

What's new in clinical trials in lupus?

Systemic lupus erythematosus is associated with substantial morbidity and involves major organs including the kidneys and the CNS. Based on randomized, controlled trials and long-term observational studies, cyclophosphamide in combination with glucocorticosteroids is considered the 'gold standard' therapy for severe lupus. However, cyclophosphamide therapy is associated with relapses and significant toxicity. Recent trials have explored the efficacy of old, widely used therapies, including the steroid-sparing effects of methotrexate, the ability of cyclosporine or glucocorticoids to prevent lupus flares and the use of azathioprine as maintenance therapy. As for newer agents, mycophenolate mofetil has been demonstrated to be at least as efficacious as, and less toxic than, cyclophosphamide as induction therapy for moderately severe proliferative lupus nephritis. Rituximab (anti-CD20 mAb) and tacrolimus have also been demonstrated to be effective in immunosuppressive-resistant cases but need to be tested in larger controlled trials.

KEYWORDS: biological therapy ■ calcineurin inhibitors ■ cytotoxic therapy ■ nephritis ■ systemic lupus erythematosus ■ trials

Systemic lupus erythematosus (SLE) is a multifaceted disease with diverse symptoms that vary from mild to severe and a chronic remitting-relapsing course. Involvement of major organs, such as the kidneys and the CNS, is associated with significant morbidity and mortality. Today, most experts agree that severe SLE with major organ involvement requires a period of intensive immunosuppressive therapy (induction therapy) to control aberrant immunological activity and halt tissue injury, followed by a longer period of less intensive and less toxic maintenance therapy to consolidate remission and prevent flares [1].

In previous years, randomized, controlled trials (RCTs) at the NIH and other institutions, mainly involving patients with severe lupus nephritis, have demonstrated the superiority of the combination of high-dose corticosteroids with intravenous (iv.) cyclophosphamide (CYC) as induction therapy for severe lupus over monotherapy with steroids or azathioprine (AZA). Despite its effectiveness, this regimen is associated with adverse effects including infections, ovarian toxicity, malignancy and disease relapses. Consequently, there have been efforts to develop alternative therapies with comparable efficacy but less toxicity. The pathogenesis of SLE involves several key components of the immune system and a better understanding of the above mechanisms has led to more targeted therapeutic interventions and the development of new biological drugs [2]. In this paper, we review the findings from recent trials in SLE regarding the use of both old and new agents.

Recent trials in old, established therapies

A summary of recent trials in old, established therapies is provided in TABLE 1.

■ Corticosteroids

Corticosteroids in different compounds and doses, administered by a range of methods, are the cornerstone of induction and maintenance therapy for SLE. For induction treatment, three consecutive pulses of methylprednisolone (MP) (1 g per pulse) are administered intravenously to suppress inflammation in severe SLE followed by single pulses every month. Orally administered corticosteroids are used between pulses starting with 0.5–0.6 mg/kg/day of prednisone followed by a gradual tapering to 0.25 mg/kg every other day within 3 months. In moderate-to-severe lupus nephritis, corticosteroids used in combination with cytotoxic agents, such as cyclophosphamide, offer superior efficacy compared with iv. MP without increasing toxicity [3,4].

Recently, Tseng *et al.* examined the effect of a short course of moderate-dose corticosteroids on preventing flares in clinically stable but serologically active SLE [5]. A total of 41 patients who experienced serological flare (defined as an elevation of the anti-dsDNA level by 25% and a decrease in C3 by 50%) were randomized to receive either prednisone (30 mg for 2 weeks, 20 mg for 1 week and 10 mg for 1 week) or placebo and were followed for 3 months (mean SLE

Styliani Ntali,
Michail Tzanakakis,
George Bertias &
Dimitrios T Boumpas[†]

[†]Author for correspondence:
University of Crete Medical
School, Voutes, Heraklion,
PO Box 2209, Greece
Tel.: +30 281 039 4635;
Fax: +30 281 039 4873;
boumpasd@med.uoc.gr

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Table 1. Published controlled trials in systemic lupus erythematosus (2005–2008).

Study	No. patients (n)	Key findings	Ref.
Abdou <i>et al.</i> (2008)	20	In premenopausal women with moderate SLE, the selective estrogen receptor downregulator fulvestrant resulted in a significant reduction in SLEDAI and the deactivation of peripheral blood T cells	[51]
Appel <i>et al.</i> (2009)	370	MMF was not superior to iv. CYC as an induction treatment for moderate-to-moderately severe lupus nephritis (response rate: 56 vs 53%)	[54]
Bao <i>et al.</i> (2008)	40	Multi-target therapy with corticosteroids, MMF and tacrolimus was superior to the combination of corticosteroids plus iv. CYC for the treatment of mixed diffuse proliferative and membranous lupus nephritis (complete remission: 50 vs 5%)	[36]
Barile-Fabris <i>et al.</i> (2005)	32	iv. CYC in combination with iv. MP was superior to iv. MP alone as an induction therapy for severe CNS lupus (clinical response: 95 vs 54%)	[16]
Bezerra <i>et al.</i> (2005)	33	Clofazimine was equally as effective as chloroquine diphosphate in controlling cutaneous lesions in SLE, but clofazimine itself could be the cause of systemic lupus flares	[55]
Cardiel <i>et al.</i> (2008)	317	Abetimus significantly reduced anti-dsDNA levels but did not significantly prolong time to renal flares when compared with placebo	[50]
Chan <i>et al.</i> (2005)	64	MMF was at least similarly efficacious with iv. CYC as an induction and maintenance therapy for diffuse proliferative lupus nephritis	[19]
Contreras <i>et al.</i> (2004)	59	Maintenance therapies with MMF or AZA following short-term CYC induction are efficacious and safe for the treatment of high-risk patients with proliferative lupus nephritis	[56]
Fortin <i>et al.</i> (2008)	86	MTX conferred a significant advantage in moderately active lupus by lowering daily prednisone dose and slightly decreasing lupus disease activity; in moderate SLE, MTX may be used as a steroid-sparing agent	[7]
Furie <i>et al.</i> (2008)	70	Belimumab (an anti-BlyS monoclonal antibody) was well tolerated and reduced peripheral B cells in SLE patients	[57]
Ginzler <i>et al.</i> (2005)	140	MMF was more effective than iv. CYC in inducing remission of lupus nephritis and had a more favorable safety profile	[21]
Grootscholten <i>et al.</i> (2006)	87	iv. CYC was superior to AZA in the prevention of renal relapses in patients with proliferative lupus nephritis	[8]
Moroni <i>et al.</i> (2006)	75	AZA and CsA, both combined with corticosteroids, had a similar efficacy in the prevention of flares in proliferative lupus nephritis	[12]
Ong <i>et al.</i> (2005)	44	MMF was at least similarly efficacious with iv. CYC as induction therapy for diffuse proliferative lupus nephritis	[20]
Tseng <i>et al.</i> (2006)	154	In clinically stable but serologically active SLE, short-term corticosteroid therapy may avert a severe flare	[5]
Wright <i>et al.</i> (2008)	60	Low-dose dietary supplementation with omega-3 fish oils in SLE reduced disease activity and improved endothelial function	[52]

