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Treating systemic lupus erythematosus in the 21st century: new drugs and new perspectives on old drugs

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Abstract

Besides treating acute flares, the management of SLE should aim at preventing organ damage accrual and drug-associated harms, improving health-related quality of life and prolonging survival. At present, therapy is based on combinations of antimalarials (mainly HCQ), considered the backbone of SLE treatment, glucocorticoids and immunosuppressive drugs. However, these regimens are not universally effective and a substantial degree of damage can be caused by exposure to glucocorticoids. In this review we provide a critical appraisal of the efficacy and safety of available treatments as well as a brief discussion of potentially novel compounds in patients with SLE. We emphasize the use of methylprednisolone pulses for moderate–severe flares, followed by low–moderate doses of oral prednisone with quick tapering to maintenance doses of $\leq$5 mg/day, as well as the prompt institution of immunosuppressive drugs in the setting of severe disease but also as steroid-sparing agents. Indications for the use of biologic agents, namely belimumab and rituximab, in refractory or organ-threatening disease are also presented. We conclude by proposing evidence- and experience-based treatment strategies tailored to the clinical scenario and prevailing organ involvement that can aid clinicians in managing this complex disease.

Key words: glucocorticoids, prednisone, methylprednisolone, HCQ, antimalarials, immunosuppressives, biologics, lupus nephritis, damage

Rheumatology key messages

- Hydroxychloroquine is the cornerstone of lupus therapy.
- Methylprednisolone pulses followed by low–medium doses of prednisone rapidly control most moderate–severe flares.
- Immunosuppressive drugs are indicated in the setting of severe disease and also as steroid-sparing agents.

SUPPLEMENT

Introduction

SLE represents the prototype systemic autoimmune disease featuring remarkable clinical heterogeneity due to synchronous and non-synchronous involvement of several organs with variable severity. As a result, treatment of SLE poses significant challenges and is often based on clinical acumen. Nevertheless, in recent times a number of controlled trials and well-conducted observational studies have focused on novel treatments and also on the more efficient use of old, conventional drugs. In this review we summarize the existing evidence on traditional and more recently introduced therapeutic agents, including biologics, in patients with SLE, followed by our proposal for disease treatment according to the clinical scenario and severity of manifestations.

Antimalarials

Antimalarials are among the oldest drugs for treating SLE [1]. Following empirical use for years, the Canadian Hydroxychloroquine Study demonstrated in 1991 the efficacy of HCQ in preventing lupus flares [2]. However, for many years the use of antimalarials was limited to

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patients with cutaneous and/or articular involvement, thus playing a marginal role in core lupus therapy [3]. This scenario has changed substantially during the last 10 years.

Clinical efficacy of antimalarials

Two observational cohort studies published in 2006 [4] and 2007 [5] showed for the first time that antimalarials can reduce mortality in SLE patients by >50% (Table 1). Both studies used propensity score–adjusted analysis, thus overcoming the confounding by indication bias. Indeed, subsequent studies have widely confirmed these results in various ethnic groups, including Latin American [6] and Chinese [7] populations.

Apart from the well-known effects of antimalarials on disease activity, improvement in long-term prognosis is mediated by a reduction in the risks of thrombosis, vascular disease and damage accrual [8]. A recent study from the Toronto Lupus Cohort showed that treatment with antimalarials for >60% of the time during the first 5 years of disease may reduce the number of flares, damage accrual and cumulative dose of glucocorticoids (GCs) [9]. In addition, protection against infections has been observed in several cohort studies [10–13]. A reduced risk of cancer was already suggested in 2007 by an early study of the Lupus-Cruces cohort [14]. A 2017 British population-based study of patients with connective tissue diseases exposed and not exposed to HCQ did not find a reduced risk of developing cancer, however, the risk of metastases and death were significantly lower in the former group [15]. More recently, a large nested case–control study including >14 000 Chinese lupus patients has confirmed a protective, dose-dependent effect of HCQ against neoplastic diseases [16].

Collectively, there is wide consensus in considering HCQ an essential drug for lupus. Recent consensus guidelines agree in recommending indefinite therapy with HCQ (unless contraindicated) for all SLE patients [17, 18], including patients with LN [19, 20] and during pregnancy [21]. However, there is some controversy regarding the optimal dose, mostly due to concerns about retinal toxicity.

