Review Article

Glucocorticoid-free Treatment of Systemic Lupus Erythematosus: Is it Feasible?

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Abstract

Glucocorticoids (GCs) remain the mainstay of treatment in systemic lupus erythematosus (SLE) more than 60 years after their discovery. Despite their effectiveness in controlling disease activity, the long-term use of GC often causes side effects that increase morbidity and mortality in SLE patients. Evidence from randomized controlled trials on the appropriate dosing and tapering of GC in SLE is scarce. Historically, high doses of GC were used in the treatment of SLE. Fortunately, there are emerging data showing a lower dose of GC is equally effective compared to a higher GC in controlling disease activity and has fewer adverse effects. The introduction of various GC-sparing immunosuppressive (IS) treatments such as cyclophosphamide (CYC), azathioprine, mycophenolate mofetil, calcineurin inhibitors, and biologic agents has assisted in reducing the GC doses in SLE. The aims of this narrative review are to give an overview on the GC mechanisms of actions, the strategies to reduce GC-related toxicity, the evidence of low GC dose protocols and finally to discuss the viability of GC-free treatment of SLE.

Key Words: *Glucocorticoids, systemic lupus erythematosus, treatment*

Introduction

The introduction of glucocorticoids (GCs) as the key treatment in systemic lupus erythematosus (SLE) has improved the prognosis of patients with severe disease.[1] Despite lack of clinical evidence, the use of high-dose oral GC, defined as 0.5–1 mg/kg/day of prednisone equivalent,[2] has been historically used in the management of SLE.[3,4] In addition, there is no standard protocol of tapering the prednisolone dose and hence patients are at risk of prolonged exposure and higher cumulative dose GC. In view of the potential significant complications of this treatment, GC-related damages such as avascular osteonecrosis, osteoporotic fractures, diabetes mellitus, cardiovascular (CV) disease, and cataracts are included in the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI).[5] Numerous studies have attempted to use a lower GC dose regimen and there is emerging evidence of its effectiveness, with fewer and less severe adverse events.[6-13] More recently, there has been a paradigm shift in guidelines toward recommendation of a lower GC dose in the management of SLE.[14-16] The objectives of this narrative review are to discuss the strategies to reduce GC-related toxicity based on its mechanism of actions, clinical evidence of low-dose GC use, and finally to review whether steroid-free treatment regimens are viable in SLE.

Search Strategy

To review the evidence of low-dose GC therapy in SLE, we searched the available literature using the OvidSP databases (Medline and Embase). Appropriate combinations of search terms including "low dose," "corticosteroids," "glucocorticoids," "prednisolone," "prednisone," "steroids," and "lupus" were used. The search was limited to publications in the English language. There was no limit of the time of publications. We also included pertinent articles obtained from searching references in the articles found in the primary search.

Glucocorticoid dose classification

In the management of patients with SLE, the dose of GC is often dictated by the severity of disease flare, with

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high-dose oral regimens or high-dose pulsed steroids reserved for acute major organ involvement activity.[15-17] Patients with mild SLE disease activity may not require GC therapy activity.[15-17] If hydroxychloroquine and/or conventional immunosuppressants do not adequately control disease, low- or moderate-dose GC may be considered to help control mild or moderate disease activity, respectively. In this review, low-dose GC is defined as ≤7.5 mg prednisone equivalent a day. Medium-dose GC is defined as >7.5 mg but ≤30 mg prednisone equivalent a day. High dose GC is defined as >30 mg, but ≤100 mg prednisone equivalent a day while a very high dose GC is >100 mg prednisone equivalent a day. High-dose intravenous GC pulse therapy is defined as ≥250 mg prednisone equivalent a day.[2]

Adverse effects of glucocorticoid use

While GCs have potent anti-inflammatory and immunosuppressant actions that can swiftly control disease activity, GCs can be considered a double-edged sword that can be associated with significant adverse effects. A large number of studies have demonstrated an independent association between GC and various adverse effects such as osteoporosis, cataract, glaucoma, myopathy, glucose intolerance, dyslipidemia, CV diseases, psychiatric disturbances, and adrenal suppression in SLE.[18-21] Although the association between damage and GC use (or dose) observed in cohort studies could be due to the confounding indication of steroid in high disease activity of SLE, a number of studies including from the Hopkins Lupus, Toronto, and Asian multicenter cohorts have demonstrated that GCs were an independent risk factor for lupus damage even after adjustment for disease activity.[22-24] A recent systematic review including over 16,000 patients concluded that the average daily GC dose was associated with future CV events (relative risk [RR]: 1.12, 95% confidence interval [CI] [1.02–1.24]) and osteoporotic fractures (RR: 1.21 [1.11–1.33]) while a higher average cumulative GC dose and a higher proportion of patients on GC were associated with osteonecrosis.[25]

GC exposure is also associated with infection risk. In a nested case–control study of 249 patients with SLE, the daily prednisolone dose was independently associated with an increased risk of infection (odds ratio [OR]: 1.10, 95% CI: 1.04–1.17).[26] Similarly, in a study of 100 patients in Western India, both GCs use and, in particular, a dose above 10 mg/day was found to be a significant risk factor for infection.[27] These wide ranges of adverse events make GC minimization and replacement with GC-sparing immunosuppressive (IS) treatments of paramount important strategy in the management of SLE.

