Treatment of proliferative lupus nephritis: a slowly changing landscape

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Abstract | Proliferative lupus nephritis is the most severe form of lupus nephritis. Outcomes of this disease are affected by ethnicity, clinical characteristics, irreversible damage on renal biopsy, initial response to treatment and future disease course (for example, the occurrence of renal flares). Initial intensive (induction) treatment of proliferative lupus nephritis is aimed at achieving remission, but optimal duration and intensity are not well defined. A combination of intravenous cyclophosphamide and corticosteroids have been shown to decrease the risk of end-stage renal disease, but are associated with substantial acute toxic effects (such as infections) and chronic toxic effects (such as ovarian failure). In white populations, low-dose cyclophosphamide is a reasonable alternative to high-dose cyclophosphamide as it is similarly effective and associated with less toxicity. Mycophenolate mofetil is as effective as high-dose intravenous cyclophosphamide in terms of inducing remission and similar in terms of safety. Although most patients respond to induction treatment, remission is often only achieved after patients are switched to maintenance treatment. As maintenance treatment, mycophenolate mofetil is superior to azathioprine and azathioprine is similarly effective to ciclosporin in terms of prevention or reducing the risk of relapse. Rituximab should be reserved for patients with refractory disease. Treatment of lupus nephritis should be individually tailored to patients, with more aggressive therapy reserved for patients at high risk of renal dysfunction and progression of renal disease.

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Introduction

Renal involvement is a frequent and serious complication of systemic lupus erythematosus (SLE). Urinalysis abnormalities occur at some point in up to 60% of adult patients with SLE.[1] Early on, proliferative lupus nephritis was distinguished from mesangial and membranous lesions as it became clear that patients with focal and diffuse proliferative lesions had a much poorer outcome.[2] The 1982 WHO classification of lupus nephritis,[3] which separated class III (focal segmental proliferative nephritis) and class IV (diffuse proliferative nephritis) lupus nephritis on the basis of either the segmental, or the diffuse type of prevailing proliferative lesions, was replaced in 2004 by the International Society of Nephrology and Renal Pathology Society (ISN/RPS) classification.[4] The ISN/RPS classification defines class III lupus nephritis (focal: involving <50% of the total number of glomeruli) and class IV lupus nephritis (diffuse: involving >50% of the total number of glomeruli) on the basis of the number of involved glomeruli with active or inactive focal segmental, or global endocapillary or extracapillary proliferative lesions. Patients with prevailing segmental lesions in >50% of glomeruli (WHO class III) are now classified according to the ISN/RPS classification as having diffuse lupus nephritis (class IV-S) and patients with prevailing global lesions in >50% of glomeruli are now defined as class IV-G. The new classification system resulted in the percentage of all biopsied patients with SLE diagnosed as having class IV nephritis increasing from 23% to 46%.[5,6]

Until recently, intravenous cyclophosphamide pulses were the only generally accepted treatment for active proliferative lupus nephritis. The therapeutic armamentarium has now expanded, however, with the introduction of mycophenolate mofetil (MMF), and first data on B-cell-targeted treatment are now available. In the future, improved assessment of disease activity and prediction of outcomes should enable more targeted, individualized treatment and will hopefully improve outcomes of patients with proliferative lupus nephritis. This Review will describe the clinical course of lupus nephritis, outcomes and predictive factors (Box 1), and will discuss recent advances in treatment options.

Outcomes of proliferative lupus nephritis

The natural history of untreated patients with diffuse lupus nephritis was very poor in the 1960s, with median survival not exceeding 2 years,[1,2] but outcomes have improved significantly over the past 50 years. Actuarial survival at 5 years among patients with SLE, lupus nephritis and WHO class IV lupus nephritis increased from 49%, 44% and 17%, respectively, in the period 1953–1969, to 92%, 82% and 82%, respectively, in the period 1990–1995.[1] Despite these improvements, however, 25–30% of patients with diffuse proliferative lupus nephritis still

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reach end-stage renal disease (ESRD) over 20 years of follow-up.[1]

The improved survival of patients with proliferative lupus nephritis may be partly explained by the fact that milder cases have been included in more recent analyses owing to earlier diagnosis and referral to nephrologists before the development of irreversible damage. However, improvements in both general medical treatment (for example, antibiotics, antihypertensives, and the availability of dialysis and transplantation) and the availability of more effective and better tolerated immunosuppressive treatments have undoubtedly had an important role.

Comparisons of the outcomes of patients with lupus nephritis is confounded by the nonhomogeneity of the patient populations studied (for example, the changing proportion of patients with type III, IV and V lesions), the relatively short-term follow-up of most studies, the prevalence of renal flares (affecting 30–40% of patients who originally went into remission), differences in treatment regimens, and the absence of universally accepted definitions and outcome criteria.

Owing to the availability of effective treatments, the incidence of hard outcomes (such as death and ESRD), is now relatively low among patients with lupus nephritis. For a clinical trial to demonstrate the effect of any treatment on these outcomes would require it to be very large and to have a very long follow-up. Therefore, clinical studies in the field of lupus nephritis usually use surrogate intermediate end points (such as a doubling of serum creatinine level), or even short-term renal end points (such as proteinuria, hematuria, remission rate and relapse rate), rather than hard outcomes. These surrogate end points might only be clinically relevant, however, if they predict patient and kidney survival.

