimal glucocorticoid dose in SLE?

Luijten et al. performed a systematic review on the level of evidence for glucocorticoid use for different SLE manifestations [10]. This review revealed that the level of evidence for many indications was based on case series (19 out of 33). In general, low-dose oral prednisone (<7.5 mg daily) was usually prescribed for mild manifestations, medium dose (7.5–30 mg) for moderate manifestations, and 30–60 mg or intravenous pulse doses (>100 mg) for severe or life-threatening manifestations. Several studies tried to assess whether there is a "safe" prednisone dose for long-term use. Data from the Hopkins cohort showed that prednisone daily dosages above 6 mg increase the risk of future organ damage by 50% [47]. Currently, studies are conducted to evaluate the results of steroid-free regimens for the treatment of SLE. A pilot study of 50 consecutive patients with lupus nephritis class III, IV, or V [48] who were treated with a steroid-less protocol consisting of two doses of rituximab (1 g) and methyl prednisolone (500 mg) on days 1 and 15, followed by maintenance treatment of mycophenolate mofetil showed promising results with response rates similar to the ones seen in the Aspreva Lupus Management Study (ALMS) [49] trial which used a combination of mycophenolate and steroids. The

Rituxilup trial (ClinicalTrials.gov Identifier: NCT01773616) comparing the steroid-less rituxilup protocol to a regimen containing methylprednisolone, oral glucocorticoids, and mycophenolate mofetil is ongoing.

Conclusion

Since the first documented use of glucocorticoids in SLE in 1950, our understanding of their pharmacokinetics and pharmacodynamics has exponentially expanded, but their therapeutic use remains riddled with controversies. There are limited data regarding the relative efficacy of the different glucocorticoid formulations. Once daily morning regimens are preferred due to a lower risk of adrenal suppression and systemic side effects. Intravenous pulse steroid therapy remains the standard of care for life-threatening lupus manifestations and has a more rapid, longer lasting, and stronger immunosuppressive effect mediated via genomic effects and more importantly by more pronounced non-genomic effects compared to lower oral prednisone dosages. The dosage used for pulse dose glucocorticoids remains controversial with limited data supporting the use of lower dosages compared to the previous standard dose of 1000 mg methylprednisolone daily for three consecutive days. Glucocorticoid use carries a significant burden of toxicity including among others, a higher risk of opportunistic infections, iatrogenic osteoporosis, and avascular necrosis, an increase in risk of cardiovascular events, cataracts, and glaucoma, as well as psychiatric adverse effects like psychosis and manic episodes. SLE patients receiving long-term prednisone therapy are at significant risk of morbidity due to permanent organ damage, and prednisone daily dosages above 6 mg have been shown to increase the risk of future organ damage by 50%. Steroid-free regimens are being actively investigated, but until reliable, evidence-based steroid-free regimens are defined, using glucocorticoids judiciously for true disease manifestations remains an essential part of treatment in SLE.

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Compliance with ethical standards

Conflict of interest
George Stojan declares that she has no conflict of interest.
Michelle Petri declares that she has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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