Antimalarial toxicity

HCQ can be considered a safe drug without serious toxicity risks in the majority of patients [8]. Minor side effects include gastric intolerance; rash; hyperpigmentation of the skin, nails and gums and aquagenic pruritus [8]. Cardiotoxicity, usually presenting as congestive heart failure and/or syncope, can rarely occur after prolonged therapy [22]. The potential prolongation of the QT interval by HCQ has recently gained attention in the context of antimalarial therapy of coronavirus disease 2019 pneumonia [23]. However, the actual risk is likely influenced by the age of the patient, concomitant therapy and the use of much higher doses than those administered in SLE. Moreover, studies focusing on lupus patients have not found a significant occurrence of QT prolongation [24].

Maculopathy continues to be the most feared side effect of antimalarials. Definite retinal damage with some degree of visual loss is estimated to occur in ~0.1% of SLE patients treated with antimalarials for >10 years [8]. Nevertheless, to detect early asymptomatic—but reversible—toxicity, the 2016 updated recommendations of the American College of Ophthalmology have advocated for the use of new monitoring techniques, such as automated visual fields and spectral-domain optical coherence tomography [25]. Although use ≥5 years and a cumulative dose of HCQ >1000 g were initially identified as the main risk factors for eye toxicity, new data point to a daily dose of HCQ >5 mg/kg (real body weight) as the principal predictor of maculopathy [26]. Renal insufficiency and concomitant therapy with tamoxifen further increase the risk for retinal damage [26]. A recent longitudinal study of 110 patients at 5 years of follow-up has revealed no new cases of eye toxicity or clinically relevant retinal thinning. Of note, 99% of patients received HCQ at a dose ≤5 mg/kg/day [27].

Regarding the relationship between dose and efficacy, low blood levels of HCQ were identified in the early 2000s as a predictor of SLE flares [28], although adapting the daily dose to measured blood levels did not result in better control of lupus activity [29]. On the other hand, measuring drug concentrations can be useful to monitor treatment adherence [30], although the determination of blood levels of HCQ is not yet widely available. Despite the lack of comparative efficacy studies of doses ranging from 200 to 400 mg/day, it is worth noting that in the studies of the Lupus-Cruces cohort showing effects on survival, thrombosis, infections and cancer [4, 10, 14], the usual dose was 200 mg/day. In the Canadian Hydroxychloroquine Study, patients took a dose ranging from 100 to 400 mg/day [3].

The role of mepacrine

Mepacrine (also known as quinacrine) was the first antimalarial drug used in cutaneous lupus and later replaced by HCQ [31]. In case HCQ has to be stopped due to retinal damage, mepacrine is a good substitute. Besides replacing one for the other in the setting of toxicity, combining mepacrine with HCQ has shown a synergistic clinical effect in patients with refractory skin and/or articular disease [31]. Yellowish skin discolouration is the most prevalent side effect of mepacrine [31].

GCs

GCs are one of the main therapeutic agents for SLE and the most useful drugs to induce rapid remission in the setting of active disease. The use of high-dose oral prednisone (usually 1 mg/kg/day) has become the rule for treating moderate–severe lupus activity, followed by poorly defined tapering schemes [32]. However, there is wide consensus that GCs are a main cause of toxicity in

