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REVIEW

The safety of pharmacological treatment options for lupus nephritis

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ABSTRACT

Introduction: The management of lupus nephritis (LN) has changed significantly over the last 10 years due to emerging evidence from large randomised clinical trials that produced good quality data and guided the formulation of two key concepts: the induction of remission and the maintenance phase of immunosuppressive therapy.

Areas covered: Optimizing cyclophosphamide and glucocorticoid regimens and the introduction of mycophenolate mofetil for proliferative and membranous LN has been pivotal. Nevertheless, concerns remain about treatment toxicity especially long term glucocorticoid use and exposure to cumulative cyclophosphamide doses. Here we discuss the conventional and newer pharmacological options for managing LN focusing on drug safety and toxicity issues.

Expert opinion: The need for effective and less toxic treatments led to the development of the role of targeted biologic therapies in LN. However, evidence from the initial randomized controlled trials has been disappointing, although this reflects inadequate trial design rather than true lack of efficacy.

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1. Introduction

Lupus nephritis (LN) is one of the most common and severe manifestations of systemic lupus erythematosus (SLE) occurring in 40–70% of patients [1,2] associated with significant morbidity and mortality.[3]

When glucocorticoids (GC) and antibiotics were first introduced for the treatment of SLE in the 1950s the reported survival rate for SLE was <50% at 4 years. Muehrcke et al. [4] first showed the improved patient outcome despite initial concerns that these treatments could worsen the existing renal injury.

Although LN may affect all compartments of the kidney, glomerular involvement is the major concern. Treatment has largely been guided by histological findings as defined by the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classification,[5] consideration of presenting clinical parameters and the degree of renal impairment (Tables 1 and 2).

Despite treatment advances 16–26% of patients (UCLH Isenberg D., unpublished observations on 673 patients) [6] with LN develop end-stage renal disease (ESRD). Life expectancy of SLE patients with renal disease and renal damage is reduced by 15.1 and 23.7 years, respectively.[7] Although better treatment of LN has considerably improved patient survival rates, therapy-related toxicity remains a major concern.

In this review the treatment options for LN, conventional and biologic, are considered. Treatment is usually divided in two main phases, induction of remission followed by maintenance therapy. The aim of induction immunosuppression is to minimize damage to the nephrons by dampening inflammation in the kidney. The maintenance phase consolidates remission and reduces the long-term risk of relapse.[8]

2. Conventional induction and maintenance treatments

A summary of conventional treatments with their main mechanism of action and common side effects is presented in Table 3 and trial acronyms are shown in Figure 1.

2.1. Glucocorticoids

Moderate to high dose of GC in addition to a cytotoxic drug is the most commonly used induction regimen in LN. Historically, a shift occurred in the 1980s from using GC alone to the use of combination therapy with immunosuppressive drugs. A series of clinical trials from the National Institutes of Health (NIH), USA showed that induction treatment with intravenous (iv) cyclophosphamide (CYC) pulses of 0.75–1 g/m^2 given monthly for 6 months followed by quarterly pulses was more effective than GC alone in preserving renal function and enabling prolonged remission. Adverse effects seen in both groups included infections, neoplasms and hospitalizations.[26,27]

2.1.1. Glucocorticoids dosing considerations

The optimum dose of GC is controversial. For induction, most guidelines [Kidney Disease: Improving Global Outcomes (KDIGO),

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NOTE: The ongoing trials are mentioned with the study's unique identifier NCT number of the registry ClinicalTrials.gov (https://clinicaltrials.gov)

Article highlights

- Lupus nephritis is one of the most common and severe manifestations of SLE and is associated with significant morbidity and mortality
- Treatment options are guided by the histologic classification of LN
- Induction immunosuppression with combination of CYC or MMF and steroids aims to minimize inflammation in the kidney, and should be followed by maintenance therapy usually MMF, AZA or Tacrolimus
- MMF is a viable alternative to CYC for induction therapy of both proliferative and membranous LN.
- Rituximab, abatacept, atacicept and ocrelizumab's trials failed to reach their primary outcomes in LN.
- Rituximab may be used as add on therapy to induction regiments, for refractory disease or as steroid sparing agent.
- Data are now available to encourage the view that LN might be treated at diagnosis using B cell depletion and avoiding oral steroids.

This box summarizes key points contained in the article.

American College of Rheumatology and the European League Against Rheumatism/European Dialysis and Transplantation Association] recommend either moderate to high dose prednisolone (or equivalent) of up to 1 mg/kg/day during 2 or 4 weeks followed by tapering schedules. In more severe forms of LN, iv pulses of methylprednisolone (250–1000 mg/day) should be considered during the first 3 days. According to the National Kidney Foundation's KDIGO guidelines, the same dose of GC that was effective in inducing original remission, can be used for treatment of relapse.[28] For maintenance therapy, low to moderate-dose prednisolone (up to 10 mg/day) is used.

There are no clinical trials directly comparing the different dosing regiments of GC. Indirect data from the Euro-Lupus Nephritis Trial (ELT) [14] suggests that a lower GC regimen (3× iv pulses of 750 mg methylprednisolone followed by 4 weeks of 0.5 mg/kg/day prednisone) has similar outcomes and less adverse effects when compared to other high dose regimen trials. Zeher et al. [29] tested the efficacy of mycophenolate mofetil (MMF) using two different GC dosages (1 mg/kg/day or 0.5 mg/kg/day) in two randomized groups after three common initial pulses of methylprednisolone (500 mg). Both groups had similar outcomes for complete remission (19% vs. 18% respectively) but differed significantly in partial remission outcomes (48% vs. 33%). Adverse effects were lower in the low GC dose group (10.3% vs. 16.7%). Ruiz-Irastorza et al. used a combination of medium-dose prednisolone (starting at 15 or 30 mg/daily depending on LN class and clinical status that was quickly tapered every 2 weeks until 10 or 7.5 mg/daily with a maintenance dose of 2.5–5 mg/daily), methylprednisolone pulses, cyclophosphamide and hydroxychloroquine. When compared with the high dose GC of the NIH regime it was found that their regime was at least as effective and with less adverse effects.[9]

Although GCs have historically been considered a mandatory component for treating LN, emerging evidence has challenged this assumption. An uncontrolled trial of Rituximab (RTX) combined with IV methylprednisolone followed by MMF in 50 patients with lupus nephritis (class III, IV or V) showed that most subjects achieved complete renal remission without any oral GC.[30] An ongoing randomized controlled trial (RCT; RITUXILUP-NCT01773616) is currently recruiting patients to answer this key question and may lead to steroid-avoiding regimens to obviate the burden of long-term GC related adverse effects.