Traditionally, the overall activity of lupus nephritis has been characterized in terms of remission or response, and relapse, flare or exacerbation. Neither uniformly accepted criteria for renal remission or response to treatment (usually a composite of proteinuria, urinalysis and renal function), nor minimum duration of (sustained) remission are defined and true remission is not clearly separated from suppression of disease activity on treatment.

In the past 5 years or so, expert panels of both the American College of Rheumatology (ACR)[7] and the European League Against Rheumatism (EULAR)[8,9] recommended unified terminology for lupus nephritis activity, response criteria and phases of treatment. The ACR renal response criteria[7] are based on the evaluation of a minimum of four end points: renal function, urinary protein level, urinary sediment and adverse events. Complete renal remission is defined as an estimated glomerular filtration rate (GFR) >90 ml/min/1.73 m^2, a urinary protein-to-creatinine ratio <0.2 mg/mg and inactive urinary sediment. The EULAR consensus statement[8] uses the term 'response' in preference to the term 'remission'. A complete response is characterized by inactive urinary sediment, a decrease in proteinuria to ≤0.2 g per day and normal or stable renal function. A partial response is defined as inactive urinary sediment, proteinuria ≤0.5 g per day, and normal or stable (if previously abnormal) GFR.

Key points

- Proliferative lupus nephritis (class III [focal] and class IV [diffuse]) is the most severe form of lupus nephritis
- Outcomes of patients with proliferative lupus nephritis improved dramatically following the introduction of corticosteroids and cyclophosphamide, but 25–30% of patients still develop end-stage renal disease over 20 years of follow-up
- Slow onset of remission and the occurrence of renal flares are associated with an increased risk of later loss of renal function
- As induction treatment, mycophenolate mofetil (MMF) is similarly effective to cyclophosphamide; however, cyclophosphamide may be inferior to MMF in black and Hispanic patients
- As maintenance treatment, MMF is superior to azathioprine, and MMF and azathioprine are superior to intravenous cyclophosphamide pulses; in white patients, ciclosporin seems to be similarly effective to azathioprine
- B-cell depletion with rituximab might be useful in patients with proliferative lupus nephritis that is refractory or intolerant to cyclophosphamide; the putative role of B-cell-targeted treatment in lupus nephritis requires further study

Box 1 | Clinical course and outcomes of proliferative lupus nephritis

- Patient survival and renal survival in proliferative lupus nephritis have improved, but a significant proportion of patients still progress to end-stage renal disease
- Race, ethnicity and presenting renal histology are the most important predictors of patient and renal outcome
- Definitions of responses to treatment differ substantially between individual studies as until recently no uniform definition existed
- Remission rates are lower in black and Hispanic patients than in white patients
- Median time to remission is usually long (10–15 months)
- Disease activity is not suppressed quickly enough by the available induction treatment, and most patients go into remission only while on maintenance treatment
- The relapse rate is still high, and nephritic relapses have a negative impact on renal outcome
- Although current maintenance treatments have decreased the relapse rate, they do not completely prevent relapse

It must be stressed that it is almost impossible to achieve complete renal remission (normal renal function) in patients who present with increased serum creatinine level and a high chronicity index on renal biopsy. Inducing complete remission is difficult even in patients with normal renal function, and prolonged time to remission with unabated disease activity may contribute to further progression of irreversible renal damage and later loss of renal function.

Relapses (that is, new activity after remission) or flares (that is, an increase in disease activity after substantial improvement) are common, particularly after cessation of immunosuppressive treatment. Relapses and flares are usually characterized by different combinations of increased proteinuria, reappearance of active urinary sediment and increased serum creatinine level. A 'proteinuric relapse' is when proteinuria increases but urinary sediment remains inactive and serum creatinine level does not change; a nephritic relapse is when active urinary sediment reappears, usually with increased serum creatinine level, and with or without proteinuria.

No international consensus exists on how to define patients who are refractory to treatment.[10] According to NIH criteria,[11] refractory patients are those who show no response to treatment and those in whom proteinuria does not decrease to less than half of pretreatment value or to <3 g per day and who have persistent active urinary casts or deterioration in serum creatinine level. According to the EULAR consensus statement,[8] nonresponders or patients with treatment failure are those who do not achieve even a partial response.

Predictors of outcome in lupus nephritis

Proliferative lupus nephritis is a very heterogeneous disease. Factors shown to predict outcome in lupus nephritis include the following: male sex, black race, Hispanic ethnicity, age <24 years, low socioeconomic status, noncompliance to treatment, elevated serum creatinine level, nephrotic proteinuria, nephritic syndrome that is not responsive to treatment, severe anemia, hypertension, low levels of complement, the presence of antiphospholipid antibodies, diffuse proliferation on kidney biopsy, high activity and chronicity index, and treatment type.[12–16] The large number of factors that affect outcome means that results of different clinical studies are not easily comparable and generalizable.