Table 1 Antimalarials and GCs in SLE

Drug group	Main indications and effects	Safety issues
Antimalarials	• HCQ is the background treatment for SLE patients, reducing the number and severity of flares, preventing damage accrual and increasing survival • Additional antithrombotic, lipid-lowering, glucose-lowering and antimicrobial effects • GC-sparing effects • HCQ may be the only therapy needed for mild SLE • CQ offers no therapeutic advantages over HCQ and has higher toxicity • MC can be used instead of HCQ in cases of confirmed ocular toxicity • MC can be combined with HCQ in SLE with refractory joint, skin, pleural or pericardial involvement	• Confirmed maculopathy in ~2% of patients on CQ and 0.1% of patients on HCQ after 10 years; ocular toxicity negligible with MC • Other side effects: gastric intolerance, rash, hyperpigmentation of the skin, nails and gums and aquagenic pruritus • Cardiotoxicity including prolongation of the QT interval is very rare with HCQ • Yellowish discolouration of the skin (MC) • HCQ and CQ are safe during pregnancy and lactation • MC is not recommended during pregnancy and lactation due to lack of safety data
GCs	• Initial and maintenance therapy of inflammatory manifestations of SLE • Methylprednisolone pulses of 125–500 mg/day for 3 days are indicated to rapidly induce remission in moderate–severe flares • Doses of prednisone >30 mg/day increase toxicity without significant additional therapeutic effects • Doses of prednisone ≤5 mg/day are indicated for maintenance therapy • Discontinuation of GCs is the ultimate goal	• Short-term toxicity: obesity, cutaneous striae, hypertension, hirsutism, acne, infections • Medium- to long-term toxicity: osteonecrosis, osteoporosis, cardiovascular disease, cataracts, infections • Dose-dependent toxicity, with chronic doses >5–7.5 mg/day increasing damage accrual • Pulse therapy up to 500 mg/day for 3 days has not been linked to damage accrual or significant side effects • Safe during pregnancy at low doses; high doses can cause adverse effects such as preeclampsia, gestational diabetes, premature rupture of membranes and infections

CQ: chloroquine; MC: mepacrine.

SLE. A number of serious complications such as osteonecrosis, osteoporosis, cardiovascular disease, infections and, in general, damage accrual and increased mortality have been consistently linked to GC exposure [32]. However, it has also become clear that GC-related toxicity is dose related, due to their biological effects.

Mechanisms of action of GCs

GCs act by two distinct ways. The genomic way consists of two different processes, namely transrepression and transactivation [33], and it is known that GC-related toxicity increases in parallel with anti-inflammatory potency as the genomic way becomes more activated [33]. GCs can also act by non-genomic mechanisms, which produce a rapid and potent anti-inflammatory action [34].

Activation of both the genomic and non-genomic ways mostly depends on the dose of GCs received, independent of the patient's weight [35]. Doses ≤7.5 mg/day of prednisone (low doses) saturate GC receptors by <50%. GC receptor saturation increases progressively with increasing doses: at 7.5–30 mg/day (medium doses), it is >50%. Almost complete saturation occurs at doses between 30 and 100 mg/day (high doses). No significant activation of the non-genomic way occurs up to this point. GC receptors are completely saturated at doses >100 mg/day (very high doses) and, in addition, meaningful activation of the non-genomic way starts at this point, reaching a maximum at 250–500 mg/day (pulse doses) [35].

In clinical terms, low doses would have both low anti-inflammatory potency and a low rate of adverse effects. At a prednisone dose >30 mg/day, genomic-dependent anti-inflammatory effects and toxicity would be close to maximum. When doses between 125 and 500 mg/day are given during a short period of time (pulse therapy), a rapid and very potent immunomodulatory action is obtained, with the potential for avoiding transrepression-/transactivation-mediated toxicity [35] and the additional advantage of priming the mononuclear cells for the genomic effects of subsequent doses [34]. Of note, methylprednisolone has higher potency than prednisone with a more selective activation of the non-genomic way [36].

Towards a balance between GC efficacy and toxicity

Large observational studies support that GC-mediated toxicity is largely dependent on the dose and the time of exposure [7, 37–39] (Table 1). The limit for a 'safe' dose