Table 1. Lupus nephritis classification.

Class I		Minimal mesangial lupus nephritis
Class II		Mesangial proliferative lupus nephritis
Class III		Focal lupus nephritis
	Class III (A)	Active lesions: focal proliferative lupus nephritis
	Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
	Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV		Diffuse lupus nephritis
	Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
	Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
	Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
		Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
	Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
	Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V		Membranous lupus nephritis
Class VI		Advanced sclerosis lupus nephritis

Adapted with permission from [5].

Table 2. LN classification-treatment regimens depending on Class of LN.

	Induction	Maintenance
Class I	Immunosuppression treatment for LN not needed Treatment should be guided by extra-renal manifestations	
Class II	Treatment decision guided by clinical features and the presence and level of proteinuria: • If proteinuria <1 g/daily treatment dictated by extra-renal manifestations • If proteinuria >3 g/daily treatment GC with or without immunosuppressant drugs (CNIs) to spare dose of GC during 6/12 months • If proteinuria 1–3 g/daily individual evaluations should be made	
Class III-IV (A)[†]	GC and immunosuppressant drugs (CYC, MMF)	Lower dose of GC and immunosuppressant drugs (MMF, AZA, MPS)
Class V	GC and immunosuppressant drugs (CYC, MMF, CsA, TAC, AZA) If not responding to an immunosuppressant, consider switching to another	Lower dose of GC and immunosuppressant drugs (MMF, AZA, CsA)
Class VI	Decrease immunosuppression unless extra-renal lupus activity present	

LN: lupus nephritis; GC: glucocorticoids; CNIs: calcineurin inhibitors; AZA: azathioprine; MMF: mycophenolate mofetil; CYC: cyclophosphamide; MPS: sodium mycophenolate; CsA: cyclosporine; TAC: tacrolimus.
[†]Treatment considered for active or active plus chronic lesions.
Based on KDIGO guidelines: Lupus nephritis. Kidney International Supplements (2012) 2, 221–232; doi:10.1038/kisup.2012.25

Table 3. Conventional treatment in LN – drug therapy and safety considerations.

Drug name	Mode of action	Main use	Main adverse effects	Main studies
Glucocorticoids	Transrepression	Adjuvant to induction & maintenance	Osteoporosis, cardiovascular risk, infection risk	Ruiz-Irastorza et al. [9]
	Transactivation			Arends et al. [10]
				Moroni et al. [11]
Azathioprine	Blocks purine synthesis	Maintenance	Pancytopenia	Dooley et al. [12]
			Herpes zoster	Tamirou et al. [13]
Cyclophosphamide	Interferes with DNA replication	Induction	Infection risk, nausea &vomiting, alopecia, gonadal toxicity, hemorrhagic cystitis, malignancies	Houssiau et al. [14,15]
				Contreras et al. [16]
				Chan et al. [17,18]
Mycophenolate	Reversible IMPDH inhibition	Induction	Diarrhea, herpes zoster, pregnancy loss, fetal malformations	Ginzler et al. [19]
		Maintenance		Appel et al. [20]
				Contreras et al. [16]
				Dooley et al.[12]
				Tamirou et al. [13]
Cyclosporine	Inhibition of activation genes for IL-2, Suppression of T cell-induced activation of TNFα, IL-1β, and IL-6	Induction	Gum hypertrophy, hypertrichosis, hypertension, arthralgia, GI symptoms	Moroni et al. [11]
		Maintenance		Austin et al. [21]
Tacrolimus		Induction	Pneumonia, herpes zoster, tremor, reversible increase in serum creatinine	Chen et al. [22]
				Liu et al. [23]
				Mok et al. [24]
				Bao et al. [25]

MPDH: inosine monophosphate dehydrogenase; GI: gastrointestinal; TNFα: tumor necrosis factor-α.

2.1.2. Glucocorticoids safety concerns

Long-term damage and increased mortality are established complications of GC. There is a direct linear correlation between increasing dose of GCs with side effects, the most important of which are increased infection risk, diabetes, high blood pressure and osteoporosis. Others included ecchymosis, leg edema, parchment-like skin, dyspnea and sleep disturbance. An elevated frequency of adverse events beyond a certain threshold value has been observed. This 'threshold pattern' has been described at >7.5 mg/day for glaucoma, depression, insulin resistance and hypertension and at >5 mg/day for epistaxis and weight gain. A lower threshold was seen for eye cataract (<5 mg/day).[31,32]

Infections are also a dose-related complication, with clinical vigilance needed especially for opportunistic infections such as pneumocystis jiroveci pneumonia, tuberculosis reactivation or overwhelming strongyloidiasis. Susceptibility to major infections occurs with the doses of >7.5 mg/day.[33] Cardiovascular risk is another major concern; a study from the Hopkins Lupus Cohort showed that a cumulative dose of oral GCs over 36.5 g doubled the risk of heart disease.[34]

Up to 24% of patients with lupus have osteoporosis, including premenopausal patients, with a 1.2-fold increased fracture risk when compared with age- and sex-matched controls.[35] This mineral bone-loss effect of GCs in LN patients is aggravated by the nephropathy. The risk of fracture depends on the dosage and duration of GC therapy. Specifically, after 3 months of GCs use, the relative risk of vertebral fracture is increased from 1.55 to 5.18 when the dose is increased from 2.5 mg/day to >7.5 mg/day.[36] Furthermore, there is a sevenfold increase in hip fractures and a 17-fold increase in vertebral fractures with doses ≥10 mg/day.[37]

More pertinent to renal disease, prolonged use of GC may actually worsen proteinuria by increasing the glomerular filtration rate and decreasing tubular reabsorption. This effect is however reversible although there are restricted relevant data.[38]

2.2. Conventional immunosuppressive drugs

2.2.1. Azathioprine

Azathioprine (AZA) is a purine analog drug that acts at the level of DNA replication and can block the *'de novo'* pathway of purine synthesis.[39] It has been used since the 1960's in LN, mainly as maintenance treatment. A pooled analysis including 250 patients with LN published in 1984 indicated that patients on AZA and CYC had a better renal outcome when compared with those given GCs alone.[40]

CLINICAL TRIAL NAMES AND ACRONYMS

ACCESS: Abatacept and Cyclophosphamide Combination Therapy for Lupus.

