The SLE review series: working for a better standard of care

It hasn’t gone away: the problem of glucocorticoid use in lupus remains

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Abstract

The treatment of SLE remains complex, and management is constrained by a lack of safe, effective, targeted therapies. Physicians, also, are constrained by a lack of evidence-based approaches with existing agents, including glucocorticoids, utilized in the majority of patients. While Cushingoid side effects of glucocorticoids are widely recognized, emerging literature now suggests that glucocorticoid use actually contributes to harmful outcomes in SLE, over and above these effects. These studies provide a compelling case for a re-evaluation of the long-term use of glucocorticoids in SLE, focusing on minimizing glucocorticoid exposure as part of the strategy to improve long-term outcomes. In this article, we review the evidence for the harmful effects of glucocorticoids in SLE, and propose therapeutic options that reduce reliance on glucocorticoids. We propose that it is time for the lupus community to have a louder conversation about glucocorticoid use, and for any residual complacency about their risk–benefit ratio to be banished.

Key words: lupus, SLE, systemic lupus erythematosus, glucocorticoids, corticosteroids, steroids, prednisolone, prednisone, damage, outcomes

Introduction

SLE or lupus is a chronic, systemic autoimmune disease of unknown aetiology. Management of lupus aims to reduce tissue inflammation and prevent irreversible organ damage, as these contribute to the morbidity and mortality of the disease [1–4]. Over the past 50 years there has been a significant improvement in mortality in lupus, with 10-year survival rates now estimated to lie between 92 and 95% [3, 5–7]. However, despite best practice, most patients accrue irreversible organ damage within 7 years of diagnosis [8].

There are a limited number of medications available for treating active lupus, and management continues to rely heavily on glucocorticoids, first used over 60 years ago. Glucocorticoids are powerful anti-inflammatory and immunosuppressant medications that rapidly and effectively suppress the immune system [9]. Glucocorticoids are used for most SLE manifestations, ranging from mild cutaneous disease to severe life-threatening disease [10]. Surprisingly, despite widespread acceptance that glucocorticoids have beneficial effects on suppressing inflammation in SLE, there is a striking lack of randomized controlled trial evidence supporting this, and minimal evidence underpins the dose and duration of glucocorticoid treatment in SLE, with no widely accepted guidelines for the commencement of or weaning from glucocorticoids. Importantly, glucocorticoid use is not without risk of harm, with well-known deleterious effects on metabolism, bone density and susceptibility to infection that are generally dose-dependent. In 2014, an international taskforce on treat-to-target strategies in lupus [11] recommended that...
lupus maintenance treatment should aim for the lowest glucocorticoid dosage to control disease, and that no safe dose of glucocorticoids exists. Consistent with this, the US Food and Drug Administration cite evidence of steroid-sparing properties among clinical trial endpoints for new lupus medications [12]. Despite these observations, studies report that up to 80% of lupus patients are exposed to glucocorticoids [13, 14], and that a majority are treated long-term [13]. The continued reliance on glucocorticoids for the management of SLE highlights the lack of suitable alternatives able to swiftly control unwanted immune system activation. However, it may also suggest that physicians have somehow become inured to the harmful long-term effects of glucocorticoids in patients with SLE.

Recently, the arguments in favour of limiting long-term exposure to glucocorticoids have grown stronger, with several publications identifying that glucocorticoids may, in addition to Cushingoid effects, independently contribute to irreversible organ damage in lupus [14, 15]. In this article, we review evidence of the harm glucocorticoids induce, including evidence that long-term glucocorticoids may compound the effects of SLE itself. We propose that it is time for a shift in mindset on the use of glucocorticoids in SLE, and advocate for strategies to reduce long-term glucocorticoid exposure without sacrificing disease control.

Glucocorticoids and harm in SLE—Cushingoid and cardiovascular consequences

In contrast to the scarcity of evidence of benefit of glucocorticoid regimens in the control of SLE disease activity, evidence for their harmful effects is abundant. In 2000, a prospective study on the association between glucocorticoid use and adverse events was published by Zonana-Nacash et al. [16]. They reported on 539 patients with SLE in the Hopkins Lupus Cohort in the USA, and found that cumulative prednisone dose was a significant predictor of cataracts, osteoporotic fractures, avascular necrosis and diabetes mellitus. The prevalence of reduced BMD among patients with SLE has been reported at almost 50%, with a strong negative relationship between glucocorticoid use and bone density [17]. In a 3-year follow-up study, daily doses of prednisolone >7.5 mg/day were associated with significant further loss of lumbar spine BMD [18]. These findings have been confirmed in numerous other studies, while low vitamin D has also been identified as a significant contributor to low bone density among SLE patients [19, 20].