TABLE 2 Immunosuppressive agents in SLE

Immunosuppressive agent	Main indications	Safety issues
MTX (oral, subcutaneous)	• Musculoskeletal, cutaneous, serosal disease • Mild GC-sparing effect	• Liver, gastrointestinal and haematological adverse events (reduced by co-administration of folic acid) • Avoid in elderly patients and/or in case of glomerular filtration rate <30 ml/min • Contraindicated during pregnancy and lactation
AZA (oral)	• Wide spectrum of manifestations, including constitutional, haematological, vasculitis and neurological disease • Maintenance of response following induction with CYC • Mild steroid-sparring effect	• Liver, gastrointestinal and haematological adverse events • Possible drug–drug interactions (avoid co-administration with allopurinol) • Safe to use during pregnancy and lactation (dose $\leq$2 mg/kg/day)
Calcineurin inhibitors (cyclosporine, tacrolimus, voclosporin)	• Used in combination with mycophenolate in selected cases of LN • Third-line option (when other options are unavailable or intolerable) in refractory cutaneous and haematological disease	• Metabolic (hypertension, dyslipidaemia, hyperglycaemia), renal (increased serum creatinine, hyperkalaemia) and gastrointestinal adverse events, gingival hyperplasia, tremor • Safe to use during pregnancy (continuous use of folic acid is recommended)
Mycophenolate (oral; mycophenolate mofetil, enteric-coated mycophenolic acid)	• First-line treatment of LN • Effective in a wide spectrum of manifestations, including moderate or severe haematological disease • Maintenance of response following induction with CYC	• Gastrointestinal, haematological (leukopenia less frequent than with AZA), infectious (especially when used at 3 g/day or with high-dose GCs) adverse events • Contraindicated during pregnancy and lactation
CYC (i.v.; low dose: 500 mg biweekly $\times$ 4 times; high-dose: 0.75–1 g/m^2 monthly $\times$ 6–7 times)	• First-line treatment of LN and severe (organ- or life-threatening) or refractory manifestations including renal, neuropsychiatric, vasculitis, haematological disease • Low dose preferred in most settings; high dose may be indicated in particularly severe disease	• Haematological, infectious and bladder (cystitis) adverse events (especially high doses) • Gonadal toxicity (age- and dose-related) with high doses • Contraindicated during pregnancy (can be used during the second/third trimester in selected cases) and lactation

has not been firmly established and doses $\leq$7.5 mg/day (prednisone equivalent) are often recommended [18, 19]. However, it seems more prudent to use 5 mg/day in the long term [37, 38], since GC-associated damage accrual can occur even at doses of 5–7.5 mg/day [38]. On the other hand, the use of doses in the range of full genomic activation, i.e. $\geq$30–40 mg/day, has been linked with the occurrence of osteonecrosis, infections and even death [32]. In terms of toxicity, pulses of methylprednisolone at doses $\leq$500 mg/day for 3 days seem virtually free of serious side effects, including infections and damage accrual [37, 39].

Clinical trials and observational studies support that SLE, including severe forms such as LN, can be successfully treated with regimens including lower doses of oral prednisone, with maximum doses $\leq$30 mg/day followed by a rapid reduction over a few weeks to 2.5–5 mg/day [40–49]. Pulses of methylprednisolone combined with the early initiation of immunosuppressive drugs, not limited to patients with severe disease, and the universal use of HCQ may contribute to rapid and prolonged control of lupus activity [48, 49] accompanied by a reduction of not only GC-related damage, but also of cardiovascular and global damage [48]. In this context, the repeated use of pulses of methylprednisolone promote the achievement of complete remission in LN [44] and spares oral GCs [49] in observational studies. Doses of 5 mg/day seem a reasonably safe limit for long-term maintenance therapy [37, 38, 48, 49].

Immunosuppressants

Non-renal manifestations

Despite limited randomized evidence, immunosuppressive agents such as MTX, AZA, mycophenolate and CYC are considered in SLE patients who respond inadequately to antimalarials and GCs (defined as any of

persistent disease activity, relapses, inability to lower GC to <5 mg/day prednisone equivalent) and/or who develop organ-threatening disease (Table 2) [17, 18].

MTX is generally efficacious in controlling musculoskeletal, skin and serosal disease [50, 51], whereas AZA has been used to treat a wider spectrum of manifestations, including constitutional, vasculitis, haematological and neurological lupus [52, 53]. An open-label controlled study in active SLE patients showed that mycophenolate was superior to AZA, both administered in combination with moderate doses of oral GCs, in inducing remission and preventing flares, including new-onset kidney disease [54]. The two drugs differ in their safety profile (leucopenia being more common with AZA and gastrointestinal complaints being more common with MMF), and AZA is compatible with pregnancy. In addition, mycophenolate (mofetil or sodium) has been successfully used in the treatment of refractory or severe manifestations such as subacute cutaneous lupus, haemolytic anaemia, thrombocytopenia, vasculitis and neuropsychiatric and musculoskeletal diseases [55]. Due to safety concerns, especially increased risk for gonadal toxicity [56] and infections [57], the use of high-dose CYC (i.v. pulses of 0.75–1 g/m^2) has been restricted to cases of major neuropsychiatric [58, 59] or life-threatening disease. In such cases, maintenance of the response can be achieved with either mycophenolate or AZA in combination with antimalarials and gradually tapered GCs. Finally, calcineurin inhibitors such as ciclosporin and tacrolimus, although infrequently used in non-renal SLE, can be useful in selected cases of refractory thrombocytopenia or during pregnancy [60, 61].