Mechanism of actions of glucocorticoids and their clinical implications

The anti-inflammatory effects of GCs occur through three mechanisms of action, namely direct and indirect genomic effects and nongenomic mechanisms.[28,29] In the genomic pathway, GCs bind to cytosolic glucocorticoid receptors (cGRs) to form GC-cGR complexes. The GC-cGR complex translocates to the nucleus where it activates genomic signaling by interacting with GC response elements. On DNA binding, conformational changes to the GC-cGR complex can lead to the recruitment of co-regulators; either coactivators (for transcriptional activation or transactivation) or corepressors (for transcriptional repression or transrepression).[28] Transactivation increases the transcription of anti-inflammatory genes (e.g., interleukin-10 and annexin A1) while transrepression inhibits the transcription of pro-inflammatory genes (e.g., interleukin-6, interleukin-8, and tumor necrosis factor-a). Indirect genomic transrepression also occurs when the GC-cGR complex prevents pro-inflammatory transcription factors, such as the nuclear factor-κB, interferon regulatory factor-3, and activator protein-1 from binding to their DNA binding site. The clinical IS effects of the genomic pathway usually occur after several hours or days.[30]

The desirable anti-inflammatory and IS effects of GC are mostly mediated by transrepression, while transactivation is considered to be responsible for some GC adverse effects, such as the induction of hepatic gluconeogenetic enzymes.[28-31] Saturation of the GC receptor occurs rapidly with 30–50 mg per day of prednisone equivalent and hence a higher dose beyond this will have a minimal additional anti-inflammatory benefit due to a nonlinear relationship between receptor occupancy and GC dose. The transactivation process that mediates the majority of the side effects of GC remains active with full saturation achieved at higher doses, typically up to 100 mg/day.[2,32]

The nongenomic pathways have rapid effects (seconds to minutes) on inflammation that are not mediated by changes in gene expression.[28,30] The nongenomic effects occur as a result of interaction between a higher concentration of GC (prednisone equivalent dose of >100 mg/day) with membrane-bound receptors or directly with the membrane which leads to inhibition of arachidonic acid release.[28,30] Although the exact mechanisms of the nongenomic pathway remain unclear, it can be mediated by 2 mechanisms: specific nongenomic effects related to the activation of membrane GC-receptors and nonspecific nongenomic effects which occur due to the saturation of all of the receptors with high-dose GCs and begin to dissolve directly in the cell membrane, leading to other intracellular metabolic changes.[28] An *in vitro* study demonstrated that the nongenomic pathway was more responsive to methylprednisolone (MP) and

dexamethasone, which are up to five times more potent at activating the nongenomic pathway than other GCs.[33]

Knowledge of the GC mechanism of action in rheumatic diseases[29-31] has contributed to several strategies to optimize the anti-inflammatory effects of GCs while minimizing their adverse events in the treatment of SLE.

Strategies to reduce glucocorticoids use and toxicity

Based on the mechanism of action of GCs, one of the earliest strategies to reduce overall GC exposure was the utilization of high-dose intravenous (IV) MP pulses to achieve rapid anti-inflammatory effects via the nongenomic pathway.[4,34] The use of other IS agents (e.g., cyclophosphamide [CYC], mycophenolate mofetil [MMF], methotrexate [MTX], and azathioprine [AZA]) and hydroxychloroquine [HCQ]) have important steroid-sparing properties by facilitating the tapering of oral GCs treatment.[35,36] Newer strategies of multi-targeted therapy approaches with MMF and calcineurin inhibitors (CNIs) [37-39] and the use of biologic agents[40-42] in SLE have also facilitated the lowering of GC exposure. These strategies are discussed in detail below.

Pulse intravenous methylprednisolone followed by lower oral prednisolone dose

Recent guidelines have recommended the use of IV MP in acute, organ-threatening disease or moderate-to-severe SLE activity.[15-17] The potent anti-inflammatory effects of MP, which mainly occur through the non-genomic pathway allows a faster tapering of oral prednisolone. In addition, MP pulse therapy has been demonstrated to produce cGR saturation in the genomic pathway leading to a rapid and dramatic downregulation of the receptors[43] which may reduce undesirable GC-related side effects occurring due to genomic transactivation.[44] The initially reported experiences of the use of IV pulse MP in lupus nephritis (LN)[34] and extrarenal lupus[45] have demonstrated an improvement of disease activity which could be maintained with a lower dose of steroids.

However, the use of high doses of oral GC was recommended in the ACR guidelines for the management of LN (published over 20 years later than the studies described above),[3] as the evidence from randomized controlled trials (RCTs) for the most appropriate oral prednisolone starting dose and tapering scheme was still lacking. The MYLUPUS trial was a pilot RCT that compared the efficacy of medium-dose oral GC (0.5 mg/kg/day) to high-dose GC (1 mg/kg/day) in patients with flare proliferative LN.[6] In this study, all subjects received 3 doses of pulse IV MP 500 mg and extended-release mycophenolic acid. There were similar complete and partial remission (CR and PR) rates in the low- and high-dose groups, 20.5% versus 19.0% (P = 0.87) and 35.9% versus 47.6% (P = 0.29), respectively, at 6 months. There was a lower rate of infections that occurred in the medium-dose GC group compared to the high-dose group (35.9% vs. 57.1%, respectively, P = 0.056). Herpes zoster was reported in seven patients, all of whom were in the high-dose group (P = 0.012).[6] Another recent small RCT in proliferative LN from a single center in Bangladesh also demonstrates similar efficacy between the medium-dose and high-dose groups, with the initial induction treatment consisting of IV MP and IV CYC although the study did not meet its sample size target and should be interpreted with caution.[13]

An observational study of two LN cohorts revealed that repeated pulse IV MP and lower GC use of ≤30 mg/day in the Spanish Lupus-Cruces University Hospital (CPC) Cohort showed better renal response compared to the French Bordeaux University Hospital Cohort (BC), who used the conventional high-dose GC protocol.[10] In this study, a significantly higher number of patients in the CPC cohort achieved complete remission (CR) at 6 months than the BC cohort (69% vs. 30%, respectively, P = 0.001) with a lower average prednisone dose at 6 months (8.3 ± 1.6 vs. 21 ± 11.7 mg/daily, respectively, P < 0.001).[10] In another comparative study of patients from the CPC cohort showed a similar disease control in patients who were treated with low-dose prednisolone (maximum ≤30 mg/day) by the autoimmune disease unit, compared to those treated with high doses (>30 mg/day) by the internal medicine department. The low-dose prednisolone group (CPC-low dose) was also able to achieve a lower prednisolone maintenance therapy of ≤5 mg/day, by using MP pulses, HCQ, and/or early IS drugs.[11] The GC-related and CV damage accrual was also lower in the CPC-low-dose group with adjusted HR (95% CI) of 0.23 (0.07–0.80) and 0.28 (0.08–0.95) respectively.[11]