Glucocorticoids are believed to have significant cardiovascular effects in addition to conventional Cushingoid adverse effects. SLE is associated with a 5- to 8-fold increase in cardiovascular events compared with the age-matched general population [21, 22], with the prevalence of traditional risk factors such as hypertension and diabetes mellitus being higher in SLE patients [23]. Significant positive associations have been found between glucocorticoid use and traditional cardiovascular risk factors, including total cholesterol, triglycerides and systolic blood pressure, and the study of Zonana-Nacash et al. [16] mentioned above also reported increased cardiovascular damage in association with glucocorticoid exposure. Total cholesterol and blood pressure take a dynamic course over time in SLE patients, varying secondarily to changes in both disease activity and treatment [24, 25]. The higher prevalence of traditional cardiovascular risk factors does not fully account for the increase in cardiovascular disease in SLE, with disease activity suggested as a contributor to this risk [23, 26]. However, glucocorticoids have been found to be independently associated with the increased risk of cardiovascular disease in multivariate models that have controlled for disease activity [27].

Glucocorticoid contribution to lupus organ damage

It is well established that the accrual of irreversible organ damage, for example, measured by the SLIC/CACR damage index (SDI), is associated with morbidity and mortality in SLE [2, 28]. In the SDI, items do not have to be attributable to lupus disease activity in order to be scored; thus treatment-related outcomes may also contribute. It is readily conceivable that certain items included in the SDI, including cataracts, osteoporotic fracture, avascular necrosis and diabetes mellitus, are associated directly with glucocorticoid use, and this was indeed found by Zonana-Nacash et al. [16]. Since 2000, there have been over a dozen published studies that have shown a deleterious impact of glucocorticoids on overall organ damage accrual in SLE (Table 1), and in many cases these studies have reported effects in domains additional to those conventionally thought of as glucocorticoid-related. As glucocorticoids are used to treat active lupus, there is a strong correlation between glucocorticoid use and disease activity. However, there is now a large body of evidence supporting a contribution of glucocorticoids to harmful outcomes in lupus independent of this association—indicating a direct harmful effect of glucocorticoids on SLE outcomes.

Some of this evidence comes from inception cohort studies. In a study in the multi-ethnic LUMINA cohort of 158 patients [33], wherein patients had no damage at baseline, predictors of shortened time to initial damage during the study period of 24 months were sought. Independent predictors of damage accrual after multivariate adjustment included disease activity, Hispanic ethnicity, thrombotic events and prednisone dosage, with dosages >30 mg/day being most harmful. The effect of glucocorticoid use, adjusted for disease activity, on accrual of first organ damage was also investigated in a study of 525 patients enrolled within 6 months of diagnosis in the Hopkins Lupus Cohort [31]. Prednisone exposure was divided into five bands of 180 mg/month increments, with the group receiving 0–180 mg/month (~6 mg/day) not exhibiting significantly increased risk of irreversible organ damage. In contrast, the group...
### Table 1: Studies in SLE associating glucocorticoid exposure with damage outcomes