LN

Both the EULAR/ERA-EDTA [19] and the ACR [20] recommend either low-dose i.v. CYC (boluses of 500 mg, biweekly for a total six times) or mycophenolate (target dose 2–3 g/day of mofetil for 6 months) as first-line induction treatment of active proliferative LN. Both regimens have shown equivalent efficacy and more favourable toxicity profiles as compared with high-dose i.v. CYC [62]. Notably, the low-dose CYC regimen has minimal impact on ovarian reserve as assessed by the anti-Müllerian hormone levels [63]. With regards to pure membranous (class V) LN, randomized evidence is limited [64], but extrapolation from the proliferative nephritis trials supports the use of the same treatments. The aforementioned agents are recommended in combination with GCs, usually including pulses of i.v. methylprednisolone followed by oral prednisone at 20–30 mg/day, depending on the severity of renal and extrarenal disease [19, 40, 41, 43, 44].

Recently calcineurin inhibitors, especially tacrolimus and voclosporin, have gained attention as part of multitarget regimens in LN [45, 65]. Whether calcineurin-based regimens should become first-line treatment of active LN remains uncertain, as scepticism remains regarding their long-term efficacy and safety. Of note, the higher the starting level of proteinuria, the longer it may take to remit [66].

Patients who manifest a sustained reduction in proteinuria with stabilization or improvement of their glomerular filtration rate can be switched to maintenance with either mycophenolate (especially if the same drug was used for induction or in more severe forms of LN) or AZA [17, 19, 20]. There is limited published evidence regarding the use of multitarget regimens [67], whereas monotherapy with calcineurin inhibitors can be considered during pregnancy or when other options are unavailable or cannot be tolerated [68, 69]. The duration of treatment is individualized but generally lasts at least 3–5 years.

Biologic agents

Belimumab

Since 2011, belimumab, a monoclonal antibody targeting B cell activating factor (BAFF) has been approved as add-on therapy for active SLE not responding to conventional treatment. The effectiveness of belimumab over the standard of care has been demonstrated in four randomized controlled trials including patients of various ethnic backgrounds [70–72]. Clinical response rates [defined according to the 4-point Systemic Lupus Erythematosus Responder Index (SRI-4) composite index] were 50.6% in belimumab-treated *vs* 38.6% in placebo-treated patients, and the respective frequencies of a low disease activity state were 13.4% *vs* 6.8% [73]. Importantly, the addition of belimumab led to a significant reduction of severe flares, lower cumulative exposure to GCs [74], lower accrual of irreversible organ damage [75, 76] and improved health-related quality of life [77], which are all important aspects in the treating-to-target context [78]. These effects are maintained or even enhanced during prolonged use of the drug, although disease exacerbations can occur [79, 80].

Post-hoc analysis of trial data has suggested that the therapeutic benefit of belimumab may be greater within subgroups of patients with high disease activity, abnormal serology (hypocomplementemia and/or high anti-dsDNA titres) or those receiving GCs [81, 82]. Nonetheless, the drug is effective also in serologically quiescent patients [83, 84]. On the other hand, smoking and existing organ damage have been associated with lower response rates [85, 86]. Better improvement is seen in musculoskeletal (except for severe arthritis) and mucocutaneous (especially acute and subacute cutaneous lupus) manifestations and serositis [84, 87]. Although belimumab has not been extensively evaluated in severe, organ-threatening disease, still it can be used to maintain the response induced by other agents, to prevent relapses and expedite GC tapering. Importantly, clinical practice and the long-term extension of randomized trials support a favourable safety profile of the drug with a relatively low incidence of serious and

opportunistic infections, although monitoring serum immunoglobulin levels is advised [88].