AZA: Azathioprine; CsA: Cyclosporine; iv. CYC: Intravenous cyclophosphamide; iv. MP: Intravenous methylprednisolone; MMF: Mycophenolate mofetil; MTX: Methotrexate; SLE: Systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index.

disease activity index (SLEDAI) was 4.2 in both arms of the trial). During follow up, severe flares occurred in six out of 20 patients on placebo compared with none of the 21 patients who took prednisone ($p = 0.007$). Severe flares resulted in increased prednisone dosage to over 40 mg/day and/or the addition of an immunosuppressive agent. Furthermore, significant improvements in SLEDAI, decreased levels of anti-dsDNA antibodies and increased levels of C4 occurred 1 month after the initiation of prednisone treatment. The results are in agreement with those of the Bootsma *et al.* study [6] and support the hypothesis that in clinically stable SLE patients with serological activity, short-term corticosteroid therapy may avert a severe flare. Apart from the small number of patients, the findings of this trial only pertain to a small subset of patients (i.e., those with anti-DNA antibodies). The calculated number of patients that must be treated in order to prevent one severe flare was demonstrated to be 3.3 patients, indicating that preventive treatment would require the exposure of patients to corticosteroids who might otherwise not have required such treatment. Accordingly, the beneficial effect of corticosteroids for the prevention of SLE flares must be weighted against risks of over treating patients with higher cumulative doses of corticosteroids.

■ Methotrexate

Methotrexate (MTX), an antifolate agent commonly prescribed for rheumatoid arthritis, has emerged as a potential steroid-sparing treatment for SLE. Fortin *et al.* evaluated the efficacy of MTX in a 12-month randomized, placebo-controlled trial in 86 SLE patients [7]. Patients had mild-to-moderate disease with mean SLEDAI and systemic lupus activity measure (SLAM) scores of 10. The most common manifestations were musculoskeletal (93%), cardiovascular (74%) and hematologic (69%). Approximately half of the patients in each group were administered oral prednisone, while 41 patients in the placebo group versus 27 in the MTX group were taking antimalaria tablets. Primary study end points were changes in the mean prednisone dose and SLAM score. Among participants with comparable baseline prednisone doses, those on MTX received an average of 1.33 mg/day less prednisone during the trial period compared with those in the placebo group. Fewer patients in the MTX group were also started on corticosteroids (5 vs 26% in the placebo group). MTX use was associated with a marginally significant reduction in the mean during-trial SLAM score of 0.86 units (96% CI: 0.01–1.71;

$p = 0.039$). Although this trial was underpowered to detect statistically and clinically significant differences between treatment arms, these data suggest that MTX could be a reasonable alternative steroid-sparing agent for mild-to-moderate SLE.

■ Azathioprine

Grootscholten *et al.* [8] examined the efficacy of AZA as induction maintenance therapy for proliferative lupus nephritis. A total of 87 European patients with biopsy-proven nephritis (eight class III-Vc and 79 class IV-Vd) were randomized to receive iv. CYC (six monthly pulses of 750 mg/m² iv. CYC followed by seven pulses every 3 months) plus prednisone or iv. MP (three daily pulses of 1 g iv. MP on 0, 2 and 6 weeks) plus AZA (2 mg/kg/day) plus prednisone (20 mg/day for the first 5 months, then tapered to 10 mg/day). After 2 years, both groups were receiving maintenance therapy with AZA (2 mg/kg/day) plus prednisone (10 mg/day). The two groups were similar in terms of renal function (mean creatinine clearance: 65 ml/min) and SLE activity (mean SLEDAI: 19); mean follow up was 5.7 years. During the first 2 years, the two groups did not differ in terms of induction of remission (mean complete remission rates: 60%), mean serum creatinine (82 µmol/l) and proteinuria levels (0.3 g/24 h). However, relapses occurred more often in the AZA group compared with the iv. CYC group (relative risk: 8.8) and in repeat biopsies ($n = 39$ patients), the mean chronicity index increased from 2.7 to 3.0 in the iv. CYC group while in it increased from 2.7 to 3.8 in the AZA arm [9]. Infections were more common in the AZA group (mainly owing to herpes zoster virus), which could be due to high corticosteroid dose but the overall hospital admission rates from infections were similar in the two groups. The results of the study are limited by the exclusion of patients with severe renal impairment which is reflected by the rarity of crescents in renal biopsies, the fact that 70% of patients were Caucasian (low-risk group) and the short duration of the trial. Nonetheless, the smaller number of relapses, a prognostic factor for adverse renal outcome [10,11], and the accrual of less renal damage indicate that iv. CYC is superior to AZA as induction maintenance therapy.