In summary, these studies demonstrate the benefit and safety of a lower prednisolone dose protocol and the use of IV pulse MP may facilitate the reduction of oral GC dose. However, it is important to note that majority of the studies involved patients with LN and larger randomized trials are needed, especially among non-LN patients to further confirm whether lower oral prednisolone protocol is applicable for all SLE patients. Table 1 summarizes high and low-dose GC protocols in SLE with or without LN, while Table 2 summarizes clinical studies which use lower background doses of prednisolone in LN. Figure 1 illustrates the paradigm shift from the conventional high-dose to low-dose GC regimens.

While high-dose IV MP may have a number of benefits over longer oral regimens, it is relatively contraindicated in SLE patients with concomitant severe infection.[15] The use of high-dose MP also may cause several other adverse effects such as uncontrolled acute hypertension and hyperglycemia.[47] Based on the saturation dose of the nongenomic mechanism and several clinical studies,

Table 1: Comparisons of treatment response and adverse events between high and low doses of glucocorticoids protocols in systemic lupus erythematosus with or without lupus nephritis

Studies	Methodology (type of study/ subjects)	Treatment protocol	IV MP dose	High-dose prednisolone group (*n*=number of subjects)	Low-dose prednisolone group (*n*=number of subjects)	Outcomes (high vs. low-dose group)
MY LUPUS, 201[6]	Randomized control trial/ LN/64% Caucasian	All received IV MP and enteric-coated mycophenolate prednisolone 0.5 mg/kg/day versus 1 mg/kg/day	500 mg×3	1 mg/kg for 10 days followed by a tapering to 5 mg/day (BW ≤65 kg) or 10 mg/day (BW >65 kg) by week 24 (*n*=39)	0.5 mg/kg for 10 days followed by a tapering to 2.5 mg/day (BW ≤65 kg) or 5 mg/day (BW >65 kg) by week 24 (*n*=42)	Similar CR (19.0% vs. 20.5%, *P*=0.87) and PR (47.6% vs. 35.9%, *P*=0.29) Infection higher in high-dose group (57.1% vs. 35.9%, *P*=0.056) Herpes zoster higher in high-dose group (16.7% vs. 0%, *P*=0.012)
Fischer-Betz *et al*., 2012[7]	Prospective observational study/first LN episode/all Caucasian	All received IV CYC No steroid for LN (the use and dose of prednisone was based solely on the presence of extrarenal SLE manifestations)	None	≥20 mg/day (*n*=21)	<20 mg/day (*n*=19)	Similar CR response rates: CR was achieved in 52.6% versus 71.4% (*P*=0.37) and PR in 26.3% versus 14.3% (*P*=0.58) Similar infection rate: 61.4% versus 52
Lupus-Cruces LN, 2014[8]	Observational case-control/ LN/≥80% Caucasian	Low-dose group: Lupus-Cruces protocol (CPC-LN) - CYC 500 mg+MP 125 mg fortnightly High-dose group: Historical cohort (NIH CYC protocol and high-dose prednisolone)	CPC-LN protocol: 250-500 mg×3 Historical cohort Median dose 0 (0-1) g	1 mg/kg/day (median 50 mg/day) with variable duration and tapering scheme (based on physician's discretion) (*n*=30)	≤30 mg/day (median 20 mg/day) with a rapid tapering to 20, 15, and 10 mg/day every 2 weeks This was followed by a tapering of 2.5 mg/day every 4 weeks until A maintenance dose of 2.5-5 mg/day was reached (*n*=15)	Higher CR and PR in CPC (low dose) group at 6 months (80% vs. 47%, *P*=0.015) and at 12 months (87% vs. 63%, *P*=0.055) GC-related AE lower in CPC group (7% vs. 67%, *P*<0.0001)
Ruiz-Arruza *et al*., 2015[9]	Observational case-control/ SLE with n SLEDAI score ≥6 (extrarenal)	Low-dose group: Lupus-Cruces protocol - versus high-dose group: Historical cohort	Low-dose group: 34% High-dose group: 10%	>30 mg/day (mean 63.4 mg/day) (*n*=30)	≤30 mg/day (mean 11 mg/day) (*n*=30)	SLEDAI improvement was similar in both groups High-dose group was more likely to accrue new damage
Ruiz-Irastorza *et al*., 2017[10]	Observational case-control/ LN/>70% Caucasian	Low-dose group Lupus-Cruces protocol: CYC 500 mg+MP 125 mg fortnightly High-dose group (French Bordeaux University Hospital) Euro-Lupus protocol	250-500 mg×3 doses	0.7-1.0 mg/kg/ day, and reduced by 2.5-5.0 mg every 2-4 weeks until the long-term maintenance dose (*n*=44)	≤30 mg/day, with a rapid tapering to 20, 15, and 10 mg/ day every 2 weeks, followed by a tapering of 2.5 mg/day every 4 weeks until A maintenance dose of 2.5-5 mg/day (*n*=29)	Patients in the low-dose group (CPC) Achieved more CR at 6 months (69% vs. 30%, *P*<0.001) and 12 months (86% vs. 43%, *P*<0.001) Similar relapse rate (7% vs. 14%, *P*=0.3) Lower GC-associated toxicity (7% vs. 34%, *P*=0.007)

Contd...