Driven by experimental evidence underscoring the role of BAFF in the formation of intrarenal germinal centre–like lymphoid structures [89], as well as post-hoc analysis of the BLISS-52/76 trials suggesting possible anti-proteinuric effects of belimumab [90], the compound has also been tested in patients with active LN. According to a press release [91], belimumab plus standard therapy (CYC or mycophenolate, followed by AZA or mycophenolate, respectively) was superior to standard therapy alone in meeting the primary efficacy endpoint. The publication of these results will help define the indications for using belimumab in lupus kidney disease.

B cell–depleting agents

Two randomized controlled studies [92, 93] failed to demonstrate the superiority of rituximab (RTX; monoclonal anti-CD20 antibody causing the depletion of B cells) over the standard of care in the treatment of SLE and LN, possibly as a result of high background therapy and underpowered study design [94]. Nevertheless, observational studies support the drug's effectiveness in difficult-to-treat lupus, including severe joint, haematological, cutaneous, renal and neuropsychiatric disease [95–98]. Approximately 65–80% of patients will respond at 3–9 months, with particularly high remission rates (61%) in immune cytopenias [99]. Relapses are not uncommon (25–40%) but can be successfully re-treated in 80% of patients. To this end, there is no definitive answer as to whether RTX should be administered repeatedly or 'on demand', although the former approach should be considered in recalcitrant cases [100]. Of note, concomitant use of immunosuppressives has been associated with a lower risk for secondary non-depletion non-response to RTX [97]. Finally, monitoring peripheral blood B cells is predictive of both treatment response and the risk for clinical relapse [97]. Other fully humanized anti-CD20 antibodies such as ofatumumab [101] and obinutuzumab have shown encouraging results and are currently being tested in SLE.

Potential indications and safety issues of belimumab and RTX in SLE are shown on Table 3.

Novel agents

In a phase 3 randomized study, anifrolumab, a monoclonal antibody directed against type I IFN receptor, was shown to induce higher response rates (assessed by the BILAG-based combined lupus assessment index) as compared with the standard of care (47.8% *vs* 31.5%) in patients with SLE (excluding active renal and neurological disease) [102]. The drug was particularly effective in controlling cutaneous—but not joint—disease, prevented flares and allowed a reduction in the dose of GCs. In line with the pivotal role of type I IFN in antiviral immunity, zoster infections were increased in anifrolumab- *vs* placebo-treated patients (7.2% *vs* 1.1%) [102]. Notably, the effect size (active drug − placebo) was comparable to that observed in belimumab trials, although different response definitions were used. Additional real-world data will be needed to reconcile differences in the efficacy of these two biologics.

Janus kinase (JAK) inhibitors represent another promising class of agents in SLE, considering their capacity to suppress signalling from multiple cytokines, including type I IFN. Anecdotal experience suggests the efficacy of JAK inhibition in improving lupus rashes and non-scarring alopecia [103, 104], and a randomized, placebo-controlled, phase 2 trial suggested a possible

Table 3 Use of belimumab and RTX in SLE

Biologic agent	Main indications	Safety issues
Belimumab (i.v., s.c.)	Add-on therapy in new-onset, persistently active or flaring disease despite standard of care (antimalarials, glucocorticoids and/or immunosuppressive agent) • Inability to taper GCs to <7.5 mg/day (prednisone equivalent) • Wide spectrum of manifestations, including musculoskeletal, mucocutaneous, vasculitis, immunological disease • Might be considered in severe (organ- or life-threatening[a]) disease with partial/inadequate response, as a maintenance agent or to expedite tapering of GCs	• No need to screen for latent infections • Low risk for infusion reactions and infections (including opportunistic) • Monitoring of serum immunoglobulins is recommended during long-term use
RTX (i.v.)	Active, organ- or life-threatening disease refractory to immunosuppressive (including CYC) treatmentsSevere arthritis ('rhupus')	• Need to screen for latent infections • Haematological (neutropenia) and infectious adverse events (need to monitor serum immunoglobulins)

[a]Belimumab is currently not licensed for the treatment of active renal or neuropsychiatric lupus.

benefit of baricitinib (JAK1/JAK2 inhibitor) in SLE [105]. Other agents currently being evaluated include proteasome inhibitors [106], low-dose IL-2 [107] and inhibitors of the mammalian target of rapamycin [108].