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>No. of patients</th>
<th>Follow-up (mean, or as indicated)</th>
<th>Outcome measure of damage</th>
<th>Glucocorticoids predictive of damage</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Sawah et al. [15]</td>
<td>2015</td>
<td>2199</td>
<td>6.2 years</td>
<td>SDI</td>
<td>Y</td>
<td>Each 1 mg/day increase in prednisone dose was associated with a 2.8% increase in the risk of developing new organ damage. Adjusted for disease activity</td>
</tr>
<tr>
<td>Yee et al. [29]</td>
<td>2015</td>
<td>382</td>
<td>7.7 years</td>
<td>SDI</td>
<td></td>
<td>Inception cohort. Accrual of damage dose-dependently associated with glucocorticoid exposure. Adjusted for disease activity</td>
</tr>
<tr>
<td>Bruce et al. [8]</td>
<td>2014</td>
<td>1722</td>
<td>≥5 years</td>
<td>SDI</td>
<td>Y</td>
<td>Inception cohort. Accrual of damage associated with glucocorticoid exposure. Adjusted for disease activity</td>
</tr>
<tr>
<td>Ruiz-Arruza et al. [14]</td>
<td>2014</td>
<td>230</td>
<td>5 years</td>
<td>SDI</td>
<td>Y</td>
<td>Five-year accrual of damage in glucocorticoid-related domains and overall dose-dependently associated with glucocorticoid exposure. Adjusted for disease activity</td>
</tr>
<tr>
<td>Petri et al. [30]</td>
<td>2012</td>
<td>2054</td>
<td>6.4 years</td>
<td>SDI</td>
<td>Y</td>
<td>Accrual of damage dose-dependently associated with glucocorticoid exposure</td>
</tr>
<tr>
<td>Thamer et al. [31]</td>
<td>2009</td>
<td>525</td>
<td>58 months</td>
<td>Time to first organ damage (SDI)</td>
<td>Y</td>
<td>Accrual of damage associated with glucocorticoid exposure recorded as yes/no. Adjusted for disease activity</td>
</tr>
<tr>
<td>Alarcon et al. [32]</td>
<td>2004</td>
<td>352</td>
<td>Up to 6 years</td>
<td>SDI</td>
<td>Y</td>
<td>Accrual of damage dose-dependently associated with glucocorticoid exposure</td>
</tr>
<tr>
<td>Toloza et al. [33]</td>
<td>2004</td>
<td>158</td>
<td>2 years</td>
<td>First organ damage (SDI)</td>
<td>Y</td>
<td>Time to damage accrual shorter in glucocorticoid-exposed patients</td>
</tr>
<tr>
<td>Gladman et al. [34]</td>
<td>2003</td>
<td>73</td>
<td>At least 15 years</td>
<td>SDI</td>
<td>Y</td>
<td>Author attribution of glucocorticoid association of damage (definitely, possibly, independent)</td>
</tr>
<tr>
<td>Zonana-Nacach et al. [16]</td>
<td>2000</td>
<td>539</td>
<td>Up to 15 years</td>
<td>SDI</td>
<td>Y</td>
<td>Glucocorticoid exposure predictive of osteoporotic fracture, cataracts, coronary artery disease, avascular necrosis, diabetes mellitus</td>
</tr>
</tbody>
</table>

SDI: SLICC/ACR damage index.
receiving the highest quintile of prednisone exposure had a 2-fold increased risk of damage compared with the group with no prednisone exposure. Bruce et al. [8] recently described risk factors for damage accrual in the SLICC inception cohort of over 1700 patients, also reporting that glucocorticoid exposure was an independent predictor of organ damage accrual after adjusting for disease activity. Indeed, the association between disease activity and damage accrual was greater among patients taking glucocorticoids, suggesting a compounding effect of glucocorticoid use and disease activity on damage accrual in SLE. Yee et al. [29] also reported an independent effect of glucocorticoid exposure on damage accrual in an inception cohort of 382 patients, after adjusting for disease activity and other variables. Finally, the pattern of accumulation of damage resulting from glucocorticoid use was examined in a smaller inception cohort study from Canada [34]. Seventy-three patients with at least 15 years follow-up were included, with each domain of the SDI designated by the authors as definitely, possibly or not-at-all related to glucocorticoid therapy. At the end of the first year of follow-up, possibly or definitely glucocorticoid-related damage accounted for 58% of damage accrued in this period, and this had increased to 80% at 15 years. These studies suggest that a significant proportion of damage accrual in SLE, both early and late, is attributable to glucocorticoid therapy.

Several other studies based on registries and similar cohorts have also been recently reported. Petri et al. [30] reported on 2054 patients with a mean follow-up of 6.4 years, and identified a dose-dependent effect of prednisone exposure on damage accrual, with an odds ratio of 1.9 in patients receiving prednisone 10–19 mg/day, increasing to 4.0 in patients exposed to >20 mg/day. Other predictors identified for damage accrual included older age, higher disease activity, low complement levels, positive dsDNA antibodies and greater number of ACR criteria for lupus, with the use of HCQ associated with less damage accrual. A subsequent paper by Al Sawah et al. [15] identified a dose–response relationship of damage with prednisone exposure, with a hazard ratio of 2.5 in patients exposed to mean prednisone >20 mg/day compared with <7.5 mg/day. It was calculated that 1 mg/day increase in prior prednisone dose over the study period (mean 6.2 years) was associated with a 3% risk of future organ damage [15].

Is there a safe dose of glucocorticoid in SLE?

Studies in RA cohorts indicate that low-dose glucocorticoid use was associated with weight gain, hyperglycaemia, hypertension, reduced bone density, and increased risk of fractures, infections and cataracts [35, 36]. In a review of glucocorticoid-related adverse events in RA [37], two distinct dose-related patterns of adverse events were suggested, a linear effect for Cushingoid phenotype, skin changes, shortness of breath and sleep disturbance and a threshold effect for other adverse effects, including cataracts, weight gain, glaucoma, depression and increase in blood pressure. Data on the threshold for damaging effects of glucocorticoids in SLE are now emerging.