Table 1: Contd...

Studies	Methodology (type of study/ subjects)	Treatment protocol	IV MP dose	High-dose prednisolone group (*n*=number of subjects)	Low-dose prednisolone group (*n*=number of subjects)	Outcomes (high vs. low-dose group)
Lupus-Cruces cohort (CPC), 2018[11]	Observational case-control/ SLE/>90% Caucasian	CPC-low dose (maximum prednisolone ≤30 mg/day) CPC-high dose (prednisolone >30 mg/day)	Low-dose group: Mean 1.3±1.0 g High-dose group: Mean: 1.3±1.3 g	Maximum prednisolone 36.8±27.9 mg/day Average prednisolone dose up to year 5: 9.4±8.9 mg/day (*n*=74)	Maximum prednisolone 15.09±14.16 mg/day Average prednisolone dose up to year 5: 2.8±2 mg/day (*n*=213)	In low-dose group versus high-dose group: Similar SLEDAI score improvement at year 5 (2.8 vs. 3, *P*=0.6) and similar mean SLEDAI scores from year 1 to 5 (3.8 vs. 4.3, *P*=0.02) Lower mean SDI score in at year 1 (0.1 vs. 0.3 *P*=0.02) and year 5 (0.35 vs. 0.6, *P*=0.03)
Ruiz-Irastorza *et al*., 2019[12]	Observational case-control/ SLE (cutaneous and arthritis >70%)/ %	Low-dose group: Lupus-Cruces cohort (CPC) High-dose group: French Bordeaux University Hospital	Low-dose group: 125-500 mg×3 High-dose group: 1 g×3	0.7-1.0 mg/kg/day, and reduced by 2.5-5.0 mg every 2 to 4 weeks until The long-term maintenance dose	<30 mg/day	The reduction in the SLEDAI score was similar in both groups (*P*>0.05 at every yearly comparison) In low-dose group, more frequent ClinROnT was achieved in cutaneous involvement (82% vs. 42%, *P*<0.001); articular involvement (82% vs. 41%), *P*<0.001; nephritis (53% vs. 21%, *P*=0.07) CNS involvement, 3/3 (100%) versus 0/6 (0%), *P*=0.012
Bandhan *et al*., 2022[13]	Randomized control trial/LN/ Bangladeshi	IV MP and monthly CYC	500 mg×3	1 mg/kg/ day (maximum 60 mg/ day) Tapered 10 mg/day every 2 weeks until 40 mg was reached, then 5 mg/day every 2 weeks until maintenance dose of 7.5 mg/day *n*=16	0.5 mg/kg/ day (maximum 30 mg/ day) Tapered 5 mg/day every 2 weeks until maintenance dose 7.5 mg/day *n*=16	Similar CR at 24 weeks between low- and high-dose groups (66.7 vs. 66.7%, *P*=0.99) GC-related AE (Cushingoid facies, abdominal stria, bruising, and infections) were numerically higher in the high-dose group

BW: Body weight, AE: Adverse event, ClinROnT: Clinical remission on treatment, CR: Complete remission, CYC: Cyclophosphamide, GC: Glucocorticoid, LN: Lupus nephritis, MP: Methylprednisolone, NIH: National Institute of Health, PR: Partial remission, IV: Intravenous, SLE: Systemic lupus erythematosus, SDI: Systemic lupus international collaborating clinics Damage Index, CPC: Lupus-cruces cohort, SJLEDAI: Systemic lupus erythematosus disease activity index

doses above 500 mg may pose a higher risk of adverse events with little additional anti-inflammatory benefit.[32] Findings from several clinical studies support this notion by demonstrating that a lower dose of MP pulses of 100–500 mg (cumulative dose ≤1500 mg) had a similar response to the conventional high-dose 500–1000 mg pulse (cumulative dose 1500–3000 mg) but with fewer serious infections and GC-related adverse events.[10,45,48-50]

Table 2: Clinical studies on lower background of prednisolone in lupus nephritis patients

Studies	Methodology (type of study)	Treatment protocol (*n*=number of subjects)	IV MP induction dose	Prednisolone starting dose and tapering scheme	Outcomes
RITUXILUP protocol[41]	Open-label observational study/40% Caucasian	2 doses of rituximab (1 g) and maintenance treatment of MMF *n*=50	500 mg day 1 and 15	0	72% (*n*=36) achieved CR (median time 36 weeks and 18% (*n*=9) achieved persistent PR (median time 32 weeks) 22% relapse
Multi-targeted induction[37]	Randomized control trial/ Chinese	Tacrolimus + MMF (*n*=181) versus IV CYC (*n*=181) for 6 months	500 mg×3	0.6 mg/kg/day for 4 weeks Tapered by 5 mg/day every 2 weeks to 20 mg/day and then by 2.5 mg/day every 2 weeks to a maintenance dose of 10 mg/day	CR higher in multi-target group than in the IV CYC group at 6 months (45.9% vs. 25.6%), *P*<0.001 Numerically higher serious infection (7.2% vs. 2.8%) and VZV (6.6% vs. 3.3%)
AURA-LV[38]	Randomized control trial/ Caucasian 47.7%	Voclosporin low dose (*n*=89) versus high dose (*n*=88) versus placebo (*n*=88) All received MMF		Initial prednisolone 20 mg/day (subjects <45 kg) or 25 mg/day (≥25 mg/day) for 2 weeks Tapered to 2.5 mg daily at week 16	Higher CR in low-dose VCS versus placebo at week 24 (32.6% vs. 19.3%, *P*<0.001) Both low-dose and high-dose VCS were superior to placebo at week 48 (49.4% vs. 39.8% vs. 23.9%) Higher AE in low-dose VCS compared to high-dose VC and placebo (28.1% vs. 25.0% vs. 15.9%)
AURORA 1[39]	Randomized control trial/38% Caucasian, 30% Asian	VCS 23.7 mg (*n*=179) versus placebo (*n*=178) All received MMF	250 mg (BW <45 kg) or 500 mg (BW ≥45 kg) × 2 doses	Initial prednisolone 20 mg/day (subjects <45 kg) or 25 mg/day (subjects ≥45 kg) for 2 weeks Tapered to 5 mg/day at week 8 and 2.5 mg/day at week 16	Higher CR in VCS group compared to placebo (41% vs. 23%) Similar adverse events between both groups (21%)
Obinutuzumab[46]	Randomized control trial/44% Caucasian	Obinutuzumab (*n*=63) versus placebo (*n*=62) All received MMF	1-3 g total	0.5 mg/kg/day, maximum 60 mg/day, with taper to 7.5 mg/day by week 12	Higher CR in Obinutuzumab group compared to placebo at week 104 (41% vs. 23%, *P*=0.026)