Race and ethnicity

Lupus nephritis is twice as common in black individuals than in white individuals.[17] Patient survival and renal survival are also much worse in black patients with lupus nephritis than in white patients.[17,18] The poor renal outcome of black patients with lupus nephritis may partly result from the fact that black patients have more severe renal lesions,[18,19] even within the same WHO class.[12] Black patients are also more resistant to treatment than white patients and have an almost fourfold higher relapse rate[20] and an increased risk of progression to ESRD. Although differences in compliance and socioeconomic status (including poverty and decreased availability of medical care) might also have a role, race itself remains a prognostic feature even after adjustment for these factors;[18,19] genetic factors are probably also very important.[19]

Hispanic patients might not have a higher risk of developing lupus nephritis than white patients,[21] but they have increased disease activity and an increased risk of relapse, death and chronic renal failure;[18] 6-year renal survival is only 50% in Hispanic patients, a rate similar to that of African Americans.[18]

The risk of lupus nephritis development is higher in Asian patients than in white patients,[21] but long-term outcomes of lupus nephritis are similar in Asian patients[22,23] and white patients;[24] one study showed that serum creatinine level doubled in only 4.4% of Chinese patients with diffuse proliferative lupus nephritis treated with oral cyclophosphamide over 92 months of follow-up, and that none developed ESRD.[22] An Italian study of 93 patients with proliferative lupus nephritis published in 2007 found that long-term outcomes of white patients with proliferative lupus nephritis might be better than originally thought: renal survival was 97% at 10 years and 82% at 20 years.[24]

Histologic predictors of outcome

Lupus nephritis type based on the WHO classification has been found to predict outcome in some,[25] but not all,[12] studies. Likewise, activity and chronicity indices have been useful for assessing outcome in some studies,[12] but not others.[26] Chronicity index seems to be a better predictor of ESRD than activity index.[27] In 2000, Korbet *et al.* reported that 5-year and 10-year patient survival rates were higher in patients with diffuse proliferative nephritis (WHO class IV) than in patients with focal proliferative nephritis affecting >50% of glomeruli (WHO class III) or combined proliferative and membranous lesions (WHO classes Vc and Vd);[14] however, these results have not uniformly been confirmed by other studies.[28–30] Some studies have shown renal outcomes to be similar for focal segmental and diffuse lupus nephritis (and ISN/RPS class IV-S and IV-G),[28,30] and serial biopsies have demonstrated transformation from one lesion type to another, which argues against the idea that the two different lesions types have a different pathogenesis.[31] Cellular crescents, subendothelial deposits and a high chronicity index in repeated renal biopsies may be a better predictor of renal outcome than findings on the original renal biopsy made at presentation.[30,31]

Remission and long-term outcome

Remission rates in patients with proliferative lupus nephritis differ widely depending on ethnicity, disease severity, follow-up duration and treatment. Poor response to treatment can be caused by genetic factors, but may result from the accumulation of chronic and irreversible changes in patients who are diagnosed late and initiate treatment late.[32] Long-term follow-up studies reported that complete or at least partial remission developed in 55% and 82%, respectively, of Chinese patients with diffuse proliferative lupus nephritis treated with oral or intravenous cyclophosphamide[33] and in 62% and 88%, respectively, of white patients with proliferative lupus nephritis who were initially treated with either cyclophosphamide or azathioprine depending on disease severity,[24] but in only 50.3% and 63% of US (mostly white) patients treated with intravenous cyclophosphamide.[20]

Median time to remission is usually longer than 6 months[14,22,32,34] and it usually takes longer to achieve complete remission than it does to achieve partial remission.[35] The low remission rate seen in a study with a follow-up of only 6 months[36] is therefore not surprising.

Patients who do not achieve remission experience more renal flares than those who achieve remission (65% versus 41% at 10 years) and their renal flares are also usually of greater severity.[14] The risk of relapse is sixfold higher in patients with partial remission than in those in complete remission.[22] In addition, 10-year patient survival and renal survival is higher in patients who achieve remission than in those who do not achieve remission (95% versus 60% and 94% versus 31%, respectively).[14]

Even partial remission is associated with significantly better outcomes than no response: Chen *et al.* found that 10-year patient survival rates were 95%, 76% and 46% and 10-year renal survival rates were 94%, 45% and 19% for complete, partial and no remission, respectively.[35] An early antiproteinuric response may be a predictor of improved long-term outcome. In the Euro-Lupus trial,[37] a 50% decrease in proteinuria was almost twice as likely in patients with good renal outcome than in those with poor renal outcome.

Renal flares

Reported rates of relapse vary from 25% at 5 years, 46% at 10 years and 36% early after discontinuation of treatment.[38–40] Flares are less common in patients who receive cytotoxic agents as well as corticosteroids than in those who receive corticosteroids alone, and in patients with longer courses of cytotoxic treatment.[20] Median time to renal flare in proliferative lupus nephritis varies widely: 32 months has been reported in Chinese patients[33] and 79 months in Greek patients.[32] Predictors of relapse include a high activity index, increased proteinuria, male sex, younger age, hypertension at presentation, delay in initiation of cytotoxic treatment, increased time to response and short duration of initial treatment. Patients with only a partial response to treatment are more prone to flares than patients with a complete response (63% versus 40% in one study).[20]

Renal flares have a major impact on renal outcome. Persistent doubling of serum creatinine occurs more frequently in patients with a higher number of renal flares, those with 'early' proteinuric flares (occurring in the first 18 months after renal biopsy) and those with nephritic flares.[41] Another study reported that doubling of serum creatinine occurred in 4.2% of patients without flares, 0% of patients with only proteinuric flares and 62% of patients with nephritic flares.[38]

Treatment of proliferative lupus nephritis

The treatment of lupus nephritis is usually divided into two phases: induction therapy and maintenance therapy. Induction is a period of intensive therapy that aims to achieve a clinically meaningful and sustained response in a patient with active disease.[8,9] Induction therapy is usually continued for at least 3 months, but may be given for 6 months or longer if the patient still has active disease. In most clinical studies, induction therapy was given for 6 months or less, which means that some patients went into remission while already on maintenance treatment (Table 1, Box 2). Maintenance therapy is a period of less-intensive therapy that follows induction therapy, usually in patients who have achieved a partial or complete response, with the aim of keeping the patient free from active disease[8,9] and preventing disease relapse (Table 2, Box 3).