In 2014, a Spanish study of 230 patients enrolled at diagnosis investigated the association between glucocorticoid use and damage accrual in SLE over 5 years follow-up [14]. This was the first study to report specifically on the effect of glucocorticoids in domains of the SDI (osteoarticular fracture, avascular necrosis, diabetes mellitus and cataracts) most directly attributable to glucocorticoids. Patients were categorized into four groups: no prednisone exposure, and low (0–7.5 mg/day), medium (7.5–30 mg/day) and high (>30 mg/day) prednisone exposure. Patients that had accrued damage at year 5 had received significantly higher mean daily prednisone, whether overall or glucocorticoid-attributable damage was considered. Medium or high doses of prednisone were associated with a greater risk of damage accrual; however, there were no differences between low and no prednisone dosages. This finding is similar to that of Thamer et al. [31], who reported no significant increase in damage accrual with doses of glucocorticoids below 180 mg/month. A study from our centre demonstrated lower damage accrual with prednisolone doses <5 mg/day in the setting of low disease activity, when compared with a cut-off of 7.5 mg/day [38]. These findings indicate the need for more stringent thresholds for prednisolone use than are commonly applied. However, studies in which glucocorticoid dose is analysed as a continuous variable, to determine what dose of glucocorticoids represents a threshold for damaging effects, are still awaited.

In summary, in addition to their long-known Cushingoid effects, emerging evidence now indicates that glucocorticoid use is predictive of lupus-related damage accrual, independent of the association of glucocorticoid use with disease activity, and at exposures that would conventionally be regarded as low dose. The biological mechanisms for such an effect are not known and require extensive additional research, but in the meantime it is clear that reduced glucocorticoid exposure is an urgent aim in the management of SLE.

Lessening the burden of glucocorticoids

Tapering of glucocorticoids

Is it possible to reduce exposure to glucocorticoids in lupus patients while maintaining disease control? In SLE, there have been no trials suggesting that ongoing, long-term administration of glucocorticoids once disease activity has been controlled has any clinical or serological benefit. In other autoimmune diseases, however, there is evidence that longer duration of glucocorticoid use is beneficial. A systematic review of prednisone withdrawal in ANCA-associated vasculitis found that late (>12 months) continuation of prednisone was associated with reduced frequency of relapses [39]. Various guidelines (e.g. [40, 41]) advocate the reduction of glucocorticoid dose in stable disease, but there are no standardized protocols to guide physicians as to the optimal rate of
tapering glucocorticoids. To highlight the heterogeneity of physician practice in tapering, a Canadian study surveyed 72 physicians with regard to glucocorticoid reduction [42]. They were presented with various scenarios of patients with LN and asked to decide whether to continue or cease prednisone. They found that in equal proportions, physicians would cease prednisone in all situations, continue in all situations or continue in some situations. This highlights the lack of an evidence-based approach to the tapering of glucocorticoids in SLE. Indeed, few prospective studies comparing different glucocorticoid-tapering regimens have been reported. In a multicentre, prospective trial of 81 patients with LN [43], following an initial 3-day pulse of i.v. methylprednisolone, patients were divided into rapid and standard steroid wean, with concurrent enteric-coated mycophenolate. At week 24, there was a 50% difference in cumulative steroid dose between the two approaches, with rates of complete renal response and mortality being almost identical. However, partial response was achieved more frequently with the standard regimen. Continuation or withdrawal of low-dose prednisone to prevent relapse of LN was studied in a small, randomized trial of 15 patients [44]. Over a 3-year period, no significant increase in relapse rate was detected in association with glucocorticoid withdrawal. These findings suggest that larger trials of prednisone withdrawal in SLE are feasible and should be undertaken.

Another retrospective study addressed the effect of glucocorticoid tapering in lupus patients on overall disease activity [45]. A total of 866 patients in the Hopkins Lupus Cohort on 5 mg/day of prednisone were identified, and sustained prednisone dosage of <5 mg/day was considered successful tapering. Lower disease activity and the absence of musculoskeletal or cutaneous lupus activity were predictors for successful tapering. The proportion of patients successfully tapering increased over time, with successful tapering after the year 2000 50% more likely than prior to 2000. This may reflect increasing awareness of glucocorticoid-related harm in lupus.