AE: Adverse event, BW: Body weight, CR: Complete remission, CYC: Cyclophosphamide, MMF: Mycophenolate mofetil, MP: Methylprednisolone, PR: Partial remission, VCS: Voclosporin, VZV: Varicella zoster virus, IV: Intravenous

Steroid-sparing immunosuppressive therapies and hydroxychloroquine

In active LN, the addition of IV CYC treatment is more effective than pulse IV MP alone in achieving renal remission and preserving long-term kidney survival[51,52] and therefore has formed the basis of early treatment strategies. In these studies, the use of high-dose CYC (0.5–1.0 g/m^2 body surface area) and GC (IV MP pulse (1 g/m^2 body surface area) was followed by high-dose oral prednisolone and thus associated with many adverse events such as infection. The use of combination therapy of lower pulse MP (6.6 mg/kg) and CYC (10 mg/kg) with a lower prednisolone dose induction regimen (≤0.5 mg/kg/day) in LN was first explored in 1992[53] and was adopted in the subsequent Euro-Lupus trial[54] and LN guidelines.[3,14] After more than 20 years of using CYC, findings from the landmark RCT of MMF (Aspreva Lupus Management Study-ALMS trial)[55] have led to MMF being one of the first-line induction treatments for proliferative LN.[3] In nonrenal lupus, MMF has been demonstrated to have steroid-sparing effects in an observational study of 170 patients.[56]

There are less data from RCTs for steroid-sparing effects of other IS therapy such as AZA, MTX, leflunomide, and CNIs in extrarenal SLE. A systematic review of small RCTs and cohort studies showed that IS treatment with MTX, AZA, and ciclosporine A had steroid-sparing effects, while CYC, AZA, and MMF may prevent disease flares.[57] Hence, EULAR has changed its recommendation from considering starting IS only in refractory or GC-long-term dependent patients in 2008,[36] to an early initiation of IS for a better control of disease with lower GC use in 2019.[15] The

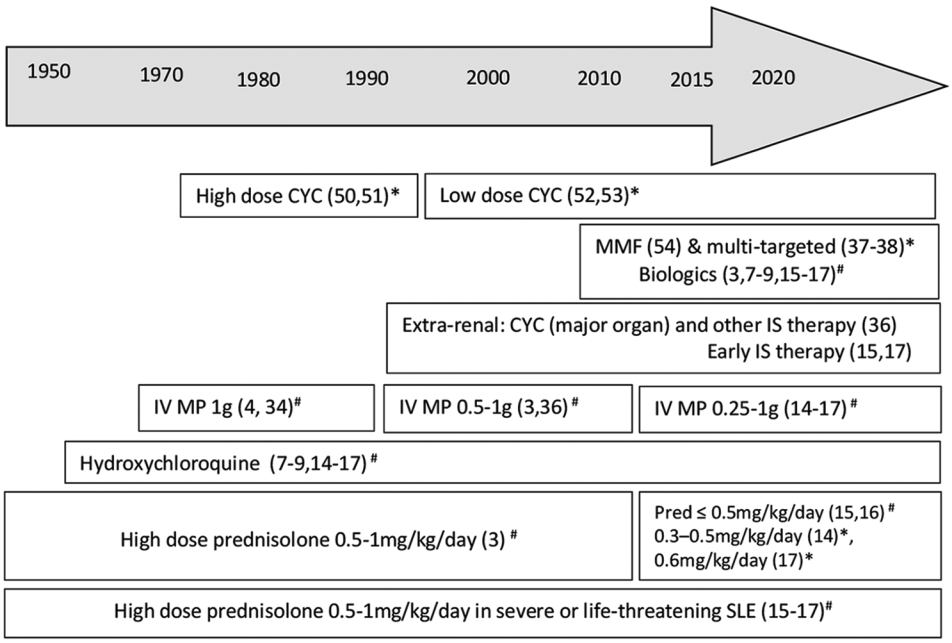

Figure 1: Evolution and paradigm shift from the conventional high-dose oral prednisolone and pulse IV MP to tower of GCs with the introduction and availability of hydroxychloroquine, cyclophosphamide, immunosuppressive agents, multi-targeted therapy, and biologics. IV: Intravenous, MP: Methylprednisolone, GCs: Glucocorticoids

same recommendation was also made in the recent Asia Pacific League of Associations for Rheumatology (APLAR) SLE guideline.[17] CYC is recommended for other organ-threatening diseases, especially cardiopulmonary or neuropsychiatric (NP) lupus.[15-17] This treatment potentially has a steroid-sparing effect as CYC use was associated with a reduction in prednisone requirements after 6 months of treatment, compared to patients who took pulse MP alone in Neuropsychiatric lupus (NPSLE) (median prednisolone 15 mg vs. 27.5 mg, respectively, $P = 0.001$).[58]