ADDRESS II: Efficacy and Safety of Atacicept in Systemic Lupus Erythematosus.

ALMS: Aspreva Lupus Management Study.

APRIL-SLE: Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE).

ATLAS: BIIB023 Proof-of-Concept Study in Participants with Lupus Nephritis.

BELONG: A Study to Evaluate Ocrelizumab in Patients With Nephritis Due to Systemic Lupus Erythematosus.

BMS: Bristol-Myers Squibb for Trial Efficacy and Safety Study of Abatacept to Treat Lupus Nephritis.

BLISS: A phase III, randomized, placebo-controlled study of belimumab.

CALIBRATE: Rituximab and Belimumab for Lupus Nephritis.

ELT: Euro-Lupus Nephritis trial.

ILLUMINATE: Study to Evaluate the Efficacy and Safety of Subcutaneous LY2127399 in Patients with Systemic Lupus Erythematosus.

LUNAR: Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study.

PEARL-SC: A Study of the Efficacy, Safety, and Tolerability of A- 623 Administration in Subjects with Systemic Lupus Erythematosus.

RING: Rituximab for Lupus Nephritis with Remission as a Goal.

RITUXILUP: Trial of Rituximab and Mycophenolate Mofetil without Oral Steroids for Lupus Nephritis.

Figure 1. Clinical trial names acronyms.

AZA is well tolerated overall. In maintenance therapy trials in patients with LN, no difference was found when comparing AZA with CYC, cyclosporine (CsA), MMF or tacrolimus (TAC) in terms of drug tolerance.[41,42] The limited toxicity of AZA has been related to the presence of a genetic polymorphism that reduces the activity of the thiopurine methyltransferase enzyme. Serious adverse events can occur in homozygous patients (≈1% of those given the drug).

2.2.2. Cyclophosphamide

For 30 years the gold standard induction therapy for severe LN consisted of GCs with CYC.[43,44] The use of intravenous CYC is based on studies in the 1980s [26] and resulted in a recommendation from the National Institutes of Health (NIH) that high-dose intravenous CYC be used as a first-line induction treatment for lupus nephritis (0.5–1 g/m^2 monthly × 6 followed by quarterly pulses for 2 years). The NIH regimen showed fewer side-effects when compared with prolonged daily oral CYC regimens.[26,45] Patients treated with short-course CYC (6 monthly pulses CYC only) have a higher probability of exacerbations than those treated with long-course CYC (monthly cyclophosphamide for 6 months followed by quarterly pulse cyclophosphamide for 2 additional years); however the risk of ovarian failure increased significantly.[46]

In summary, the NIH treatment regimen is effective but concerns about its associated adverse effects (including leukopenia, alopecia, infections, gonadal toxicity, hemorrhagic cystitis, and predisposition toward malignancies). There are different thresholds for different side-effects; however, lifetime exposure to CYC should not exceed 25 g.[16] Safety concerns associated the fact that cyclophosphamide toxicity rises with a cumulative dose [15] led to development of newer regimens.

In the 1990´s, a reduced-dose intravenous CYC regimen (500 mg every 2 weeks × 6 doses) was introduced and later compared with the NIH regimen in the ELT.[14] Renal response, mortality, relapse rates were similar between both groups and encouragingly remained similar in the 10-year follow-up study.[47] However, after six CYC doses the ELT group were given maintenance therapy with AZA at week 12, whereas the NIH regimen continued with quarterly CYC pulses and started AZA at week 44. Therefore, it may be difficult to draw definitive conclusions from a direct

comparison of the CYC doses after week 12. However, ELT was pivotal as a 'proof of concept' study showing that a shorter course of a toxic immunosuppressant could be followed by maintenance treatment with a less toxic one with no decrease in efficacy and a favorable safety profile.[48] Subsequently another concern with the ELT has arisen regarding the selection and demographics of recruited patients who had milder renal disease than the NIH cohort and were predominantly Caucasian, who have lower risk of severe renal involvement. Recent studies have proven the efficacy of this low dose regimen in an ethnically diverse LN population; however more randomized trials are needed in order to make further recommendations.[49,50]

In conclusion, low-dose iv CYC is a safer option without compromising effectiveness. However, there is a lack of robust evidence about its use in non-Caucasian or severe LN patients. The American College of Rheumatology (ACR) and the European League Against Rheumatism/European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) guidelines thus recommend this low-dose cyclophosphamide regimen only for Caucasians with mild to moderate LN.[51,52]

Regarding the route of administration there are many factors to consider, including patient compliance, efficacy and side effect profiles. Daily oral CYC for induction may be more effective than iv pulses, but has higher ovarian toxicity, so it should be considered only in high-risk or refractory LN patients.[53] Patients with poor adherence to oral treatments should benefit from iv treatment. Overall, female patients of reproductive age are suboptimum candidates for CYC treatment. Alternative treatments, including novel biologics may be beneficial. The use of a gonadotropin-releasing hormone analogs during CYC treatment in woman of child-bearing age with SLE was associated with a significant reduction of premature ovarian failure.[54] For both female and male patients, relevant counseling and fertility preservation is sensible.

Intravenous CYC was superior to a regimen of AZA plus GC pulses in preventing renal relapses, but other renal function parameters did not differ. In terms of adverse effects Herpes Zoster was more frequent in the AZA group while ovarian toxicity was the major concern in CYC group. Infection rates were similar.[10,55] Maintenance treatments with MMF or AZA seem to be more efficacious and safer than long-term therapy with intravenous CYC.[15]

2.2.3. Mycophenolate

Mycophenolic acid has potent cytostatic effects in B and T lymphocytes. It is a reversible inosine monophosphate dehydrogenase (IMPDH) inhibitor that joins with high affinity with the isoform of IMPDH in active lymphocytes. This drug has a selective action in the lymphocytes with less hematological toxicity. Mycophenolic acid is an active pharmacologic form that can be obtained by first-pass metabolism and entero-hepatic recycling after the administration of the pro-drug MMP or directly from the sodium salt that is sodium mycophenolate (MPS).[56]

2.2.3.1. Mycophenolate mofetil. The original pilot study of MMF in LN compared MMF (2 g/day for 6 months and then 1 g/24 h for 6 months) and oral CYC (2.5 mg/kg/day). Both groups received GCs. Complete remission, partial remission, relapse rates and rate of kidney disease were similar between both groups with black, Latin–American and mixed patients responded better to MMF on sub-analysis. Although there were more infections in the CYC group, this was not statistically significant.[17,18]