Azathioprine has long been considered a safe and efficacious option for maintenance therapy in SLE. Moroni *et al.* compared AZA with cyclosporine (CsA) as maintenance therapies in a RCT of 69 patients with diffuse proliferative lupus nephritis and preserved renal function [12]. As induction therapy, patients received three

consecutive daily pulses of 1 g iv. MP followed by prednisone and oral cyclophosphamide for 3 months. Following this, they were assigned to receive either CsA (4 mg/kg/day for 1 month and then tapered to 2.5–3 mg/kg/day) or AZA (1.5–2 mg/kg/day for 2–4 years). The rate of flare-ups (the primary study outcome) was comparable in the two groups (seven patients in the CsA group vs eight in the AZA group) and there were no differences in proteinuria and blood pressure levels. Both agents were well tolerated. The results of this trial, although limited by the inclusion of only mild-to-moderate nephritis cases, the short duration of induction therapy and the moderate doses of immunosuppressive agents, confirmed the efficacy of AZA and highlighted the potential use of CsA as maintenance treatment in lupus nephritis patients with preserved renal function.

■ Cyclophosphamide

Cyclophosphamide is the treatment of choice for severe manifestations of lupus and its efficacy is continuously confirmed by recent controlled trials and observational cohort studies. To this end, the 10-year renal survival rate in Chinese patients with diffuse proliferative lupus nephritis treated with cyclophosphamide (oral or iv.) has been 83% of late [13]. In the Euro-Lupus Nephritis Trial, patients with moderately severe nephritis (mean serum creatinine: 1.2 mg/dl, mean proteinuria: 3.0 g/day) were randomized to receive high-dose (six monthly pulses of 0.5–1 g/m² followed by two quarterly pulses) or low-dose (500 mg biweekly for a total of six pulses) iv. CYC as induction therapy followed by AZA maintenance therapy [14,15]. Mean survival rate at 10 years was 92% for both groups; primary end points, such as end-stage renal disease and doubling of serum creatinine rates, did not differ between the two groups. Adverse effects (severe infections, hematologic or gonadal toxicity) tended to be less common in the low-dose regimen although the differences did not reach statistical significance [14]. Therefore, low-dose iv. CYC could be an alternative therapeutic protocol for non-high-risk Caucasian SLE patients with moderate-to-moderately severe nephritis.

Barile-Fabris *et al.* reported the superiority of iv. CYC compared with iv. MP therapy for severe neurological manifestations in SLE [16]. In this trial, 32 patients were randomized to receive three pulses of 1 g iv. MP followed by one of the following two treatments: pulses of 1 g iv. MP (monthly for 4 months, then bimonthly for 6 months and subsequently every 3 months for 1 year) or iv. CYC (0.75 g/m² monthly for 1 year, then every 3 months for another year). Seizure was the most

common neurological syndrome (n = 11); other manifestations included peripheral neuropathy (n = 7), optic neuritis (n = 5), transverse myelitis (n = 4), brainstem disease (n = 2), coma (n = 2) and internuclear ophthalmoplegia (n = 1). Clinical response (defined as a ≥20% improvement from basal conditions in clinical, laboratory or specific neurological testing variables) was observed in 18 out of 19 patients who received iv. CYC compared with seven out of 13 who received iv. MP. Based on this trial and on older case-series, this combination of iv. MP pulses with iv. CYC is considered the treatment of choice for severe inflammatory neurologic manifestations in SLE [17].

Novel therapies in SLE

A summary of novel therapies in SLE is provided in TABLE 1.

■ Mycophenolate mofetil

Mycophenolate mofetil (MMF), originally used in transplantation, exerts its immunosuppressive effects through the inhibition of T- and B-lymphocyte proliferation. Its efficacy in SLE has been demonstrated in several uncontrolled studies; recently, a number of RCTs have compared MMF versus cyclophosphamide or AZA as induction and maintenance regimens in proliferative lupus nephritis.

Induction therapy

Four RCTs have compared the efficacy of MMF versus cyclophosphamide as an induction therapy in proliferative lupus nephritis. Two of them (Chan *et al.* [18,19] and Ong *et al.* [20]) involved Asian patients with moderate-to-severe lupus nephritis and demonstrated equal efficacy of MMF (2 g/day for 6 months) compared with cyclophosphamide (monthly iv. pulses of 0.75–1 g/m² in one study and orally administered 2.5g/kg/day in the other) with similar remission rates. The small number of patients, the short follow up and the inclusion of only Asian patients are important limitations of these trials. Ginzler *et al.* reported that MMF was superior to iv. CYC as an induction therapy for proliferative lupus nephritis in a RCT that included multiracial American populations (56% African–American) [21]. In this study, patients were assigned to receive MMF (3 g/day) or iv. CYC (0.5–1 g/m²) for 6 months combined with a tapering dose of steroids starting from 1 mg/kg/day. The study allowed crossover at 3 months for treatment failure or toxicity. Complete and partial remission was 23 and 30% in the MMF group compared with 6 and 35% in the iv. CYC group, respectively. Treatment failure was higher in the iv. CYC group

(69 vs 48%) and cross-over was more frequent in this group (20 vs 8%). The results of this trial should be interpreted with caution in view of the short follow up and the fact that MMF was compared with iv. CYC alone and not combined with monthly pulses of iv. MP, which is routinely carried out nowadays in severe lupus nephritis. Patients with severe renal impairment (baseline serum creatinine > 3 mg/dl) were excluded from the trial. Importantly, this was a nonsuperiority trial with inadequate power for a superiority trial.