Hydroxychloroquine has numerous benefits including antithrombotic, lipid, and glucose-lowering effects.[59] Although data from RCTs are scarce, HCQ is recommended in all SLE patients and to be continued indefinitely unless contraindicated.[15-17] The potential steroid-sparing effect of HCQ is demonstrated in the recent Toronto Lupus Cohort[60] which reported that treatment with antimalarials (AMs) for >60% of the time during the first 5 years of disease had a better disease control with higher prevalence of low disease activity among this group compared to the AM <60% and non-AM groups (82.2% vs. 76.1% vs. 70.4%, respectively, $P = 0.03$). Patients in the AM >60% group also had fewer flare events compared to the AM <60% and non-AM groups (2.66 ± 1.96 vs. 3.16 ± 2.23 vs. 3.23 ± 2.79, respectively, $P = 0.04$) and lower cumulative doses of GC (14.60 ± 11.06 vs. 20.22 ± 13.35 vs. 23.50 ± 15.04, $P < 0.001$). A significantly less damage accrual was observed in the AM >60% group as the increment of SDI score was significantly lower in this group compared to the AM <60% and non-AM groups (0.61 ± 0.95 vs. 0.85 ± 1.30 vs. 1.01 ± 1.33, respectively, $P = 0.003$).[60]

Multi-targeted therapy

Multi-targeted therapy approaches using a combination therapy of MMF, CNI, and lower GC doses have emerged in recent years. This strategy may facilitate the use of lower GC and subsequently minimize GC usage and toxicity. The first reported clinical trial of multi-targeted therapy as an induction treatment in LN found that the combination of MMF plus tacrolimus had a superior efficacy at 24 weeks compared to IV CYC (CR rate of 45.9% vs. 25.6%, $P < 0.001$). In this study, all subjects received three doses of IV MP 500 mg followed by medium-dose oral prednisolone of 0.6 mg/kg/day which was tapered quickly to 10 mg/day by week 16.[37] The subsequent maintenance treatment was either to continue the multi-targeted therapy, or switch to AZA in the IV CYC arm, plus oral prednisolone 10 mg daily for 18 months. There was a similar low relapse rate in the two groups (5.47% for multi-targeted therapy and 7.62% for CYC/AZA).[61] This study suggests that short-term good outcomes could be achieved with the multi-targeted therapy and a much lower GC regimen than in previous LN studies including MMF and CYC.[51,52,55]

Since the use of lower dose GC regimens is shown to be effective in controlling disease activity in the previous studies,[6,37] more recent clinical trials of multi-targeted therapy in LN have used lower doses of MP pulses combined with a lower starting GC dose and more rapid GC tapering. The phase 2 AURA-LV clinical trial evaluates the combination of a low or high dose of voclosporin (VCS), a novel CNI, with MMF as an induction therapy in LN. This study used a much lower dose of

initial oral prednisolone (20–25 mg/day) than the previous studies with a fast tapering of prednisolone to 2.5 mg/day at week 16. Results of this trial demonstrate superiority in achieving CR among the low-dose VCS group compared to placebo at 24 weeks (32.6% vs. 19.3%, respectively, OR = 2.03; 95% CI: 1.01–4.05, *P* = 0.045). A higher efficacy of both low- and high-dose VCS compared to placebo was also noted at 48 weeks. A total of 49.4% of subjects in the low-dose VCS group achieved CR (OR = 3.21; 95% CI: 1.68–6.13; *P* < 0.001) and 39.8% of subjects in the high-dose VCS group (OR = 2.10; 95% CI: 1.09–4.02; *P* ¼ 0.026), compared with 23.9% in the placebo group.[38]

Subsequently, the phase 3 VCS trial (AURORA 1) also showed a higher efficacy in achieving and maintaining CR by adding low-dose VCS to the standard MMF therapy, with a lower maximum GC dose (prednisolone 20 mg/day for body weight <45 kg and 25 mg/day for ≥45 kg) and a fast tapering dose of oral prednisolone to 5 mg/day at week 8 and 2.5 mg/day at week 16.[39] In this study, CR was achieved in 41% of patients in the VCS group as compared to 23% in the placebo group at week 52 (OR 2·65; 95% CI 1·64–4·27; *P* < 0·0001). Therefore, both AURA-LV and AURORA-1 demonstrate that multi-target therapy with VCS in LN allows lower total doses and more rapid tapering of oral prednisolone protocol.

Biologics

Rituximab (RTX) in the management of LN[40,41] has been shown to facilitate the tapering and withdrawal of oral prednisolone. First, in an open-label study of 18 patients with class III/IV/V LN who received RTX induction therapy and MMF maintenance therapy, 33.3% achieved CR while 44.4% achieved PR at 12 months.[40] At 24 months, almost one-third (33.3%) managed to stop their prednisolone.[40] Although this was not a randomized trial with head-to-head comparisons, the renal response at 12 months was similar to the previous Euro-Lupus trial, but vast majority of the patients in the Euro-Lupus were continued with oral GC (prednisolone 5–7.5 mg OD) until 30 months after inclusion.[54]

Subsequently, a pilot observational study exploring clinical remission in LN without the use of oral steroids was conducted in 50 patients.[41] In this study, patients with LN (class III, IV, or V) who were not taking long-term oral steroids received a combination of RTX plus IV MP 500 mg (2 doses) and MMF maintenance with no oral steroid treatment (RITUXILUP protocol). At 26 weeks, this protocol had resulted in CR and PR in 32% and 30%, respectively, and this had increased at 1 year to 52% and 34%, respectively.[41] Only three patients required a repeat RTX course due to persistent proteinuria (polymerase chain reaction ≥50 mg/mmol) by 52 weeks, one of whom then had CR. One patient achieved CR after optimization of the MMF dose while another patient had a concomitant diabetic change on repeat biopsy which may have accounted for the poor renal response.[41] Although not a head-to-head trial, the achievement of CR and PR of 62% at 26 weeks with RITUXILUP protocol was numerically higher compared to patients treated with MMF and CYC groups in the ALMS trial, which reported 56.2% and 53% renal response, respectively.[55] However, the RITUXILUP protocol had a much lower CR rate at 12 months than the MMF and CYC groups in Chan *et al*.'s study (52% vs. 81 vs. 76%, respectively).[62]