The largest randomized clinical trial (RCT) comparing MMF with CYC in LN patients is the Aspreva Lupus Management Study (ALMS). This 24 weeks study had a two-phase design to test both induction and maintenance strategies.[12,20] The induction component included 370 patients with ISN/RPS III, IV or V LN randomized for to receive MMF (3 g/day) or CYC 6 monthly intravenous infusions (0.5–1.0 g/m^2) with GC used in both groups. Renal outcomes such as decrease in urine protein/creatinine ratio, stabilization or improvement in serum creatinine and complete renal remission, were similar in both groups and adverse events showed no significant difference (96.2% for MMF versus 95.0% for CYC).[20] Later studies have shown similar results in complete/partial remission, mortality, incidence of end-stage kidney disease and renal relapse. [19,57,58]

Treatment with MMF had lower risk of ovarian failure, leukopenia and alopecia when compared with CYC either orally [17] or intravenously.[19,20,57] MMF is not associated with increased risk for bladder toxicity.[59] Major infections occur more often in oral CYC treated patients compared to those treated with MMF,[17] but there was no difference between MMF and iv CYC.[19,20] The only adverse event more prevalent in the MMF group was diarrhea.[41] These studies suggest that MMF is at least as effective as iv CYC as an induction agent for LN with less severe adverse effects.

With regards to variation of incidence of side effects in different ethnics groups, the ALMS study showed that although patients from Asia reported the fewest infections, those infections were more likely to be severe, resulting in hospitalization or death. Furthermore, patients in the Asian MMF group had a higher withdrawal rate due to adverse events, compared with other racial groups, suggesting that Asian patients had less tolerance of high-dose prednisone and MMF (3 g/day). Moreover seven of the nine deaths in the MMF group were Asians (mainly Chinese). However, firm conclusions cannot be drawn from this *post hoc* exploratory analysis of the study as the trial was not designed to be powered to detect an effect of a specific region, race or ethnicity.[60]

After the study of Contreras et al. [15] the use of CYC as a maintenance agent has become very uncommon, as it was shown that both MMF or AZA were more efficacious and safer than iv CYC, and equally effective with oral CYC. When comparing AZA with MMF for maintenance therapy in proliferative LN, there are two meta-analyses which found no differences in terms of safety and efficacy.[61,62] In the MAINTAIN trial and its follow-up study,[13,63] 105 patients were randomized to MMF or AZA. At 48 months follow-up there were no differences in terms of efficacy (number of relapses, time to relapse, and activity). However, in the second phase of the ALMS [12] and other study including Hispanic and African–American patients [64] the relapse rates and time to treatment failure was favorable for MMF. The main difference regarding the

safety profile of AZA versus MMF was a higher risk of leukopenia in AZA treated patients.[12,63]

Importantly MMF, unlike AZA, is contraindicated in pregnancy and not recommended during breastfeeding, although there are no data on excretion into breast milk. MMF is compatible with paternal exposure, but this recommendation is based on limited evidence and further studies are necessary.[65]

2.2.3.2. Sodium mycophenolate. The evidence for the effectiveness and safety of MPS in LN patients is less compelling. A retrospective analysis of 52 pediatric patients with LN treated over 13 years comparing MPS with other immunosuppressive therapies showed higher efficacy and survival rate in the MPS group. The rate of progression to stage 3 chronic kidney disease was similar and there were no significant differences in adverse events. However, the heterogeneity in the timing of treatment, duration of follow-up and diversity of the control group treatments are important limitations of the study.[66] MFS has also been compared with iv CYC in patients with resistant-type lupus nephritis with less adverse events than the latter.[67] Other studies reported similar outcomes; nevertheless large prospective trials are still needed in order to make objective recommendations.

2.2.4. Calcineurin inhibitors

CsA and TAC are widely used in immunosuppression post-organ transplantation and they are also effective in LN. Calcineurin inhibitors have two potential beneficial modes of action in the LN. The immunosuppressive action of calcineurin inhibitors is associated with their ability to inhibit the transcription of the early activation genes of interleukin-2 (IL2) and suppress T cell-induced activation of tumor necrosis factor-α (TNFα), IL-1β, and IL-6. Thus signals for B cell activation, class-switching and immunoglobulin production are indirectly attenuated.[68] The anti-proteinuric effect of CsA has been related to its ability to stabilize the actin cytoskeleton in kidney podocytes.[69]

2.2.4.1. Ciclosporine. CsA has been shown to be as effective as CYC in induction and maintenance treatment in LN patients with preserved renal function.[70] CsA is more effective in membranous LN than induction regimens using GC alone.[21,71]

Moroni et al. [11] performed a comparison between maintenance regimes comparing AZA versus CsA in a cohort of class IV and V LN patients. No differences were observed in reducing proteinuria, blood pressure or improving creatinine. CsA improved proteinuria and kidney histology in patients with relapsing disease who did not respond to maintenance treatments with CYC or AZA.[72,73] It is thus an option in these patients. However, CsA is associated with transient renal function impairment hypertension, hirsutism, gingival hyperplasia and paresthesia, so often TAC is preferred.[71]

2.2.4.2. Tacrolimus. TAC is effective in treating membranous LN and refractory disease. CYC and TAC have similar efficacy but CYC has more side-effects.[22] 'Multi-target' therapy with TAC and MMF is more effective than iv pulse CYC in mixed proliferative and membranous LN with no increasing of adverse events.[25] When comparing this combined treatment with intravenous CYC in ISN/RPS class III, IV, V or mixed III–IV and V LN there is a higher complete response rate and the median time to response is shorter in the 'multi-target' treated group. The most important adverse events in the 'multi-target' treatment group are serious infections (including pneumonia and herpes zoster) and tremor.[23]

In a Chinese cohort, 150 patients with active LN (ISN/RPS class III, IV, or V) were randomized to an induction treatment with MMF or TAC. TAC was found to be non-inferior to MMF. When analyzing the subgroup of patients with pure membranous disease TAC was not significantly more efficient. In terms of adverse effects, Herpes zoster infection and diarrhea were significantly more common in patients treated with MMF. In contrast, more alopecia, diabetes mellitus, leg cramps and neurological symptoms which resolved on dose reduction, were reported in the TAC-treated patients. Reversible increase in serum creatinine (by 30%) was exclusively observed in TAC-treated patients.[24] TAC is safe in pregnant LN patients [74] unlike MMF which is contraindicated during pregnancy being linked to an increased incidence of first-trimester pregnancy loss and fetal malformations.[75]

3. Biologic therapies

Despite the progress made in the treatment of SLE with conventional therapies, the long-term prognosis of LN has changed little in the last 30 years.[76] The need for newer effective drugs that may facilitate earlier remission and reduce relapse rates has driven clinical research toward the direction of targeted treatments.[77] The 'biologics era' has seen many targeted novel biologic agents being developed and combination therapies of conventional with biologic agents have become the treatment paradigm in diseases such as rheumatoid and psoriatic arthritis.