In agreement with the results of the aforementioned trials, three meta-analyses of RCTs have also demonstrated the superiority of MMF against cyclophosphamide as an induction therapy for proliferative lupus nephritis [22–24]. However, the strength of evidence in these meta-analyses is limited by the flaws of the original studies. To settle this issue, the Aspreva Lupus Management Study (ALMS) failed to demonstrate the superiority of MMF over iv. CYC. This is one of the largest and most racially diverse RCTs in lupus nephritis and included a total of 370 patients, 27% of which had renal impairment (estimated glomerular filtration rate [GFR] < 60 ml/min/1.73m²) [25]. Response rates were similar for both groups (56% for the MMF group and 53% for the iv. CYC group); moreover, there were no differences regarding adverse events (total events: 96% in the MMF arm vs 95% in the iv. CYC group; infections: 69 vs 62%, respectively) [101]. Taken together, these data suggest that MMF is a reasonable option for patients with mild-to-moderately severe lupus nephritis. To date, no RCT has compared MMF with AZA as an induction therapy.

Maintenance therapy

Contreras *et al.* compared MMF (0.5–3 g day) versus AZA (1–3 mg/kg/day) or quarterly pulses of iv. CYC as maintenance therapy in severe proliferative lupus nephritis [26]. Most patients had diffuse proliferative nephritis and were Black and Hispanic. After a follow up of 34 months, MMF and AZA were demonstrated to be superior to iv. CYC in terms of relapse-free survival (78% for MMF, 58% for AZA and 4% for iv. CYC), mortality, infections and amenorrhoea. Chan *et al.* also compared MMF with AZA as maintenance therapy following induction with either oral cyclophosphamide or MMF (2 g/day) for 6 months [19]. The MMF dose was reduced by 25% after 6 months and after the first year was continued at a dose of 500 mg twice daily for another year before further tapering in stable patients. There were no significant differences in rates of infection (herpes zoster virus), amenorrhoea and progression to

end-stage renal disease between the MMF and the AZA–cyclophosphamide groups. The results of these two trials are summarized in one meta-analysis, which concluded that maintenance therapy with MMF did not decrease the rate of death, end-stage renal disease, renal relapse or the doubling of serum creatinine values compared with AZA [24]. Collectively, and until the results of two other ongoing multicenter RCTs (Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis [MAINTAIN] Trial and Aspreva Lupus Management Study [ALMS], maintenance therapy part) are available, MMF and AZA may be considered as comparable options for maintenance therapy of moderate-to-moderately severe proliferative lupus nephritis.

■ Calcineurin inhibitors

Cyclosporine, an inhibitor of T-cell-mediated responses that was initially used in transplantation, has been tested in a variety of autoimmune diseases. A recent trial compared the efficacy of CsA, iv. CYC and corticosteroids in 42 patients with lupus membranous nephropathy (median glomerular filtration rate [GFR]: 83 ml/min/1.73 m²; median proteinuria: 5.4 g/day) [27]. All patients received alternate-day oral prednisone (initiated at 1 mg/kg every other day for 8 weeks, followed by gradual tapering to 0.25 mg/kg every other day). Each treatment group received one of the following regimens: corticosteroids alone, iv. CYC every other month (six doses of 0.5–1 g/m² adjusted to leukocyte nadir) or CsA (initiated at 5 mg/kg/day and then adjusted according to changes in serum creatinine) for 11 months. At 1 year, the cumulative probability of remission was 27% with prednisone, 60% with iv. CYC ($p = 0.04$ vs the prednisone group) and 83% with CsA ($p = 0.002$ vs the prednisone group). However, relapses of nephrotic syndrome occurred significantly more often after completion of CsA than after iv. CYC therapy; rates of relapse per 100 patient-months were 2.0 units with CsA versus 0.2 units with iv. CYC ($p = 0.02$). Ten patients who failed to respond to prednisone alone or CsA, or who relapsed after initial response to CsA, were treated with iv. CYC for a median duration of 24 months. Eight out of ten patients achieved remission with stable renal function. Important limitations of this trial are the small number of patients and the short follow up. Moreover, patients with baseline GFR at less than 67 ml/min/1.73 m² were not allowed to be randomized in the CsA group, and CsA dose was reduced based on changes in serum creatinine levels. However, these results suggest that although

CsA is effective as an induction therapy in membranous nephropathy, CsA may require maintenance therapy (with lower doses of CsA, AZA or MMF) to prevent relapses.

Cyclosporine (1.5–5 mg/kg/day) has also been used in refractory-to-conventional treatment of proliferative nephritis, either in combination with corticosteroids or between quarterly doses of iv. CYC, demonstrating good efficacy (complete remission rates of up to 90% were achieved in some uncontrolled studies) [28–32].

Relapse of proteinuria is common after discontinuation of the treatment. As stated previously, Moroni *et al.* compared CsA with AZA as maintenance therapy for proliferative lupus nephritis and reported similar rates of reduction in proteinuria and relapses [12].

Tacrolimus is another calcineurin inhibitor that has also demonstrated efficacy in uncontrolled studies of proliferative and membranous lupus nephritis [33,34]. In a recent trial, 18 patients with biopsy-proven lupus membranous nephropathy received tacrolimus (0.1–0.2 mg/kg/day in two divided doses) and prednisone (30 mg/day with gradual tapering) for 6 months [35]. Patients were compared with 19 historic controls who received AZA or cyclophosphamide plus steroids. In the tacrolimus group, complete and partial remission rates were 39 and 40%, respectively, at 24 weeks compared with 37 and 58% in the control group. Mean proteinuria was reduced by 76% in the tacrolimus group and by 47% in the control group. Although these results are limited by the lack of head-to-head comparison, the small number of patients and short follow up, they provide some evidence for the efficacy of tacrolimus in membranous lupus nephritis. Currently, one ongoing RCT in China enrolling 100 patients is testing the efficacy of tacrolimus (0.06–0.1 mg/kg/day) compared with MMF (2–3 g/day) in the treatment of proliferative and membranous lupus nephritis [102].