One important aspect of this issue is that symptoms such as fatigue, arthralgia, myalgia, headaches, mild cognitive symptoms and lassitude may be treated with glucocorticoids. These symptoms can be attributable to active SLE, but also to non-inflammatory causes such as FM [46, 47], depression [48] and hypothyroidism [49], which are common in lupus patients. Tools to reliably distinguish these conditions from active SLE are currently lacking, and their development may allow a more empirical approach to the use, and withdrawal, of glucocorticoids in these settings.

LN—no oral glucocorticoids. Is this possible?

In 2013, an innovative study was published that described 50 consecutive patients at a single centre in the UK, where oral glucocorticoids were not utilized in the treatment of LN [50]. Patients received two doses of rituximab (1 g) and methylprednisolone (500 mg), 2 weeks apart. Ninety percent of patients (45/50) achieved partial or complete remission of LN, with no apparent increase in relapse rates, at up to 3 years of follow-up. This is the first regimen published that does not incorporate oral glucocorticoids in the treatment of LN. Results from a multicentre, randomized controlled trial of this regimen that is underway are awaited, but of note, rituximab is not currently approved for the treatment of LN because the single randomized controlled trial of its use as an add-on to standard of care did not report a significant benefit [51]. Although not currently approved, both the ACR and EULAR recommendations for the treatment of LN now include use of rituximab [52, 53].

Optimizing existing therapies in lupus

The ability to achieve disease control with lower doses of glucocorticoids through combination therapy with other agents is often referred to as steroid-sparing, although there is little evidence that existing agents have direct effects enhancing the activity of glucocorticoids per se. Nonetheless, there is a growing literature suggesting that optimizing immunosuppressant therapy may improve patient outcomes [54], with the potential thereby to reduce reliance on glucocorticoids. One recent study suggested that leucocyte levels of glucocorticoid-induced leucine zipper are associated with the control of SLE by oral glucocorticoids [55], potentially representing a biomarker for glucocorticoid adequacy, but this requires confirmation in a longitudinal study. In contrast, direct measurement of blood levels of non-glucocorticoid medications has been shown to be of value.

Anecdotal reports and physician experience suggest HCQ is steroid sparing, but no controlled study has demonstrated this [56]. In contrast, optimum use of HCQ in SLE has recently been closely examined, with several studies addressing the utility of measurement of HCQ levels [57]. In a prospective, 6-month study of 143 patients, low HCQ concentrations were associated with more active disease and were a strong predictor for disease flare [58]. These results were supported by a second, multicentre prospective study of 300 patients with cutaneous lupus, which found that complete disease remission was associated with higher blood HCQ concentrations [59].

MMF, an immunosuppressant initially used in transplantation, is administered as a pro-drug that is hydrolyzed to its active metabolite, mycophenolic acid (MPA). Steroid-sparing properties of mycophenolate have been suggested in both renal and non-renal lupus [60–63], and recent literature has indicated that low MPA levels may correlate with increased flare risk [64]. Similarly, a cross-sectional study of 71 lupus patients found a clear inverse correlation between MPA levels and SLE disease activity [65].

Similarly, Griffiths et al. [66] reported a randomized study of 39 patients suggesting that AZA was an effective steroid-sparing agent, with doses of prednisolone reduced by 50% at 12 months accompanying AZA use. Measurement of the thiopurine metabolite, 6-thioguanine nucleotide, is common in the management of IBD as it is supported by evidence of clinical benefit [67]. In contrast,
there is a lack of data regarding monitoring of thiopurine metabolite levels in SLE, with two small studies failing to detect an association between 6-thioguanine nucleotide concentration levels and lupus disease activity [68, 69]. This disparity with the IBD literature is surprising, and may reflect study design and low patient numbers. The ability of MTX to be used as a steroid-sparing agent in SLE has been suggested by a randomized, controlled trial, where MTX-treated patients were able to reduce the average daily dose of prednisolone by 22% [70]. Additionally, there is evidence that ciclosporin has significant steroid-sparing properties in patients with non-renal lupus manifestations [66], and a recent report suggested a specific action of ciclosporin on Th17 cytokine pathways, associated with markers of severe SLE [71], that are resistant to suppression by glucocorticoids [72].

**Emerging therapies and reduction of glucocorticoids**

Reduction in glucocorticoid use in SLE will be achievable only in the context of control of disease activity. The ability of new treatments to demonstrate steroid-sparing properties has emerged as a key end point in the development of new lupus medications. Unfortunately, the paucity of positive clinical trials for novel therapies in SLE limits the option for physicians to use these approaches today. For example, early treatment with rituximab suggested its use enabled a reduction in glucocorticoid burden [73]; however, efficacy of rituximab in subsequent controlled trials was not demonstrated [74].