3.1. Pathogenesis and potential targets

Understanding the role of certain cells and molecules in the pathogenesis of SLE and LN has facilitated the development of biologic agents. Although SLE is predominately a B-cell driven phenomenon influenced by genetic, hormonal and environmental factors, there are also proposed roles for both B and T-cells in the induction of glomerular inflammation in the pathogenesis of lupus nephritis.[3,8,78] The pathways implicated in LN and the potential targets with the respective drugs are explained in **Figure 2**.

3.2. Clinical trials of biologics in LN

Although many target molecules and pathways have been trialed for the treatment of non-renal SLE and other rheumatic conditions, there are few studies specifically designed for LN, and regrettably none of them has reached its primary end point.

A summary of the key RCTs in LN is presented in **Table 4**. The mode of action and side effect profile of these biologics is described in **Table 5**. Extrapolated data and sub-analysis of big pooled SLE studies also provide indirect data for certain biologic drugs (see **Table 6**) together with more obscure target

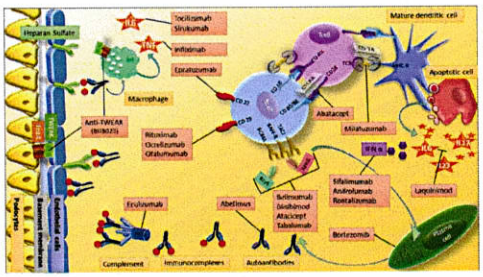

Figure 2. This figure illustrates the pathogenesis of LN and potential targets with the respective biologic drugs. When the mononuclear-phagocytic system fails to clear apoptotic cells (right upper corner in figure), an inflammatory response occurs. The surface apoptotic vesicles containing nuclear debris such as dsDNA and RNA antigens activate dendritic cells which in turn trigger INFα production and T-cell response with interleukin production. IFNα contributes to the diffeentiation of monocytes to macrophages which present self-antigens to T and B cells. IFNα also leads to the differentiation of B-lymphocytes to plasmatic cells, activation of T-Lymphocytes and maturation of dendritic cells.
Simultaneously B and T-lymphocytes interact and co-stimulate each other. The activation of B-lymphocytes leads to expression of BlyS/BAFF and APRIL and their differentiation into plasmatic cells that produce autoantibodies. The immunocomplexes formed by the autoantibodies and the nuclear antigens activate the complement system. In the kidney, both the autoantibodies and antigen/antibody complexes may cause inflammation by deposition at the level of the glomerular basement membrane or by binding to basement membrane components (e.g. heparan sulfate) leading to tissue damage. Activated effector T-cells can also inflict tissue injury with chemokine receptors and activation markers allowing them to migrate into the kidney.
On the other hand, Fibroblast Growth factor (FGF)-inducible molecule 14 (Fn14) is expressed on a wide variety of cell types including mesangial, tubular cells, interstitial fibroblast and podocytes (left side of figure). In normal tissues it is expressed at relatively low levels but it can quickly rise in response to inflammation. When the cytokine tumour necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) joins with its receptor (Fn14), it activates multiple downstream signalling pathways, with the nuclear factor kB (NFkB) pathway being the most relevant. These activated pathways also lead to glomerular and tubular injury.

Table 4. Main biologic drugs for LN – completed trials.

Drug name	Study name	Participants	Treatment groups	Main results
Rituximab	LUNAR [79]	72 patients (ISN/RPS III, IV)	Rituximab (1 g 15 days apart at weeks 1 and 24) vs. placebo In addition: MMF and GC	Renal response rates similar at 52 weeks
Ocrelizumab	BELONG [80]	378 patients (ISN/RPS III, IV)	2 Ocrelizumab courses (0.4 g or 1.0 g, 4 months apart) vs. placebo In addition: GC, plus either MMF or CYC–AZA	Renal response rate similar at 32 weeks Prematurely terminated due to an excess of serious infections in ocrelizumab group
Abatacept	BMS [81]	298 patients (ISN/RPS III-V)	Abatacept (10 mg/kg or 30 mg/kg for 3 months followed by 10 mg/kg) vs. placebo In addition: prednisone 30 mg daily for 4 weeks, then tapered, plus MMF 2 g daily (3 g daily for African–American patients)	Complete renal response rate and time to renal response similar at 52 weeks
	ACCESS [82]	134 patients (ISN/RPS III, IV)	Abatacept 10 mg/kg monthly for 6 infusions vs. placebo In addition: prednisone 60 mg/kg daily for 2 weeks, then tapered over 10 weeks, plus CYC–AZA	Complete renal response rate similar at week 24
Atacicept	Ginzler et al. [83]	6 patients (ISN/RPS III, IV)	Atacicept 150 mg twice a week for 4 weeks, then once weekly, vs. placebo In addition: prednisone 0.8 mg/kg daily or 60 mg daily plus MMF 3 g daily	Prematurely terminated due to a decline in serum IgG levels and serious infections in atacicept group

ISN/RPS: International Society of Nephrology/Renal Pathology Society; MMF: mycophenolate mofetil; GC: glucocorticoids; CYC: cyclophosphamide; AZA: azathioprine.

therapies, but these will not be described in detail as they have not reported outcomes.

The use of biologics in the context of a LN regimen could be broadly categorized in the following roles in the induction setting:

(i) an 'add on' treatment to conventional therapies (usually GC and immunosuppressant like MMF or CYC) (e.g. LUNAR, BELONG)
(ii) a potential steroid sparing agent (e.g. RITUXILUP) where the biologics allows for a low dose or GC free approach
(iii) an option for refractory cases with suboptimal approach to standard of care therapy (e.g. RING)

Finally a biologic agent could be used as a potential long-term maintenance agent, although there are no trials yet testing this idea.