■ Multitarget therapy for lupus nephritis?

Bao *et al.* recently reported encouraging results regarding the treatment of mixed diffuse proliferative and membranous lupus nephritis using a combination of agents [36]. This subtype of nephritis tends to respond less well to conventional immunosuppressive treatment and is associated with poor prognosis. In this prospective study, combination treatment with steroids, MMF, and tacrolimus was compared with iv. CYC plus corticosteroids. Enrolled patients (n = 40) had preserved renal function (estimated GFR: 98 ml/min), proteinuria at

4.4 ± 2.0 g/24 h and SLEDAI of 14 ± 2; 70% had received previous therapy with MMF or cyclophosphamide. Tacrolimus was used at 4 mg/day, MMF at 2 g/day and iv. CYC monthly pulses were administered at 1 g/m² (total of six to nine pulses). All patients received iv. MP (0.5 g/day) for three consecutive days followed by oral prednisone. After 6 months, ten patients (50%) in the ‘multi-target’ group versus one patient (5%) in the iv. CYC group achieved complete remission. Partial remission rates were 40% in both groups. In multivariate analysis, patients on the multi-target therapy were 6.5 times more likely to enter complete remission compared with those treated with iv. CYC. Repeat biopsies demonstrated significant improvement in activity index scores in patients who had complete remission. Combination therapy was well tolerated and no major effects were observed, neither was nephrotoxicity from calcineurin inhibitors. These results should be interpreted with caution in light of limitations, such as the small number of patients and the short trial duration, which might bias the study to demonstrate benefits for a regimen with a more rapid onset of action. In addition, patients with an increased chronicity index score (>4) were excluded. Additional studies with a larger number of patients and longer follow up are needed to establish the efficacy, safety and specific indications of such multidrug therapies in lupus nephritis.

■ Rituximab

Rituximab, a chimeric monoclonal antibody directed against the B-lymphocyte antigen CD20, has been successfully used for a variety of autoimmune diseases. Evidence from several case-series suggests that rituximab may be an effective alternative therapy in the refractory-to-conventional treatment of lupus manifestations. To date, a total of 162 SLE patients reported in 11 studies have been treated with rituximab (the most commonly used therapeutic scheme is four weekly doses of 375 mg/m²), including patients with nephritis (n = 84), cytopenias (n = 23) and CNS lupus (n = 27) (TABLE 2) [37–46]. More than half of these patients relapsed after treatment with corticosteroids and cyclophosphamide. Rituximab in combination with corticosteroids, iv. CYC, AZA or other immunosuppressants resulted in a clinical response in 89 of 162 patients (54%), 36% of whom achieved complete response. This included improvements in disease activity index scores, renal parameters (proteinuria and hematuria),

Table 2. Summary of published studies on the use of rituximab in systemic lupus erythematosus.

Study	No. patients (n)	SLE features	Concomitant treatment	Clinical response	No. relapses	Adverse events	Ref.
Boletis <i>et al.</i> (2009)	10	Nephritis (IV)	MMF, GC	Eight CR, two PR	2	None	[45]
Jonsdottir <i>et al.</i> (2008)	16	Nephritis (n = 9) Serositis (n = 3) Vasculitis (n = 3) CNS (n = 1)	CYC	13 (nine had remission with SLEDAI < 3)	7	None	[43]
Kumar <i>et al.</i> (2009)	9	Thrombocytopenia (n = 5) Hemolytic anemia (n = 3) Both (n = 1)	–	Nine CR	2	Infusion reaction (n = 1)	[46]
Melander <i>et al.</i> (2009)	20	Nephritis (15 IV, 5 V)	CYC	12 (CR plus PR)	1	Infections (n = 5) Neutropenia (n = 4)	[58]
Ng <i>et al.</i> (2007)	32	Nephritis (n = 21) Cytopenias (n = 5) Serositis (n = 11)	CYC, GC, HCQ	Improvement in median BILAG from 13 to 5	18	Severe infection (n = 1) Serum sickness (n = 1) Death (n = 1 owing to pancarditis)	[40]
Reynolds <i>et al.</i> (2009)	11	CNS (n = 3) Hematological (n = 3) Renal (n = 2) Cardiorespiratory (n = 2)	GC, CYC	Ten demonstrated improvement in median BILAG by 7.5	4	Infusion reaction (n = 1) Infection (n = 1)	[59]
Smith <i>et al.</i> (2006)	11	Nephritis (n = 6) CNS (n = 3) Lung involvement (n = 2)	CYC, AZA, MMF, GC	Six CR, five PR Improvement in mean BILAG from 14 to 3	7	Serum sickness (n = 1) Serious bacterial infections (n = 4)	[37]
Tamimoto <i>et al.</i> (2008)	8	Nephritis (n = 4) Cytopenias (n = 3) CNS (n = 3)	GC, CsA, CYC	Seven (CR plus PR) Improvement in mean SLEDAI from 18 to 7	5	Infections (n = 4) Death (n = 1 owing to progression of pre-existing renal insufficiency)	[44]
Tanaka <i>et al.</i> (2007)	15	Nephritis (n = 7) CNS (n = 6) Cytopenias (n = 3)	GC, CYC, AZA, CsA, MTX	Nine (CR plus PR) Improvement in mean BILAG from 13 to 7	–	Serious infections (n = 3)	[41]
Tokunaga <i>et al.</i> (2007)	10	CNS	Betamethasone	Ten demonstrated improvement in mean SLEDAI from 20 to 6	6	Pneumonia (n = 2) Herpes zoster (n = 1) Chickenpox (n = 1)	[42]
Vigna-Perez <i>et al.</i> (2006)	22	Nephritis (n = 22, 2 III, 18 IV, 2 V) CNS (n = 3) Cytopenias (n = 16) Serositis (n = 12)	GC, AZA, MMF, MTX, CYC	Five CR, seven PR (renal disease)	NR	NR	[38]