Belimumab, a treatment developed specifically for SLE, which targets B cell-activating factor of the TNF family (BAFF) [75], has recently been approved in many countries after two successful phase III trials of belimumab that included reduction in prednisone dose as a secondary end point [76, 77]. For example, Navarra et al. [76] found a significant increase in the proportion of patients achieving sustained reduction in prednisone dosage of at least 50%, or to <7.5 mg/day, in response to belimumab. Indeed, post hoc analyses of the BLISS trials [78] confirmed a steroid-sparing effect, with more patients who received belimumab on prednisone doses >7.5 mg being able to reduce dosage by >25%.

Longer-term, post-marketing observational cohort studies of belimumab use in the USA have recently been reported [79]. Sustained improvement in SLE disease activity was observed in 501 patients who had received at least eight infusions of belimumab, an outcome achieved in the setting of reduction in glucocorticoid use. At baseline, 77% of patients were receiving glucocorticoids, at a mean prednisone dose of 19.9 mg/day. By 6 months, over 85% of patients had reduced or discontinued prednisone, and the mean prednisone dose had reduced to 8.4 mg/day, which fell further by 24 months. This evidence supports the steroid-sparing effect of disease control via use of belimumab. Supporting this effect of BAFF inhibition, another anti-BAFF monoclonal antibody, tabalumab, has recently been studied in two large phase III clinical trials [80, 81]. The primary efficacy end point was achieved in only one trial, in which numerically more patients in a tabalumab-treated arm were also able to reduce glucocorticoid exposure. However, as efficacy end points were not met in both trials, development of this drug has not continued.

Several anti-type I IFN therapies have also undergone evaluation in recent clinical trials. The anti-IFN-α mAb rontalizumab and sifalimumab have completed phase II trials [82, 83]. Both trials demonstrated a reduction in clinical disease activity measures; however, rontalizumab failed to significantly meet primary end points. Sifalimumab demonstrated superior reduction of disease activity and achievement of glucocorticoid tapering compared with placebo, raising the prospect that anti-type I IFN treatments may offer a way to reduce glucocorticoid use in SLE. In keeping with this possibility, anifrolumab is a type I IFN receptor antagonist, and patients are currently being recruited for a phase III trial (NCT02446899). A recent phase II trial of anifrolumab in 305 patients, with the primary end point being a composite of reduced disease activity along with a sustained reduction of oral glucocorticoid dose, has been reported in abstract form [84]. This end point was achieved in significantly greater proportion of anifrolumab-treated patients compared with placebo. A secondary end point of at least 25% reduction in glucocorticoid dose was achieved in the lower-dose (300 mg monthly) anifrolumab group.

Together, the positive findings suggest the possibility of control of disease activity with less reliance on glucocorticoids in favour of more specific SLE treatments. However, other than belimumab, none of these treatments are expected to be widely available outside trial settings for several years. It is hoped that the balance of efficacy vs safety for these targeted therapies will be much more favourable than we now know to be the case for glucocorticoids.

**Conclusions**

The treatment of SLE remains an area of considerable uncertainty, with many conventional approaches not backed by high-quality evidence. While glucocorticoids are considered highly effective in treating the inflammatory manifestations of SLE, a surprisingly scant literature supports this, and little or no evidence base supports current approaches to glucocorticoid initiation, reduction or cessation. While recognition of traditional Cushingoid adverse effects of glucocorticoids is longstanding, the lack of safe, effective targeted therapies for SLE has resulted in a degree of acceptance, or even nihilism, among physicians regarding the inevitability of glucocorticoid-induced harm. Neuer evidence now provides a compelling case that the long-term use of glucocorticoids in SLE is associated with harmful effects on disease outcomes, independent of the association of glucocorticoid use with active disease, implying a direct compounding harmful effect of glucocorticoids on SLE itself over time. These data strongly suggest that a change in paradigm is needed, wherein reduction in glucocorticoid burden...
becomes an integral and empirically driven part of treatment regimens in SLE. We believe that it is time for a major research agenda to validate glucocorticoid-reduction strategies, and that glucocorticoid reduction should be recognized as a treatment end point in itself in studies of therapies for SLE. In the meantime, it is time for the conversation about reducing glucocorticoids among physicians, and between them and their patients, to be louder.

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