A proposal for treatment of SLE

Treating lupus is not just treating lupus flares [17, 78]. Additional objectives are to prevent or minimize damage accrual and serious drug side effects, prolong survival and improve quality of life [17, 78]. Accordingly, every effort should be made to design therapeutic schemes that rapidly control lupus activity, prevent future flares, do not increase damage by themselves and prevent other short and long-term complications.

To achieve these objectives, combinations of the previously discussed drugs can be used. Unfortunately, many choices are not guided by strong evidence and mostly depend on the experience and preferences of the treating physicians. While the role of HCQ or different immunosuppressive regimes in LN have been extensively studied, the indication for individual agents in other disease manifestations is supported by weaker evidence (see previous sections). An example of the variability in real-world clinical practice has been recently shown by a study revealing the great differences in GC use among the different SLICC participating centres [109].

A number of preliminary steps should be considered. Photoprotection is universally recommended, particularly in patients with photosensitivity and/or skin disease. All patients should receive HCQ as background therapy unless contraindicated, in which cases mepacrine can be considered.

In inducing a rapid remission of active lupus, GCs are still the main weapon. Data suggest that pulses of methylprednisolone can help control moderate–severe disease activity and allow the use of lower starting doses of prednisone (much less than the dogma of 1 mg/kg/day), with quick tapering [49]. In the long-term prevention of flares, GCs should be considered on a case-by-case basis according to disease activity, with the final goal of discontinuation, if possible. If not, prednisone doses should not exceed 5 mg/day for chronic treatments [38, 48].

As recommended by the EULAR, immunosuppressive drugs should be added early in severe disease and also to minimize the adverse effects of long-term GC treatment whenever prednisone cannot be rapidly reduced due to recurrent activity [17, 49]. It is also recommended [17] that all patients on long-term GC therapy should be supplemented with calcium and vitamin D with monitoring of 25-hydroxyvitamin D levels.

Specific regimes are available, based on the different clinical scenarios (Table 4) [18, 110–112]. Specifically, we propose that mild flares can be initially managed with minor increases in the dose of prednisone up to 7.5 mg/day, with tapering to $\leq$5 mg/day in no more than 2 weeks. If there is no rapid response or if a relapse occurs upon withdrawal, then therapy for a moderate flare should be started.

Moderate flares can be managed with three consecutive pulses of methylprednisolone of 125–250 mg/day, followed by prednisone of 5–20 mg/day, again with rapid tapering to $\leq$5 mg/day. If the disease is not adequately controlled, methylprednisolone pulses can be repeated in 2–4 weeks and then an additional drug should be added, depending on the clinical scenario. To this end, our selection based on evidence and personal experience includes the following agents:

- Joint or skin manifestations:
  - Mepacrine 50–100 mg/day (in combination with HCQ)
  - MTX at a starting dose of 5–15 mg/week
  - Gradual increase in dose until disease activity is under control
  - Doses >25 mg/week not recommended.
- Thrombocytopenia or haemolytic anaemia:
  - AZA 1.5–2 mg/kg/day.
- Serositis:
  - MTX at a starting dose of 5–15 mg/week
  - Mepacrine 50–100 mg/day (in combination with HCQ).

In addition, mycophenolate and tacrolimus can be used in any of these settings as second-line agents.

Severe flares, i.e. those involving vital organs, severe haemolytic anaemia or thrombocytopenia, or moderate flares not responding to the abovementioned scheme, should be managed more aggressively. By extrapolation from the acute treatment of LN, initial therapy consists of pulse methylprednisolone, 250–500 mg/day for 3 days (dexamethasone 40 mg/day, oral or i.v., for 4 consecutive days is our preferred option for severe thrombocytopenia or haemolytic anaemia) followed by prednisone at a maximum starting dose of 20–30 mg/day, reduced every 2 weeks (20–15–10–7.5 mg/day) to 5 mg/day. Towards the goal of minimizing exposure to GCs, the prednisone dose should be tapered independent of the clinical course of the patient, therefore options to keep patients off of high doses of prednisone must be accomplished, in order to decrease the risk of infections or other serious side effects such as diabetes, osteonecrosis, severe skin changes or weight gain [37, 39, 48, 49].