AZA: Azathioprine; BILAG: British Isles Lupus Assessment Group; CR: Complete response; CsA: Cyclosporine; CYC: Cyclophosphamide; GC: Glucocorticoids; HCQ: Hydroxychloroquine; MMF: Mycophenolate mofetil; MTX: Methotrexate; NR: Not reported; PR: Partial response; SLE: Systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index.

neurological manifestations and MRI findings, and reductions in the mean daily dose of corticosteroids. The combination of rituximab with cyclophosphamide or MMF is also efficacious and is safe in patients with proliferative lupus nephritis, refractory to either iv. CYC or MMF alone [37]. Toxicity data in SLE are limited but the extensive use of rituximab in other clinical settings has provided evidence of a satisfactory safety and tolerability profile. However, vigilance is required with regard to the risk of opportunistic infections.

Randomized, controlled trials are mandatory for establishing the efficacy and indications of rituximab alone or in combination with other immunosuppressive agents. This is even more important in view of preliminary results from the Efficacy and Safety of Rituximab in Patients With Severe Systemic Lupus Erythematosus (EXPLORER) trial [103], a randomized, double-blind trial that assessed the efficacy and safety of rituximab (1000 mg/dose of four doses) versus placebo in 257 SLE patients with moderate-to-severe extra-renal disease. Baseline immunosuppressive drug(s) were continued and prednisone (0.5–1.0 mg/kg/day and then tapered) was initiated as part of the study protocol. After 52 weeks, rates of complete and partial clinical response and adverse events did not differ between rituximab- and placebo-treated patients, and approximately 70% of patients in both groups had no response. Currently, the efficacy of rituximab in lupus nephritis is being evaluated in two RCTs (EXPLORER and Lupus Nephritis Research [LUNAR] [104]) and their results are expected to be published in 2010.

■ Other agents

Leflunomide, which is currently used for the treatment of rheumatoid arthritis as a disease-modifying drug, has also been used in SLE. Uncontrolled studies have demonstrated some efficacy of leflunomide in lupus nephritis with complete and partial response rates ranging from 21 to 58% and 42 to 52%, respectively, after a follow up of 6–12 months [47–49]. The concurrent use of corticosteroids and the short follow up are important limitations of these studies.

Abetimus sodium (LJP394) has been used to prevent renal flares in SLE patients. A double-blind, placebo-controlled trial involving 317 patients evaluated the effect of weekly iv. administration of 100 mg abetimus sodium or placebo for 22 months on prolonging the time to renal flares [50]. The primary end point of the study was

not reached, but the authors reported a reduction in the rate of renal flares in abetimus patients by 25% compared with the placebo group, as well as a reduction in anti-dsDNA levels and proteinuria. In the ongoing Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN), an interim analysis demonstrated that abetimus (300 and 900 mg doses) resulted in significant and sustained reductions in anti-dsDNA antibody titres in lupus nephritis patients, but more definite data on the efficacy of abetimus in maintenance of remission in lupus are not yet available.

Clofazimine (CFZ), an antimicrobial drug that is used in the treatment of leprosy, has been evaluated and compared with chloroquine diphosphate (CDP) for the treatment of cutaneous involvement of SLE. Bezarre *et al.* conducted a prospective, randomized, controlled, double-blind clinical trial where 16 patients were randomized to receive clofazimine at 100 mg/day and 17 received chloroquine at 250 mg/day for 6 months. At the end of the study, 12 CFZ-treated patients (75%) and 14 CDP-treated patients (82.4%) had complete or near-complete remission of skin lesions; intention-to-treat analysis demonstrated no significant difference in the response rates between the groups. However, five CFZ-treated patients and one CDP-treated patient dropped out owing to the development of a severe lupus flare. The authors concluded that CFZ was equally as effective as chloroquine in the treatment of cutaneous lesions in SLE patients but suggested that CDP should be reserved for patients who have exclusively cutaneous manifestation of the disease, since CFZ might contribute to the development of severe lupus flares.

Novel biological therapies are becoming available, including anti-B-cell targets (anti-CD22 mAb and anti-BAFF mAb) and peptide vaccinations and are currently being tested in RCTs (TABLE 3).

■ Adjunct therapy

Therapeutic approaches other than using corticosteroids or immunosuppressive drugs have been reported in SLE treatment. Abdou *et al.* evaluated the efficacy of the selective estrogen receptor downregulator fulvestrant in 20 premenopausal women with moderate SLE [51]. Ten patients received 250 mg fulvestrant intramuscularly for 12 months and ten received placebo. After 15 months, the mean SLEDAI was reduced from 8.3 ± 2.6 to 3.5 ± 2.9 ($p = 0.002$) in the fulvestrant group, whereas a nonsignificant decrease occurred in the placebo group (from 7.9 ± 4.9 to 6.6 ± 3.1). Fulvestrant therapy also decreased

Table 3. Biological agents in development for systemic lupus erythematosus.