Induction treatment

Cyclophosphamide

The use of corticosteroids[42] and cyclophosphamide[43] dramatically improved outcomes of patients with proliferative lupus nephritis. Several NIH studies published in the 1980s and early 1990s demonstrated that the combination of pulsed cyclophosphamide and prednisolone was superior to prednisolone alone in the treatment of lupus nephritis in terms of renal survival[44–46] and doubling of serum creatinine after at least 5 years of follow-up,[47] but that it had no impact on mortality rates (which remained high mostly as a result of infections and central nervous system involvement).[46] A combination of monthly pulsed cyclophosphamide and methylprednisolone has also shown superiority over monthly pulses of methylprednisolone alone in terms of increased remission rates (85% versus 29% at 5 years) and reduced relapse rates.[34] Intravenous cyclophosphamide pulses (1 g/m^2 monthly for 1 year and then quarterly for another 2 years) were similarly effective, but significantly less toxic than high doses of oral cyclophosphamide (up to 4 mg/kg per day). The high-dose cyclophosphamide NIH regimen was associated with a high number of toxic effects including life-threatening infections, hemorrhagic cystitis, ovarian failure, cervical dysplasia and cancer.[34,47–49] Compared to more recent cohort studies and randomized controlled trials, however, the NIH studies probably recruited more patients with advanced chronic changes (such as glomerular sclerosis, tubular atrophy and interstitial fibrosis) that are less amenable to therapeutic response.

These early studies clearly had many serious drawbacks.[50] Patient groups were small, proliferative, membranous and sometimes even mesangial lupus nephritis cases were grouped together, and patients with diffuse proliferative lupus nephritis represented only slightly more than 50% of patients and were not randomly distributed among different treatment regimens.[46] In addition, randomization was not blinded and patients were recruited over long periods of time and randomized to different regimens in early and late periods, which resulted in different lengths of follow-up in different treatment arms. Moreover, cyclophosphamide doses were unacceptably high and accompanied by serious short-term and long-term adverse effects. Despite the toxic effects, high-dose intravenous cyclophosphamide pulses were generally accepted as a 'standard' treatment for proliferative lupus nephritis.

In 2006, a study confirmed that cyclophosphamide treatment was also associated with good long-term outcomes when used to treat diffuse proliferative lupus nephritis in a Chinese population.[23] Patients were treated with either oral or pulsed intravenous cyclophosphamide; 59% of patients achieved complete remission and 85% of patients achieved at least partial remission, and renal survival was 83% at 10 years and 71% at 15 years.[23] Adverse events were common, however, and more frequent in patients treated with oral cyclophosphamide than in those treated with pulsed intravenous cyclophosphamide.

Improved awareness of lupus nephritis resulted in an increasing number of patients being diagnosed earlier with milder forms of the disease, which led to recommendations for a more flexible approach to treatment (for example, low-dose cyclophosphamide, early switch to azathioprine, or azathioprine for induction).[51,52]

Table 1 | Selected recent studies of induction treatment in proliferative LN

Study	Patients	Race/ethnicity	Proliferative LN class	Follow-up duration	Results	Adverse events
Low-dose vs high-dose intravenous CYC						
Houssiau *et al.* (2002)[53]	44 on low-dose CYC vs 46 on high-dose CYC*	76 white, 6 Asian, 8 Afro-Caribbean	62 class IV, 21 class III, 7 class Vc/Vd	Median 41 months	Treatment failure: 16% vs 20% (n.s.); renal remission: 71% vs 54% (n.s.); renal flare: 27% vs 29% (n.s.)	No significant difference
Houssiau *et al.* (2010)[54]	41 on low-dose CYC vs 43 on high-dose CYC	Similar to above (exact numbers unknown)	Similar to above (exact numbers unknown)	10 years	Death: 11% vs 4% (n.s.); sustained SCr doubling: 14% vs 11% (n.s.); ESRD: 5% vs 9% (n.s.)	Not reported
AZA vs CYC						
Grootscholten *et al.* (2006)[58]	37 on oral AZA+MP pulses vs 50 on CYC+MP pulses	80% white in CYC limb, 70% Caucasian in AZA limb	90% class IV or Vd, 10% class III or Vc	5.7 years	SCr doubling: more frequent in AZA limb (RR 4.1); relapse: more frequent in AZA limb (RR 8.8); renal remission: no difference	Infections more frequent in AZA limb; no difference in ovarian function
MMF vs CYC						
Chan *et al.* (2000)[60]	21 on MMF vs 21 on CYC	100% Asian	100% class IV	1 year	CR: 81% vs 76% (n.s.); PR: 14% vs 14% (n.s.); relapse: 15% vs 11% (n.s.)	Nonsignificant tendency to higher infection rate in CYC limb (33% vs 19%); amenorrhea (23%), hair loss (19%), leukopenia (10%) and death (10%) only in CYC arm
Chan *et al.* (2005)[61]	33 on MMF vs 31 on CYC*	100% Asian	100% class IV	Median 63 months	Remission rate: >90% in both groups; time to remission: 15.3 months vs 19.7 months (n.s.); relapse rate: no difference; SCr doubling: 6.3% vs 10% (n.s.)	Fewer infections and infections requiring hospitalization in MMF group, and much less frequent amenorrhea (3.6% vs 36%)
Ginzler *et al.* (2005)[36]	71 on MMF vs 69 patients on CYC	56% black, 19% Hispanic, 17% white, 8% Asian	55% class IV, 15% class III, 20% class V, 10% mixed membranoproliferative	6 months	CR at 6 months: 22.5% vs 5.8% (P=0.005); PR: 29.6% vs 24.6% (n.s.)	Severe infections and hospitalizations for vomiting and dehydration occurred only in CYC limb; diarrhea more frequent in MMF limb
ALMS: Appel *et al.* (2009)[62]	185 on MMF vs 185 on CYC	39.7% white, 33.2% Asian, 27% other (~50% black)	68.1% class IV+V, 15.7% class III+V, 16.2% class V only	6 months	Response rate: 56.2% vs 53% (n.s.); MMF better in "other" (mainly black and mixed-race) and Hispanic patients	No significant difference in the rate of adverse events, severe adverse events, or infections (vomiting more frequent with CYC; diarrhea more frequent with MMF)
CyA vs CYC						
Zavada *et al.* (2010)[81]	40 patients with newly diagnosed active proliferative LN randomized to CyA, or CYC, as induction–maintenance	White	16 class III, 24 class IV	18 months	Remission rate: no difference; response rate: no difference; proteinuria: lower at 9 months in CyA arm	Infection rate: similar; GFR: transient decrease with CyA at 9 months (no difference at 18 months); BP: transient increase with CyA (by 4.5 months)