Table 5. Main biologic treatment in LN – drug therapy and safety considerations.

Drug name	Mode of action	Main use	Main adverse effects	Main studies in LN
Rituximab	Monoclonal antibody Anti-CD20 IgG1 (chimeric murine/human)	Induction	Leukopenia and lymphoma, opportunistic infections, infusion reaction, infection risk, PML	Rovin et al.[79] RITUXILUP (NCT01773616) RING (NCT01673295)
Ocrelizumab	Fusion protein composed of the Fc region of IgG1 fused to the extracellular domain of CTLA-4 which inhibits T cell costimulation	Induction	Increased infection risk	Mysler et al. [80]
Atacicept	TACI-Ig fusion protein that inhibits BLyS and APRIL	Induction	LRTI/URTI, injection site reaction, fever, arthralgia, dizziness, depression	Ginzler et al. [83]
Abatacept	Human IgG1 heavy chain fused with CTLA4 that blocks T cell activation by B cells	Induction	Herpes Zoster, GI symptoms, headache, infusion reaction, fever, hypertension, back pain, infections	Furie et al. [81] ACCESS Trial Group [82]

GI: gastrointestinal; PML: progressive multifocal leukoencephalopathy; LRTI: low respiratory tract infections; URTI: upper respiratory tract infections.

In terms of safety, most of these biologics have an established side-effect profile when tested in SLE and other rheumatic conditions. Long-term toxicity data in patients with renal disease are scarce. However, the burden of disease in the LN population and the complexity of the clearance of medication through an affected filtering mechanism is an additional cause for caution (i.e. additional vigilance with drug-level monitoring and dose adjusting for renal function).

3.3. Rituximab

Rituximab is a humanized monoclonal antibody against CD20 and was the first biologic to be used in the treatment of SLE. Most investigators consider RTX to be effective in treating refractory SLE, although two large trials, LUNAR (study of lupus nephritis) [79] and EXPLORER (study of non-renal patients) [93] did not meet their primary end points. However, both the ACR and EULAR guidelines for the treatment of SLE and LN mention RTX as a possible therapy.[51,52]

In the LUNAR study, 72 patients with LN (class III or IV) were randomized in each arm to receive two course of RTX or placebo, in addition to standard-of-care (SOC) treatment, of MMF and GC. Although there was a significant difference in rituximab-treated patients having a bigger improvement in anti-dsDNA titers and C3 levels, there were no differences in CR or partial remission between both groups (p = 0.55). The trial concluded that in proliferative LN, addition of rituximab to induction therapy with MMF did not provide better (short-term) results.[79]

The LUNAR trial has been criticized because of its poor design relating to its statistical power defined on an extremely optimistic superiority effect in favor of RTX. If the LUNAR trial data were analyzed according to the BLISS trials design [94,95] (which were successful trials for belimumab in SLE that included some patients with mild to moderate renal involvement) then the beneficial effect of RTX would have reached statistical significance.

RTX is also being currently trialed as a GC sparing agent. The RITUXILUP trial is based on published pilot data suggesting that the addition of RTX to MMF without oral GCs is at least as effective at inducing a renal response as the standard of care therapy comprising MMF and high dose oral GCs.[96] RITUXILUP (NCT01773616) is an investigator-initiated, proof of concept, open labeled, multicentre RCT aiming to demonstrate whether the addition of RTX to MMF therapy is useful in treating a new flare of LN and whether it has a long lasting steroid-sparing, beneficial effect with equal efficacy and greater safety than a conventional regimen of MMF and oral prednisolone.

Finally, RTX has been broadly used by experienced lupologists as a potential option for refractory LN. The ongoing RING trial (NCT01673295), another investigator-initiated open international RCT is currently recruiting patients to test whether RTX is able to achieve complete renal response in LN patients with persistent proteinuria (≥1 g/day) despite at least 6 months of standard of care.

3.4. Safety

Side-effects include infusion reactions (fever, bronchospasm, rash and hypotension) which usually settle on stopping the infusion. Patients are screened pre-infusion and usually followed up for infections such as tuberculosis (TB) and hepatitis B or C. The effect of B cell depletion lasts for 6–12 months usually, and it is important to monitor immunoglobulin levels and CD19 + B cell count bimonthly until B cells normalize, as accumulated doses of rituximab may cause hypogammaglobulinemia linked with higher risk of infection.[97,98] Progressive multifocal leukoencephalopathy (PML) has been rarely reported in SLE, however it is now clear that immunosuppression *per se* is the cause for this, rather than a specific agent.[99]

3.5. Ocrelizumab

Ocrelizumab (OCR) is a fully human monoclonal antibody against CD20 tested for efficacy in patients with LN in a phase III RCT (BELONG). Despite reaching an overall response rate of 66–67% in the ocrelizumab treatment arm, the difference in response versus standard of care treatment did not reach statistical significance.[80]

3.6. Safety

The BELONG trial was terminated early because of serious infection rates in the OCR arm when the study drug was combined with MMF given as background immunosuppressive therapy. The proportion of patients with serious infections was double in patients who received concomitant MMF (32% vs. 16% in the placebo arm). Interestingly, it was increased principally in Asian patients. It is important to highlight that many

Table 6. Future biologic treatment in LN – drug therapy and safety considerations.