Agent	Stage in development	Main result
Abatacept (CTLA4Ig)	Phase II, placebo-controlled trial Two ongoing trials in lupus nephritis	In patients with moderate-to-severe extra-renal disease, the adjudicated BILAG-based primary and secondary end points were not met after 1 year of treatment
Atacicept (TACI-Ig)	Phase I, placebo-controlled trial Ongoing Phase II/III trial in generalized SLE A Phase II/III study in lupus nephritis terminated owing to toxicity	Intravenous atacicept was generally well tolerated, both systemically and locally, in patients with mild-to-moderate SLE. Its biological activity was demonstrated by its marked effect in reducing B cells and immunoglobulin levels in SLE
Anti-IL-10 mAb	Phase I, open-label trial	Cutaneous lesions, joint symptoms and SLEDAI significantly improved during the 6-month follow up. A steroid-sparing effect was observed
Belimumab (anti-BLyS)	Phase II/III, placebo-controlled trial	In seropositive SLE patients, belimumab resulted in sustained improvement in disease activity through 3 years of continuous treatment. The frequency of flares declined in the 3 years that subjects remained on belimumab therapy
Eculizumab (anti-C5 mAb)	Phase I, open-label trial	Eculizumab was safe and well tolerated and resulted in a C5 blockade
Epratuzumab (anti-CD22 mAb)	Phase II, placebo-controlled trials Ongoing Phase II trial	Epratuzumab treatment resulted in clinically significant improvements in health-related quality of life and disease activity over 12–48 weeks. A steroid-sparing effect was also observed
Infliximab (anti-TNF)	Open-label trial Ongoing open-label trial in lupus membranous nephropathy	Infliximab in combination with azathioprine led to rapid, pronounced reduction in proteinuria in lupus nephritis patients
MEDI-545 (anti-IFN α mAb)	Phase I trial Two ongoing Phase I/II trials	Anti-IFN- α therapy resulted in the neutralization of other signaling pathways including GM-CSF, TNF, IL-10, IL-1 β and BAFF in SLE patients
Spliceosomal peptide P140 (IPP-201101)	Phase II, open-label trial	A total of 50% of the patients in the effective dose group demonstrated a SLEDAI reduction of at least 50%, and 80% of the patients had significant reductions in anti-dsDNA titers. The drug was safe and well tolerated.
Tocilizumab (anti-IL-6 mAb)	Phase I, open-label trial	Biological effect was observed with a decrease in acute-phase reactants, and a decrease in immunoglobulin levels and anti-dsDNA. Swollen joint counts, SLEDAI and SLAM scores decreased

BAFF: B-cell-activating factor; BILAG: British Isles Lupus Assessment Group; BLyS: B-lymphocyte stimulator; GM-CSF: Granulocyte-macrophage colony-stimulating factor; mAb: Monoclonal antibody; MEDI: Mediator complex subunit 1; SLAM: Systemic Lupus Activity Measure; SLE: Systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index.

CD154 (CD40L) levels and calcineurine expression in peripheral blood T cells. Fulvestrant was demonstrated to be relatively safe and had no significant impact on menstruation. More extended and larger studies are needed to better define the role of fulvestrant in the treatment of SLE patients.

Wright *et al.* reported the results of a randomized, placebo-controlled trial of supplementation with polyunsaturated fatty acids on endothelial function and disease activity in patients with moderate SLE [52]. A total of 30 patients received n-3 polyunsaturated fatty acids and 30 received placebo for 24 weeks. The authors reported reductions in British Isles Lupus Assessment Group (BILAG) and Systemic Lupus Activity Measure-Revised (SLAM-R) scores, improvements in endothelial function and a reduction of oxidative stress with a potential impact on the cardiovascular burden of disease.

Dehydroepiandrosterone (DHEA) is an inactive steroid that naturally occurs in adrenal glands, testes and ovaries and its metabolite is a

major circulating adrenal steroid. Patients with active SLE have lower levels of DHEA. Seven RCTs including 842 patients have been carried out to assess the efficacy and the safety of DHEA in SLE. A meta-analysis of these RCTs demonstrated that DHEA had little clinical effect in patients with mild-to-moderate disease (measured by SLEDAI or SLAM) but had no effect in those with severe disease [53]. DHEA treatment resulted in a moderate, but clinically significant, improvement in health-related quality of life measurements.

Conclusion

Although the treatment of SLE has been challenging and a subject of controversy during the past decades, a consensus is finally emerging based on RCTs and expert opinions [10,17]. In proliferative lupus nephritis, MMF is considered a reasonable alternative as an induction therapy for moderate-to-moderately severe disease. Patients with mild disease may be treated