In terms of renal relapse, in the RITUXILUP protocol pilot study, a total of 12 renal relapses occurred in 11 patients (22%), at a median time of 65.1 weeks (20–112) from remission. Of these, one patient relapsed twice likely related to MMF withdrawal due to recurrent persistent upper respiratory tract infections. Repeat biopsies in 4/11 relapsed patients showed class V LN while 6/11 showed class III or IV. Another RTX course was given for the seven relapse episodes in six patients with class III or IV in the repeat biopsies. As a result, CR was achieved in three relapses, PR in one, and another three failed to respond. The short-term relapse rate reported in this protocol was lower than the Euro-Lupus study which reported 27.3% and 36.9% of renal flares at 12 months for the low-dose and high-dose CYC groups, respectively.[54]

Long-term follow-up over ≥ 5 years of 42 patients in the RITUXILUP study showed CR or PR in 88% of patients. Over a median of 77 months, 30/39 (77%) patients with complete data at the time of review, had never received oral GCs. Although 52% of patients who achieved CR and PR had flare (median time to renal flare was 24 months), most responded to retreatment with RTX in 13/19 patients with no oral steroids (in 79%) and did not predict poor outcomes.[63] These findings highlighted the potential role of RTX in minimizing or even avoiding the use of oral prednisolone in proliferative LN treatment. Although the relapse rates were high, good responses were observed with repeated courses of RTX treatment.

In nonrenal lupus, an observational study of eight patients who received RTX and CYC showed a greater numerical reduction in the mean global BILAG score at 6 months of treatment compared to the historical control SLE patients that were treated conventionally with other IS agents (−12 vs. 13.22, respectively). There was a trend of a lower mean cumulative prednisolone dose at 6 months in patients who received RTX and CYC compared to conventional IS treatment (1287.3 mg vs. 2834.6 mg), but this did not reach statistical significance.[42] Subsequently, a larger cohort of 16 newly diagnosed SLE patients with predominant extrarenal manifestations showed potential GC-sparing effects and fewer flare episodes with RTX as first-line therapy.[64] In this comparative case–control study, patients who received B-cell depletion therapy (BCDT) were compared with 48 "historic cohort" (HC) patients treated conventionally (GC with HCQ and other IS treatment,

e.g., CYC, MMF, and AZA). The BCDT treatment protocol consisted of 1 g of RTX and MP 100 mg on days 1 and 14 and 750 mg of CYC on day 2, with HCQ and maintenance AZA. During the median follow-up of 4.5 years, there was a trend of fewer disease flares in the BCDT compared to the HC group (2.63 ± 3.01 vs. 4.00 ± 3.61, P = 0.14). The mean cumulative prednisolone dose in the BCDT group was significantly lower at 6 months (842.64 ± 854.3 mg vs. 4247.93 ± 613.1 mg, P = 0.02) and at 5 years (4745.67 ± 6090 mg vs. 12 553.92 ± 12 672 mg, P = 0.01).[64] Therefore, in this nonrenal lupus study, the use of RTX had steroid-sparing effects and fewer relapse episodes.

Data from other B-cell modulating therapy such as belimumab and obinutuzumab (a novel B-cell depleting therapy) trials also demonstrate their role as steroid-sparing agents in SLE patients. From the phase III belimumab trials, fewer patients in the belimumab group had increases in oral GCs compared to placebo (18.4% vs. 30.7%) and their mean cumulative decreases in GC dose were greater (−740.8 vs. −542.0, P < 0.0165) at 52 weeks.[65] In the recent obinutuzumab trial, a greater achievement of CR in proliferative LN was also demonstrated in the obinutuzumab group compared to placebo at week 104 (41% vs. 23%, P = 0.026). In this study, all patients received MMF with moderate oral prednisolone 0.5 mg/kg/day and rapid taper to 7.5 mg/day by week 12.[66] In another retrospective study of 9 SLE patients who received obinutuzumab for secondary nonresponse to RTX, there were significant reductions in median SLEDAI-2K score from 12 to 6 (P = 0.014) and numerical BILAG-2004 score from 21 to 2 (P = 0.009) at 6 months. In addition, four patients (44.4%) managed to reduce the prednisolone to 5 mg/daily at 6 months.[67]

The use of anifrolumab, a newly Food and Drug Administration-approved monoclonal antibody against the type I interferon receptor subunit 1, also demonstrated a potential GC-sparing effect in the TULIP-2 trial.[46] A higher percentage of patients in the anifrolumab group achieved the primary outcome of BILAG-based composite lupus assessment response at week 52 compared to placebo (47.8% vs. 31.5%; P = 0.001) and significantly more patients had sustained prednisone reduction to ≤7.5 mg/day 51.7% vs. 30.1%, P = 0.01).[46] This study demonstrates that anifrolumab treatment allows a lower maintenance dose of oral prednisolone with better control of disease activity.

Glucocorticoid-free treatment of systemic lupus erythematosus: Limitations and future strategy

The RITUXILUP protocol was the only induction protocol which incorporated a no-oral steroid strategy in patients with proliferative LN.[41] Unfortunately, the RITUXILUP RCT (NCT01773616) which aimed to confirm these observational studies was stopped prematurely due to loss of funding for the drug, and challenges with recruiting sufficient numbers of patients.[68] The feasibility and cost of RTX may therefore pose a challenge, especially to many other less-resourceful countries. Access to RTX biosimilars may help to reduce the cost and it is an acceptable alternative treatment to originator RTX in the Asia Pacific guideline.