For severe flares, we recommend that GCs should always be combined with immunosuppressive drugs, the drug of choice depending on the clinical scenario. In general, CYC is preferred for life-threatening disease, like pneumonitis, alveolar haemorrhage, psychosis, cerebral vasculitis or acute myelitis. Although high doses have been recommended, we also advocate for the Euro-Lupus regime, i.e. 500 mg i.v. every 2 weeks for a total of 3 g. Intravenous immunoglobulin (2 g/kg total dose, distributed within 2–5 days) can be used in patients with severe immune haemolytic anaemia or thrombocytopenia or whenever a concomitant infection is suspected, although these are off-label indications.

TABLE 4 Proposal for the treatment of SLE according to clinical scenarios (adapted with permission from Fanouriakis and Bertsias [110] and Ruiz-Irastorza *et al*. [111])

	Mild activity	Moderate activity	Severe activity
Clinical scenario	Polyarthralgia, small joint mono-oligoarthritis, limited skin lesions	Polyarthritis, moderate thrombocytopenia (20 000–50 000/mm^3), haemolytic anaemia with a low rate of haemolysis, widespread skin lupus lesions, non-severe pericardial effusion/pericarditis, pleural effusion, mild flares refractory to treatment	LN, pneumonitis, severe thrombocytopenia (<20 000/mm^3), haemolytic anaemia with a high rate of haemolysis, severe pericardial effusion, refractory pleural effusion, severe neuropsychiatric manifestations, moderate flares refractory to treatment
Background therapy GC therapy	HCQ 200 mg/day Prednisone 2.5–7.5 mg/day, gradually tapered down over 1–2 weeks to 2.5–5 mg/day	HCQ 200 mg/day • Pulse methylprednisolone (125–250 mg/day for 3 days) followed by: • Prednisone 5–20 mg/day, gradually tapered down over 2–4 weeks to 2.5–5 mg/day • Pulse methylprednisolone can be repeated in 2–4 if needed	HCQ 200 mg/day • Pulse methylprednisolone (250–500 mg/day for 3 days) or dexamethasone 40 mg/day × 4 days[a] • followed by: • Prednisone at a maximum starting dose of 30 mg/day, reduced every 2 weeks (20–15–10–7.5) to 5 mg/day • Pulse methylprednisolone and dexamethasone can be repeated in 2–4 weeks if needed
Additional therapy		If the clinical course does not allow a reduction in prednisone dose, other drugs should be added, depending on specific organ involvement (see text): • Mepacrine (skin, joints, serositis) • MTX (skin, joints, serositis) • AZA (immune cytopenias) • Mycophenolate • Tacrolimus • Belimumab (second-line drug)	Depending on severity and specific organ involvement (see text): • CYC 500 (+ methylprednisolone 125 mg) every 2 for 3–6 months • Mycophenolate • Tacrolimus/cyclosporine • RTX
Maintenance therapy	HCQ ± prednisone 2.5 mg/day	• HCQ + prednisone 2.5–5 mg/day ± • Mepacrine • MTX • AZA • Mycophenolate • Tacrolimus • Belimumab	• HCQ + prednisone 2.5–5 mg/day + • AZA • Mycophenolate • Tacrolimus/cyclosporine • Belimumab

[a]In severe thrombocytopenia.

AZA, MTX, mycophenolate and sometimes tacrolimus [61] can be used as maintenance therapy, depending on the target organ. Recommendations for LN have been recently updated [19].

To date, the role of biologic drugs is mostly limited to disease refractory to conventional therapy. Despite being an off-label drug for SLE, RTX is usually chosen in acute settings, including immune cytopenias or severe lung disease [110]. Belimumab is licenced for patients with persistent non-life-threatening activity despite combination therapy with HCQ, low-dose prednisone and/or immunosuppressive drugs [110]. Future indications of these drugs may include earlier use of belimumab [76] and sequential therapy of RTX–belimumab [113]. The role of newer agents will hopefully be clarified in the near future.

In summary, SLE can be successfully managed today in the vast majority of patients, taking as cornerstone principles the universal prescription of HCQ, the initial administration of methylprednisolone pulses to treat

moderate–severe flares, the use of low–medium initial doses of prednisone with very rapid tapering to maintenance doses $\leq$5 mg/day and the utilization of immunosuppressive drugs not only in the setting of severe disease, but also as steroid-sparing agents. Current and future biologic drugs may provide additional solutions in the minority of patients not responding to the standard of care.

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