*Both groups received AZA maintenance. Abbreviations: AZA, azathioprine; BP, blood pressure; CR, complete remission; CyA, ciclosporin A; CYC, cyclophosphamide; ESRD, end-stage renal disease; GFR, glomerular filtration rate; i.v., intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; MP, methylprednisolone; n.s., not significant; PR, partial remission; RR, relative risk; SCr, serum creatinine; SLE, systemic lupus erythematosus.

The Euro-Lupus Nephritis Trial, which included 90 patients with proliferative lupus nephritis (most of whom were white), showed that a low cumulative dose of cyclophosphamide (3 g, given as six fortnightly pulses at a fixed dose of 500 mg) was comparable to a high cumulative dose of cyclophosphamide (mean of 8.5 g, given across eight pulses), followed by azathioprine in both cases, in terms of both efficacy (median time to remission was 9 months in each group) and safety (Table 1).[53] Early decrease in proteinuria (to ≥75% of baseline or to <1 g/24 h at 6 months) predicted good long-term outcome (preservation of normal serum creatinine during follow-up).[37] Outcomes in both groups were also comparable in terms of 10-year mortality, risk of ESRD and doubling of serum creatinine level (Table 1).[54]

Compared with the traditional NIH regimen,[34] low-dose cyclophosphamide had a comparable remission rate (71% versus 62%), a somewhat higher relapse rate (27% versus only 7%, although relapses were defined somewhat differently), and much lower rates of gonadal toxicity.[34,53,54]

Compared with the NIH trials,[34] much lower proportions of patients in the Euro-Lupus Nephritis Trial[47] were Afro-Caribbean, had nephrotic syndrome or impaired renal function, so the generalizability of its results to other ethnic groups and to patients with more severe renal involvement remains uncertain.

Low-dose cyclophosphamide pulses have become the most commonly used induction treatment of lupus nephritis in white patients,[55] but monthly cyclophosphamide pulses are still advocated as the 'gold standard' induction treatment for lupus nephritis in other ethnic groups.[56] Short-term (2–4-month) treatment with relatively low doses of oral cyclophosphamide (1–1.5 mg/kg body weight), followed by maintenance treatment either with azathioprine or MMF, may be an effective alternative even in high-risk (including black) patients with proliferative lupus nephritis,[57] with a relatively high rate of complete or partial remission (70%) and a low rate of adverse events (<10%). Oral continuous cyclophosphamide (or intravenous cyclophosphamide at higher doses per pulse or more frequent pulses) might be suitable in patients who are refractory to the standard regimen of intravenous cyclophosphamide pulses.

Box 2 | Induction treatment for proliferative lupus nephritis

- High-dose cyclophosphamide pulses or oral mycophenolate mofetil (MMF) may be useful in black and Hispanic patients, but low-dose cyclophosphamide pulses are a safer alternative to high-dose cyclophosphamide pulses in white patients
- Oral azathioprine is inferior to cyclophosphamide, but may be useful in patients not tolerating cyclophosphamide and before and during pregnancy (in informed and consenting patients); this agent can be also considered as a first-line treatment in patients with low disease activity
- Rituximab may be useful in patients refractory (or intolerant) to cyclophosphamide and/or MMF; however, overall experience and data on long-term outcome and safety are limited and its efficacy has not yet been confirmed by randomized controlled trials

Azathioprine

In the NIH studies, azathioprine was never shown to be inferior to cyclophosphamide as an induction treatment for lupus nephritis. According to a meta-analysis of these early studies, azathioprine plus steroids had no effect on renal outcome, but was associated with decreased mortality compared with steroids alone.[49] A randomized controlled study in patients with proliferative lupus nephritis found that oral azathioprine (2 mg/kg daily) and cyclophosphamide pulses (750 mg/m^2) were similarly effective in inducing complete remission and at least partial remission (Table 1).[58] After a median of 5.7 years, doubling of serum creatinine (the rate of which was low in both arms of the study, partly because patients were white, diagnosed early, on long-term maintenance treatment, and followed up for only 3 years) tended to be more frequent and relapses and herpes zoster infection were more common in azathioprine-treated patients. Moreover, repeat renal biopsy after 2 years of treatment showed that activity index decreased similarly in both arms, but that the increase in the chronicity index was significantly higher in the azathioprine arm than in the cyclophosphamide arm.[59] From these results it seems that azathioprine and cyclophosphamide suppress the clinical and histologic activity of lupus nephritis to a similar extent, but