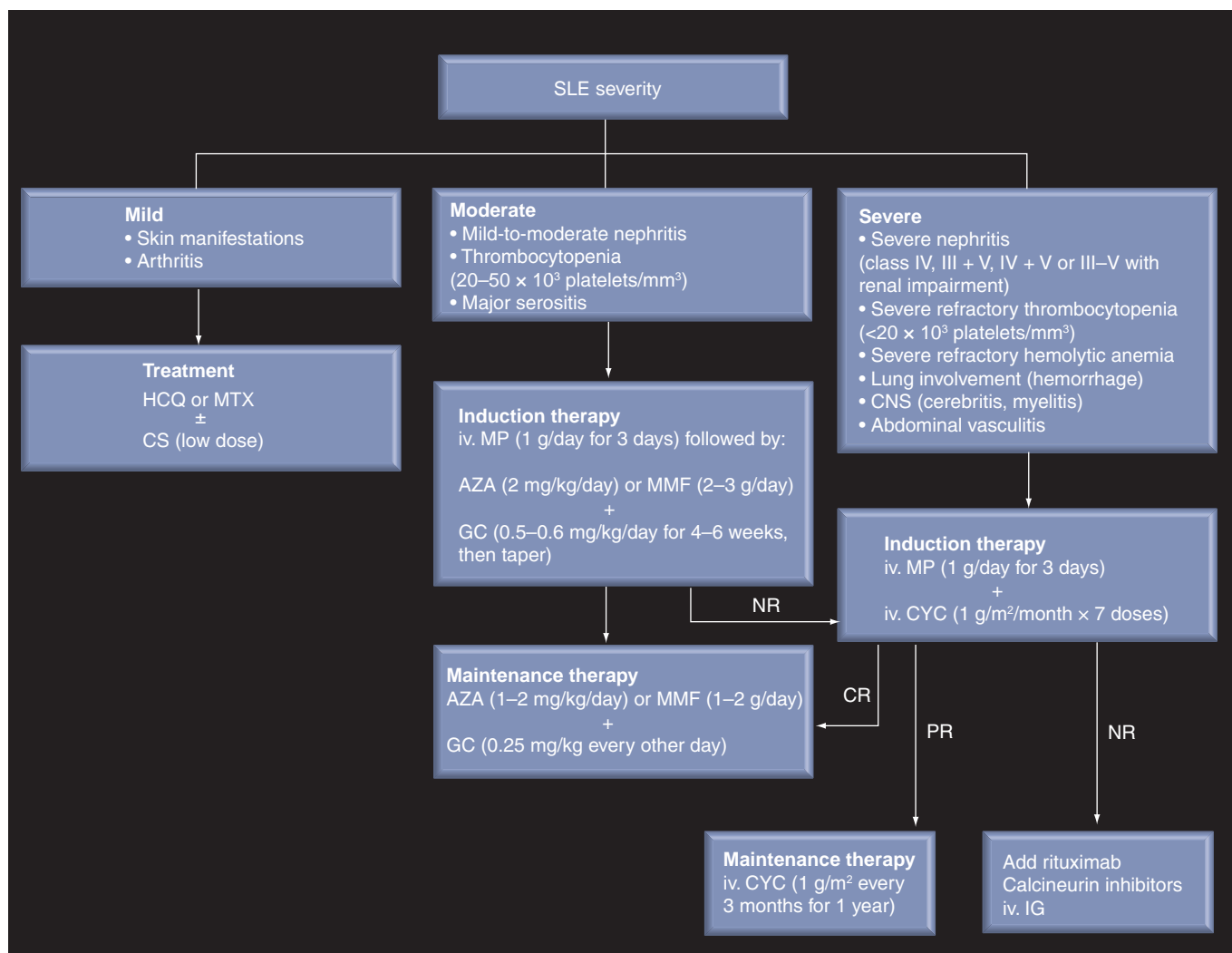


Figure 1. Algorithm for the management of systemic lupus erythematosus. Treatment of SLE according to the severity of manifestations.

AZA: Azathioprine; CR: Complete response; CS: Corticosteroids; CsA: Cyclosporine; GC: Glucocorticoids; HCQ: Hydroxychloroquine; iv. CYC: Intravenous cyclophosphamide pulse therapy; iv. IG: Intravenous immunoglobulin; iv. MP: Intravenous methylprednisolone pulse therapy; MMF: Mycophenolate mofetil; MTX: Methotrexate; NR: No response; PR: Partial response; SLE: Systemic lupus erythematosus.

with less expensive agents such as AZA, which is widely used as a steroid-sparing agent and as a means towards consolidating remission (FIGURE 1). Both AZA and CsA are safe to use during pregnancy, an attractive feature for young women of the reproductive age. In refractory-to-conventional immunosuppressive therapy cases, novel biological (rituximab) and calcineurin inhibitors may be of benefit in experienced centers since there are no standardized protocols and formal indications. Several other biological therapies are currently being tested in SLE trials, which are often plugged by generic issues such as the heterogeneity of disease manifestations, the number of patients meeting enrolment criteria and the variable outcome measures. Nonetheless, these new agents have increased the available

therapeutic options in the hands of physicians who now have the opportunity to individualize the treatment of SLE according to the needs and characteristics of each patient. The majority of available RCTs mainly involve patients with lupus nephritis, with recommendations for the treatment of nonrenal SLE being based on extrapolation of these data.

Future perspective

In spite of considerable achievements, treatment of established lupus is a difficult task. Complete remission of mild disease with mucocutaneous or joint disease remains a challenge with a significant number of patients demonstrating residual activity in spite of improvement. On the other hand, although lupus involving major organs

can be put into complete remission by the use of higher doses of corticosteroids and immunosuppressive therapy in most cases, this is associated with considerable toxicity owing to the therapy and there is a significant risk of relapse. Finally, severe disease, refractory-to-standard immunosuppressive and biological therapy, albeit uncommon, remains a challenge.

In the future, the presence of autoantibodies in patients with lupus, together with emerging biomarkers for disease activity/severity, should enable earlier intervention before generalization of disease activity occurs. Notwithstanding current limitations of therapy for lupus, the

achievements so far are unsurpassed by any other in other autoimmune diseases, a fact that justifies, in our opinion, cautious optimism.

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Executive summary

- Treatment of moderate and severe systemic lupus erythematosus (SLE) involves a period of intensive induction therapy followed by a longer period of less intensive maintenance therapy.
- Pulses of intravenous cyclophosphamide in combination with corticosteroids is considered as 'the standard of care' for induction therapy for severe SLE.
- Mycophenolate mofetil may be used as an induction therapy for moderately severe SLE under close observation. Failure to achieve complete response or remission within 3–6 months should evoke discussions regarding intensification of therapy.
- In resistant-to-conventional treatment for SLE manifestations, the addition of calcineurine inhibitors (cyclosporine or tacrolimus) or rituximab is a safe and efficacious option.
- Mycophenolate mofetil and azathioprine appear to be equally effective as maintenance therapy, while in patients with stable renal function, cyclosporine may be a reasonable alternative.
- Methotrexate could be an alternative steroid-sparing agent in SLE patients with mild-to-moderate disease, having potential beneficial effects on disease activity.
- Combination therapy is a valid option in lupus. In addition to pulses of corticosteroids and cyclophosphamide, initial data suggest that the combination of mycophenolate mofetil with calcineurin inhibitors in a background of corticosteroids may result in higher rates of remission in an expedited fashion.
- Sequential therapy is a valid option with cyclophosphamide or mycophenolate mofetil used for induction of remission and azathioprine or cyclosporine used for maintenance of remission.

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