Drug name	Mode of action	Main use	Main adverse effects	Main studies
Epratuzumab	Monoclonal antibody against CD22 molecule (humanized)	No LN study	Infusion reaction, nausea, fatigue, generalized aches	Phase III for non-renal SLE (NCT01262365)
Ofatumumab	Monoclonal antibody against CD20 molecule (fully human)	No LN study	Infusion reactions, rash, rhinitis, nausea, URTI, headaches, fatigue, flushing	Not used in LN Case report in SLE [84]
Belimumab	Monoclonal antibody bind to BLyS (humanized)	Induction	Nausea, diarrhea, headaches, URTI, fever, cystitis, infusion reaction	Phase III in LN (CALIBRATE- NCT 02260934) (BLISS-LN- NCT 01639339)
Tabalumab	Monoclonal antibody targets both membrane bound and soluble BLyS (fully human)	No LN study	URTI, UTI, injection site reactions, myocardial infarct, diciitis, osteomyelitis, breast cancer, CVA, pulmonary fibrosis	Phase III in SLE not LN (ILLUMINATE-1) [85]
Blisibimob	Recombinant protein BAFF antagonist	No LN study	Injection site reactions, URTI, UTI	Phase II in SLE (PEARL-SC) [86]
Milatuzumab	Monoclonal antibody targeting CD74 (humanized)	No LN study	Not known in LN	Phase Ib study (NCT01845740)
Sifalimumab	Monoclonal antibodies anti-interferon alpha	Humanized	Infusion reaction, fatigue, URTI/UTI, sinusitis, dizziness, arthralgia, headache, lymphopenia, anemia	Phase III in SLE including LN [87]
Rontalizumab		Humanized		Phase II in SLE (NCT00962832)
Anifrolumab		Fully human		Phase II in LN recruiting (NCT02547922)
Tocilizumab	Monoclonal IgG1 antibody to IL6 receptor	Induction	Infections, GI perforation, non-melanoma skin tumors, malignancies, abnormal LFT, high cholesterol levels, suppression of CRP	SLE and LN (Phase I in 5 LN patients) [88] Phase II study in LN completed (NCT01972789)
Sirukumab				Phase I in SLE [89]
Eculizumab	Monoclonal antibody against membrane attack complex (humanized)	No LN study	Not known in LN	Phase III LN (NCT01499355)
Anti-TWEAK (BIIB023)	Monoclonal antibody reduces NF-κB activity (humanized)	Future target	Not known	Phase IIa in LN [90]
Laquinimod	Molecule. Reduces NF-κB activity and modulates antigen-presenting cells	Induction	Not defined yet in LN patients	
Abetimus sodium	Tetrameric oligonucleotide conjugate against anti-dsDNA antibodies	Withdrawn	Headache, dizziness, and rash	Phase III LN [91]
Bortezomib	Molecule. Proteasome inhibitor	Induction	Infections, nausea, headache, polyneuropathy, fever, allergic skin reactions	Phase II Study in SLE [92] Phase IV in LN stopped (NCT01169857)

LN: lupus nephritis; SLE: systemic lupus erythematosus; URTI: upper respiratory tract infections; UTI: urinary tract infections; GIT: gastrointestinal tract; LFT: liver function test; CRP: C reactive protein; NF-κB: nuclear factor kB; CVA: cerebrovascular accident; BLyS: B lymphocyte stimulator; BAFF: B cell-activating factor; anti-dsDNA: anti-double stranded DNA.

more MMF patients had received ≥1 g iv methylprednisolone compared with patients on the ELT background arm, suggesting that it may well have been the increased iv GC use that caused the higher infection rate observed in patients treated with the combination of OCR and MMF.

3.7. Atacicept

Atacicept is a transmembrane activator and calcium-modulator and cyclophilin-ligand interactor (TACI) fusion receptor protein. It inhibits both B lymphocyte stimulator (BLyS) and A proliferation-inducing ligand (APRIL) in B-cells, ranging from immature to mature. By inhibiting BLyS and APRIL it causes a reduction in B-cell proliferation, interferon gamma and immunoglobulin production. The doses used in the phase II/III RCT in lupus were 75 or 150 mg.[100]

3.8. Safety

In the APRIL-SLE randomized trial, the 150 mg atacicept arm was terminated early due to two fatal infections.[100] Apart from the two deaths encountered (one from leptospirosis) in the 150 mg atacicept group in the APRIL-SLE trial, there was not significant difference in the rate of serious infections between the 75 mg atacicept and the placebo arm. The most common infections encountered included hemophilus influenza pneumonia, *Legionella* pneumonia and *Bacillus* bacteremia. The serious infection and death rate in this study were virtually identical to those reported on the BLISS trials.

A LN study of atacicept was terminated after the enrolment of only six patients (two on placebo) because of the severe decrease in the level of immunoglobulins. However, upon review subsequent to the trial being halted it was realized that the fall in the IgG levels had mainly taken place during the 2 weeks before the atacicept was started when the patients were on MMF.[101] Interestingly, available data suggested that 150 mg dosing reduced the incidence of flares with decrease in B-cells, immunoglobulins and increase in complement levels. The 75 mg arm did not meet the primary end point, which was defined as a significant decrease in the proportion of patients experiencing at least one flare of BILAG A or B.[100] Further phase II/III clinical trials in patients with lupus are currently undergoing (ADDRESS II- NCT01972568).

3.9. Abatacept

Abatacept is a combination of human IgG (Fc portion) and CTLA-4 that blocks stimulation of B cells leading to a reduction in antibody formation and immune response.[102] The phase II/III trials in LN are ACCESS [82] and the BMS trial (NCT01714817). They compared a combination of abatacept with CYC and MMF respectively versus placebo and these conventional drugs. They did not meet the primary end points, although when the same data were analyzed using different criteria (LUNAR trial response criteria) there was a 20% response rate in the abatacept arm compared to placebo.[79]

3.10. Safety

The side effect profile is comparable to other biologics with main side effects including infections such as herpes zoster and gastrointestinal symptoms.

3.11. Others

3.11.1. Anti-IL6 agents (Sirukumab)

Sirukumab is a humanized monoclonal antibody against IL6, similar to tocilizumab. Preliminary results from a small phase II trial of 25 patients reported favorable renal outcomes with a reduction from the baseline proteinuria in the treatment arm. [103] The side effect profile is similar to Tocilizumab and less severe than other biologic agents. In general, treatment with IL-6 inhibition is associated with suppression of C-reactive protein (CRP), hematological abnormalities, non-melanoma skin tumors, and malignancies.[104]

3.11.2. Laquinimod

Laquinimod is an oral drug that reduces NF-κB activity and modulates antigen-presenting cells used in multiple sclerosis, showing anti-inflammatory effects in murine LN models. Preliminary data from a RCT of 46 patients showed a greater improvement in kidney function and proteinuria in laquinimod-treated patients compared with standard of care alone at 6 months with no significant increase of adverse events in the active arm.[90]

3.11.3. Anti-interferon alpha

Sifalimumab, rontalizumab and anifrolumab are anti-IFNα monoclonal antibodies. Neutralization of IFNα leads to a reduction of inflammation by a reduction in BAFF/BLyS levels, mature B cells, antibody production and T-cell activation. The results from the early phase clinical trials showed a reduction in SLE disease activity. Phase III trials for sifalimumab [87] and phase II for rontalizumab (NCT 00962832) and anifrolumab (NCT02547922) showed that the drugs were well tolerated with side effect rates being similar to the placebo arms. However anifrolumab is the only drug to go ahead with further trials.