Newer generation anti-CD20 monoclonal antibodies such as obinutuzumab and the sequential combination therapy of RTX and belimumab study may improve depletion and prevent or delay the repopulation of pathogenic B-cell clones by concomitant targeting of B-cell–activating factor (BAFF).[68] In the BEAT-Lupus trial, additional belimumab after RTX reduced the risk of severe flare (BILAG A flare) compared to placebo at 52 weeks. This study protocol used a lower and faster tapering of prednisolone dose in both arms, in which the maximum prednisolone dose was 20 mg/day and the dose was encouraged to be reduced by 50% from baseline by 6 months.[69] However, the BEAT-Lupus trial was limited by the small number of subjects and therefore requires a larger RCT to look into the efficacy and safety. In addition, the use of both biologic agents incurs higher costs, and thus, this strategy may not be cost-effective. Most importantly, the current strategy of using B-cell depletion and B-cell modulation takes a longer time of at least 3–6 months to take effect, and hence, GC may be the only treatment of choice for moderate-to-severe or life-threatening SLE.

The data on the efficacy of multi-targeted approach are quite promising as the rapid achievement of CR in the CNI-based trials can be due to the added antiproteinuric effects of the agent.[70] However, the main concern of the CNI multi-targeted therapy, is the increased risk of infection and the absence of long-term safety and efficacy data.[71]

The majority of trials using reduced-GC protocols were for LN. Although the data are quite promising, less data are available for other organ-threatening manifestations of SLE including NPSLE lupus, cardiopulmonary disease, and severe cytopenias. Due to less evidence for reduced-GC protocols in extrarenal SLE, the EULAR 2019 guidelines recommend that the dose and route of GC depend on the type and severity of organ involvement.[15] A moderate-to-high-dose oral prednisolone is still recommended in severe extrarenal such as severe thrombocytopenia and NPSLE.[15,17]

There is also a lack of evidence on the low-dose GC use among non-Caucasian patients as vast majority of the studies were from predominant Caucasian cohorts, as illustrated in Table 1. Asian, Hispanic, and African-American SLE patients tend to experience more severe disease with higher disease activity levels,[72] but they are under-represented in majority of the clinical trials.[73] A pilot study in treatment-naïve proliferative LN patients at a single center in India which compared the medium-dose

oral prednisolone (0.5 mg/kg/day) versus the standard high dose (1 mg/kg/day) was terminated prematurely. This is because the interim report revealed a strikingly inferior response of the medium-dose group at the completion of one-third of the sample size. In this study, all patients also received MP pulses of 750 mg/day for 3 days preceding oral steroids, MMF (titrated up to 2 g/day), HCQ (6 mg/kg/day) as well as renin–angiotensin system blockade.[74] Due to limited data in Asian populations, the APLAR guideline still recommends moderate-to-high-dose prednisolone in proliferative LN and in extrarenal manifestations.[17]

GCs are also essential in preventing disease relapse in SLE as discontinuation of the treatment is associated with relapse of the disease. A retrospective analysis in 91 patients who attempted GC withdrawal during the 6 years of follow-up, the treatment was successfully stopped in 77 patients (84.6%). For those patients who successfully stopped GCs, a total of 18 flares were recorded involving 23% of patients, over a median follow-up period of about 2 years, and reintroduction of GCs was necessary in almost all patients (94.4%).[75] A more recent study, the CORTICOLUP study also highlighted the important role of steroid to prevent flare. This study was a randomized controlled trial involving 61 patients who continued taking 5 mg/day prednisone (maintenance group) while another 63 patients whom the prednisolone was stopped (withdrawal group) after being clinically inactive disease for the last 1 year.[76] In this study, the proportion of patients experiencing a flare was significantly lower in the maintenance group (4 patients) as compared to the withdrawal group (17 patients), RR: 0.2 (95% CI: 0.1–0.7), P = 0.003. The damage accrual and adverse events were similar between the two groups, suggesting that a low maintenance dose of prednisolone at 5 mg daily can prevent flare with no substantial increase in the side effects.

Similarly, a meta-analysis revealed that GC discontinuation had an increased risk of flare compared with GC continuation, RR: 1.38 (95% CI: 1.01, 1.89), but GC withdrawal was associated with reduced organ damage (measured using the SLICC/ACR Damage Index) compared with GC continuation, RR: 0.64 (95% CI: 0.38, 1.09).[77]

The data on the cost–benefit of low-dose GC protocol which involve IS agents and biologics are still not well established. Cost-effectiveness analysis on MMF, belimumab, and VCS is mainly derived from European and United States studies[78-80] and thus it may not be applicable to other health-care systems or populations. Most importantly, GCs are cheap and hence are more affordable in many of the under-resourced countries.

Further research to understand and determine the specific mechanisms of action by which GCs mediate swift anti-inflammatory effects is needed for development of novel therapeutic agents that can address this issue. In order to optimize the anti-inflammatory effects of GC and to minimize its adverse events, research into more selective and targeted GC pathway modulators is needed.[81] The selective GC receptor modulators which promote transrepression over transactivation have been developed in the hope of replacing the conventional GC in the treatment of various autoimmune diseases.

Conclusion

GC remains the cornerstone of treatment in active SLE. Although GC-free treatment is currently not feasible in SLE, the lowest effective of GC doses in combination with early introduction of other immunosuppressants and/or biologics are recommended. More recent RCTs of immunosuppressant and biological drugs either sequentially or in combination have used lower doses, and more rapidly tapered GC regimens than historical trials. Ongoing research into the mechanism of action of GCs in SLE and how this relates to adverse events is crucial to enable us to use GCs more safely. The development of newer therapies and increased use of combination therapies will allow lower-dose GC regimens to be developed, moving toward the possibility of GC-free treatment in the future.

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Conflicts of interest

There are no conflicts of interest.

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