Table 2 | Selected studies of maintenance treatment in proliferative lupus nephritis

Study	Patients	Race/ethnicity	Proliferative LN class	Follow-up duration	Results	Adverse events
MMF vs AZA vs intravenous CyA						
Contreras *et al.* (2004)[68]	Patients who achieved remission with i.v. CYC randomized to AZA (n=19), MMF (n=20), or i.v. CYC (n=20)	29 Hispanic, 27 black, 3 white	46 class IV, 12 class III, 1 class Vb	72 months	Event-free survival rate*: higher in MMF and AZA than CYC; relapse-free survival: higher in MMF vs CYC (P=0.02)	Infections, severe infections, amenorrhea, nausea and vomiting more frequent with CYC
MMF vs AZA						
Houssiau *et al.* (2009)[74]	105 patients who achieved remission with Euro-Lupus regimen randomized to MMF or AZA	Mainly white	Class III, IV, Vc, or Vd	53 months	No difference in time to renal flare and severe systemic flare	Infectious side effects similar; hematological cytopenias more frequent with AZA (P=0.03)
Wofsy *et al.* (2010)[67]	Patients who achieved treatment response in ALMS were randomized to MMF (n=116) or AZA (n=111)	43% white, 10% black, 33% Asian, 13% other	Not available	36 months	MMF superior to AZA in primary end point‡ (P=0.003), regardless of induction treatment	No difference in treatment-emergent adverse events, including infections
CyA vs AZA						
Moroni *et al.* (2006)[73]	Patients in remission after CYC induction randomized to CyA (n=36) or AZA (n=33)	100% white	60 class IV, 9 class Vc or Vd	4 years	7 vs 8 flares (n.s.); no difference in proteinuria and SCr at end of follow-up	Minor infections and leukopenia more frequent with AZA; gastrointestinal disorders and arthralgias more frequent with CyA

*For composite end point of death and chronic renal failure. ‡Primary end point: time to treatment failure (death, ESRD, sustained doubling of Scr, renal flare). Abbreviations: AZA, azathioprine; CyA, ciclosporin A; CYC, cyclophosphamide; ESRD, end-stage renal disease; i.v., intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; n.s., not significant; SCr, serum creatinine; SLE, systemic lupus erythematosus.

Box 3 | Maintenance treatment for proliferative lupus nephritis

- Mycophenolate mofetil (MMF) and azathioprine are superior to intravenous cyclophosphamide pulses in terms of both relapse-free survival and survival without chronic renal failure; however, the available data come from small studies and should be confirmed in larger studies and other ethnic groups
- MMF is superior to azathioprine in terms of time to treatment failure (possibly only in higher risk Hispanic and black patients: the difference may not be apparent in low-risk white patients)
- Ciclosporin is similarly effective to azathioprine in white patients in terms of relapse prevention; however, generalizability to other ethnicities is uncertain and length of treatment with ciclosporin should be limited as ciclosporin nephrotoxicity is a major concern with long-term treatment

that cyclophosphamide is more effective in preventing relapse and progression. Azathioprine as an induction treatment should be reserved for young female patients who strongly wish to conceive and are willing to accept the increased risk of relapse and infection.

Mycophenolate mofetil

Over the past decade, MMF, a noncompetitive reversible inhibitor of inosine monophosphate dehydrogenase, has been evaluated as a potential induction (and maintenance) treatment for lupus nephritis (Table 1).

A study from Hong Kong published in 2000 reported that MMF (2 g per day for 6 months; 1 g per day for another 6 months) was similarly effective to oral cyclophosphamide (2.5 mg/kg per day for 6 months followed by azathioprine 1–1.5 mg/kg per day for 6 months) in patients with diffuse proliferative lupus nephritis, in terms of complete and at least partial remission at 1 year.[60] Infection rate was similar in the two groups, but amenorrhea, hair loss, leukopenia and death occurred only in cyclophosphamide-treated patients. The similar efficacy of the regimens was confirmed in an extended follow-up study involving 64 patients (median follow-up 63 months).[61] Complete or partial remission was achieved in >90% of patients, time to complete remission was similar in the mycophenolate and cyclophosphamide–azathioprine groups (15.3 weeks versus 19.7 weeks), no differences in relapse rates were seen and serum creatinine level was stable in both groups.[61] Adverse events were, however, less common in the MMF group. These promising data from a population of Chinese patients, 62.5% of whom had nephrotic-range proteinuria (>3 g/24 h) but who had relatively preserved renal function (only 26.6% of patients had elevated serum creatinine levels), needed confirmation in other ethnic groups and in patients with more severe renal involvement.

A study published in 2005 involving a multiethnic population of 140 patients with biopsy-proven active lupus nephritis reported that induction therapy with MMF (initial dose 1,000 mg per day increasing to 3,000 mg per day) was superior to monthly intravenous pulses of cyclophosphamide (0.5 g/m^2 increased to 1.0 g/m^2) in terms of complete remission at 24 weeks,[36] with no difference in partial remission rate (Table 1); patients in both groups received corticosteroids. As in the Chinese study, MMF-treated patients had fewer severe infections and hospitalizations, but diarrhea was more common.