3.11.4. Belilumab

Belimumab is a monoclonal humanized immunoglobulin which binds to the BLyS protein approved for treatment of mild to moderate SLE affecting the skin and joints.[81] A pooled *post hoc* analysis of the combined phase III studies suggested a possible benefit in lupus nephritis.[84] There are ongoing and planned trials to look at combinations of rituximab followed by belimumab in LN (BLISS–LN-NCT01639339/CALIBRATE-NCT02260934/BEAT-LUPUS). Pooled data from one phase II and two phase III RCT reported adverse events rates ranging from 13.5% to 19.5% with placebo at 16.6% which were not dose dependant.[105]

3.11.5. Abetimus sodium

Abetimus sodium is a tetrameric oligonucleotide conjugate that safely reduces anti-dsDNA antibodies. Administration of abetimus to patients with SLE was associated with reductions

in circulating anti-dsDNA antibodies, however, two pivotal trials with large numbers of lupus nephritis patients failed to demonstrate statistically significant prolongations in time to renal flare. A further RCT was terminated in 2009 due to futility.[106]

3.12. Future targets

There are many other potential target molecules such as other B cell surface receptors (CD22, CD20), BLyS, BAFF, complement targets, TWEAK with many respective novel drugs that are detailed in Table 6. Many of these have been or are currently trialed in SLE and other rheumatic conditions.

4. Conclusion

The main aim of treatment in LN is to prevent renal impairment and end-stage renal failure leading to renal replacement therapy. To achieve this, both induction of remission and prevention of disease recurrence are needed while minimizing side effects from any pharmacological therapy.

Depending on the class of LN an appropriate regimen can be selected based on the histopathological diagnosis in combination with the clinical picture and associated risk factors for each phenotype. The existing conventional therapy paradigms with the well trialed ELT and NIH induction regiments based mainly on CYC and steroids, can be improved, or refined with the addition of or replacement by potentially safer and less toxic biologics adjuvants. However, for maintenance therapy there are many conventional drug options and an unmet need for trials of novel therapeutics with long-term follow-up data.

5. Expert opinion

The armamentarium of therapies for LN may have significantly expanded over the last 30 years. However, the emphasis in treating LN patients necessitates striking the right balance between giving a robust and effective immunosuppressive regimen that is potent enough to control inflammation and preventing long-term kidney and extra renal damage.

LN is a challenging and complex entity and although there have been encouraging steps toward novel and safer therapies, sadly, the clinical trials for most of the newer biologics agents have been disappointing. The reasons why trials of biologic drugs in SLE have often been unsuccessful include poor design, excessive use of concomitant GC and immunosuppressives or early termination due to unexpected toxicity. Other common pitfalls in the trial design included poor definition of the primary outcome measures and overambitious effect estimation based on a superiority design that did not match the statistical power definition. There is also likely to have been an underestimation of the importance of ethnicity and genetic characteristics when assessing specific cohorts.[77]

It is therefore important to standardize clinical trial outcomes and define the end points for LN trials. Improving trial design and recruiting from a more diverse ethnic population through collaborative and networking bodies (e.g. Lupus Nephritis Trial Network) should enable collection of good quality trial data. This is very important not only from a clinical perspective, but also from a health economic point of view. Evidence-based recommendations are necessary to enable access to these high-cost medication through designated pathways and ensure they are used appropriately for the right population and indications. Although some of the novel treatments may be significantly more expensive that the conventional therapies, being mindful of the excessive cost of renal replacement therapy, avoidance of only a few cases of end-stage renal disease might be cost-effective in the LN population.

Finally, when discussing the pharmacological safety of treatments, common sense and a tailored approach to the individual patient is the safest way forward. There are improved regimens of conventional therapies such as MMF and AZA with long-term safety data now being available. However, the toxicity profile of long-term GC use and cumulative CYC exposure are suboptimal and may become unacceptable options, especially in the light of newer target specific biologic agents with equivalent efficacy and favorable adverse effect profiles. Emerging evidence is supporting the view that LN might be treated at diagnosis using B cell depletion and avoiding oral steroids which carry a significant morbidity burden. If this concept is successfully proven in the ongoing RCT, it has the potential to be a truly 'game-changing' and dramatically alter the management of lupus nephritis. Nevertheless, the potential for unexpected toxicity and the absence of long-term follow-up data with novel therapies is a significant and challenging consideration when exploring new treatment concepts and regimens.

There are of course additional issues that are important in managing patients with LN safely, especially in the context of significant immunosuppression. These include timely vaccination, osteoporosis prevention, and cardiovascular risk factor surveillance. In addition to the low-dose combination of conventional immunosuppressive agents (cocktail), steroid sparing agents and minimization of the use of steroids already discussed, it is important to be aware of the need of drug-level monitoring to reduce toxicities where possible (i.e. tacrolimus, cyclosporine, MMF etc.).

Safety in pregnancy should also be considered. Among the conventional drugs, the compatible options are GC, AZA, CsA and TAC unlike CYC and MMF which should be avoided. The recently published British guidelines [65] highlight CYC as a known teratogen and gonadotoxic agent; therefore it is recommended it should only be considered in pregnancy in cases of severe life/organ threatening maternal disease. MMF is contraindicated during pregnancy and treatment with MMF should be stopped at least 6 weeks before a planned pregnancy.

When considering biologic drugs there is insufficient evidence to make general recommendations. Limited evidence has not shown RTX to be teratogenic and only second/third trimester exposure is associated with neonatal B cell depletion. Therefore, unintentional RTX exposure early in the first trimester is unlikely to be harmful, which is also the case for abatacept and belimumab.[65] Data from pregnancy registries would be useful to further assess safety of newer agents for use in pregnancy.

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The safety of pharmacological treatments in LN is ultimately based on applying a balanced combination of sound clinical judgment, careful evaluation of robust evidence from well-designed trials. In the near future individualized patient genetic and genomic characteristics will guide clinical decision making and facilitate the choice of appropriate treatment. We hope the introduction of a wider selection of validated and well tested treatment options; will decrease the mortality and morbidity for LN patients reducing or abolishing progression to end-stage renal disease.

Declaration of interests

D Isenberg has consulted for a number of pharmaceutical companies in the past 5 years included Roche, Merck Serono, Eli Lilly and Glaxo Smith Kline. The honoraria offered are passed onto a local arthritis charity. D Isenberg is supported by the Biomedical Centre Award to University College Hospial/University College London. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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