The Aspreva Lupus Management Study (ALMS), a large randomized controlled study published in 2009, randomly assigned 370 patients of different ethnicities with class III–V lupus nephritis to MMF (target dose 3 g per day, median achieved dose 2.6 g per day) or intravenous cyclophosphamide (0.5–1 g/m^2 in a median of six monthly pulses) (Table 1).[62] Prednisone at a starting dose of 60 mg/day was gradually tapered in both arms. The primary efficacy end point (a prespecified decrease in urine protein-to-creatinine ratio and a stabilization or improvement in serum creatinine level) at 24 weeks was achieved in 56% of patients treated with MMF and in 53% of patients treated with intravenous cyclophosphamide. Only 8% of patients in each group achieved complete remission by 24 weeks and adverse event rates were similar in the two groups. Extrarenal activity of SLE was also similarly suppressed by the two treatments.[63] Response rates with the two treatments were similar in Asian and white patients, but MMF was found to be more effective than cyclophosphamide in patients classified as "other" (mostly black or mixed-race patients) and in Hispanic patients.[62]

The ALMS study therefore concluded that MMF was as effective as, but not superior to, high-dose cyclophosphamide pulses and that the short-term safety of the therapeutic regimens was comparable. MMF seems to be similarly effective across different races and ethnicities, but cyclophosphamide might be less effective in subgroups of black and Hispanic patients and patients from Latin America,[64] populations at increased risk of a more aggressive disease course.[65] Patients in the cyclophosphamide limb of ALMS may not have been sufficiently immunosuppressed, however, as recommended NIH doses were not achieved in many patients because of gastrointestinal toxicity. In these high-risk populations, MMF needs to be shown to be similarly effective to a short (3-month) course of oral cyclophosphamide, which is still commonly used in patients with lupus nephritis.[57,66] Why ALMS[62] failed to show the superiority of MMF over cyclophosphamide demonstrated by the previous US study[36] is not completely clear, but a possible explanation is that the previous study included a much higher proportion of black patients, who seem to have a poorer response to cyclophosphamide.

Information on the long-term outcome of patients with lupus nephritis treated initially with MMF has been rather limited. The extended Chinese study[61] reported a nonsignificant trend towards an increased relapse rate and more cases of proteinuria >1 g per day and serum creatinine >177 μmol/l in the MMF arm, which suggests that patients treated initially with MMF might be at increased risk of progression to ESRD in the long term. Data now reported from the maintenance phase of ALMS,[67] however, suggest that long-term outcome and response to maintenance treatment is similar in patients treated initially with MMF or cyclophosphamide.

In our opinion, MMF might be particularly useful as an induction treatment in patients not

responding to cyclophosphamide, those not tolerating cyclophosphamide, those exposed to a high cumulative dose of cyclophosphamide and in young women planning to become pregnant (although MMF must be withdrawn before conception and during pregnancy).

The low remission rates at 6 months[62] and the long time to remission indicate that current treatments (both cyclophosphamide and MMF) are unable to suppress the activity of lupus nephritis sufficiently, or at least sufficiently early, which means that irreversible renal damage can occur and might affect long-term renal outcome.

Maintenance treatment

Maintenance treatment aimed at preventing relapse is necessary in patients with proliferative lupus nephritis.[68] Prolonged administration of quarterly intravenous pulses of cyclophosphamide for 2 years after induction treatment decreased the rate of relapse from 35% to 15% compared with shorter (1-year) administration.[47] Another study showed that maintenance treatment with azathioprine reduced renal flares by 49% and nephritic renal flares by 68% compared with no maintenance treatment.[33] Cessation of maintenance immunosuppression treatment also frequently results in renal relapse, with a risk of progression to ESRD.[20]

The minimum duration of maintenance treatment is very important. To reduce the risk of relapse, maintenance treatment should only be completely withdrawn in patients treated for at least 5 years who have maintained remission for at least 2 years;[39,69,70] drugs should be tapered very slowly and patients should be strictly monitored.[71,72] Currently available maintenance treatment reduces the risk of relapse, but does not prevent relapse completely.[23,47]

A randomized controlled trial conducted in Italy demonstrated that ciclosporin and azathioprine were similarly effective in preventing relapse in patients with diffuse proliferative lupus nephritis.[73] Patients who achieved remission after a 3-month course of corticosteroids and oral cyclophosphamide were randomized to either ciclosporin (mean starting dose 3.5 mg/kg per day) or azathioprine (mean starting dose 1.6 mg/kg per day). After 4 years, the incidence of renal flares was similarly low in both groups (10.6 flares versus 13.4 flares per 100 patient-years) and decreases in proteinuria were comparable. Despite small reversible early decreases in creatinine clearance in the ciclosporin arm, blood pressure and creatinine clearance were not significantly different from baseline at the end of follow-up.

A US study in mostly Hispanic and black patients with proliferative lupus nephritis compared oral MMF (0.5–3 g per day), oral azathioprine (1–3 mg per day) and quarterly intravenous cyclophosphamide pulses as maintenance treatments in patients who had achieved remission with the same induction treatment (pulsed cyclophosphamide combined with corticosteroids).[68] Over 6 years of follow-up, the rate of survival without death or chronic renal failure was significantly higher in the MMF and azathioprine groups than in the cyclophosphamide group. Relapse-free survival was significantly higher in the MMF group than in the cyclophosphamide group. Patients treated with MMF or azathioprine had significantly lower rates of amenorrhea, infections and nausea and vomiting than those treated with cyclophosphamide. These findings indicate that MMF and azathioprine seem to be more effective and safer than long-term treatment with intravenous cyclophosphamide pulses.

The MAINTAIN study, which included mainly white patients with proliferative lupus nephritis who achieved remission with the Euro-Lupus regimen, reported that oral mycophenolate (2 g per day) was not superior to oral azathioprine (2 mg/kg per day) in terms of number of renal flares, time to renal flare, doubling of serum creatinine and infectious adverse effects.[74] Hematological cytopenias were, however, more frequent in azathioprine-treated patients.

Data now published from the maintenance phase of the large, multiethnic ALMS study, however, show the superiority of oral MMF (2 g per day) over oral azathioprine (2 mg/kg per day) with respect to the primary end point of time to treatment failure (defined as any of the following: death, ESRD, sustained doubling of serum creatinine, proteinuric or nephritic renal flare and requirement for rescue therapy owing to deterioration of renal function, or exacerbation of lupus nephritis), regardless of induction therapy type.[67] The incidence of treatment-emergent adverse events (including infections) was similar in both treatment arms.

The optimal maintenance treatment still remains to be established, but some other therapies have shown promise. For example, a small study showed that intravenous immunoglobulins might be equivalent to cyclophosphamide pulses[75] and LJP 394 (abetimus sodium) has been shown to reduce renal flares and time to renal flare.[76] These and other newer drugs require further investigation, and the role of different regimens of corticosteroid tapering and their withdrawal remains to be defined.

In conclusion, ciclosporin seems to be comparable to azathioprine as maintenance therapy, at least in white populations, and MMF seems superior to azathioprine in terms of time to treatment failure (possibly only in 'higher risk' Hispanic and black patients). Further analyses of the MAINTAIN and ALMS maintenance studies are eagerly awaited. In long-lasting diseases such as proliferative lupus nephritis, rotating agents with different mechanisms of action and different adverse effects might be necessary to improve long-term effectiveness and avoid or minimize toxic effects.[73]

Other possible lupus nephritis treatments

Many other drugs, including ciclosporin, tacrolimus, mizoribine, leflunomide and fludarabine, have been investigated for the treatment of SLE and lupus nephritis, but often only in small uncontrolled studies in patients refractory to previous 'standard' treatment in which patients with lupus nephritis represented only a (sometimes small) part of the study population. The efficacy and safety of these drugs should be compared with

cyclophosphamide (or MMF) in sufficiently powered long-term randomized controlled trials in multiethnic populations. Bortezomib, imatinib and irinotecan have been shown to taper the activity of experimental lupus nephritis, and biologic agents have shown some promise. Patients with lupus nephritis and persistent proteinuria (>1 g per day) despite resolution of active lupus nephritis should also be treated with angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers, which may further decrease proteinuria.[77]

Ciclosporin

Several small uncontrolled studies have shown that ciclosporin can induce remission (decrease proteinuria) and suppress the histologically observed activity of proliferative lupus nephritis.[78] One pilot study in 11 patients with SLE showed that after 1 year of treatment, ciclosporin decreased both proteinuria and activity index on repeat renal biopsy with no increase in chronicity index and no signs of ciclosporin nephrotoxicity.[79] The long-term efficacy and safety of ciclosporin is a major concern, however. A study of 31 patients with lupus nephritis found that after 90 months of follow-up, ciclosporin remission was induced in 93.5% of patients treated with ciclosporin and although 45% of patients flared, renal function remained stable at the end of follow-up.[80]

A small randomized controlled study published in 2010 randomly assigned patients with active proliferative lupus nephritis to a sequential induction and maintenance regimen based on either cyclophosphamide pulses or oral ciclosporin.[81] Remission (defined as normal urinary sediment, proteinuria <0.3 g/24 h and stable serum creatinine level) and response (defined as stable serum creatinine, 50% decrease in proteinuria and either normalization of urinary sediment or significant improvement in complement C3) rates were similar in cyclophosphamide-treated and ciclosporin-treated patients at the end of the induction and maintenance phases, and no differences in relapse-free survival were observed at the end of follow-up. Treatment with ciclosporin was associated with a transient increase in blood pressure and a reversible decrease in GFR but with no differences in infection-related adverse events.

Ciclosporin might be a useful induction treatment as an alternative to cyclophosphamide in selected white patients with proliferative lupus nephritis under close monitoring of blood pressure and renal function. Treatment with ciclosporin should ideally not last longer than 2 years to minimize the risk of chronic nephrotoxicity.[78]

Tacrolimus

In patients with lupus nephritis, tacrolimus might not only decrease proteinuria,[82,83] but may also suppress the extrarenal activity of lupus.[83] In 63 patients with lupus nephritis (40% with proliferative lupus nephritis) tacrolimus decreased proteinuria significantly more than did placebo.[84] A study of a high-risk population of 40 patients with combined proliferative and membranous lupus nephritis found that the combination of MMF (1 g per day) and tacrolimus (initial dose 4 mg per day) was more effective than pulses of intravenous cyclophosphamide.[85] After 6 months, complete or at least partial remission had been achieved in 50% and 90% of patients on the combination treatment compared with only 5% and 45% of patients on intravenous cyclophosphamide. The follow-up duration was short (9 months), which means that tacrolimus nephrotoxicity and the impact of treatment on relapse rate and long-term renal outcome were not determined, but this study clearly shows that in patients with a more aggressive disease course, more effective modes of treatment, including the combination of several immunosuppressive drugs, are needed. Further studies (preferably randomized controlled trials) with longer follow-up are necessary to define the role of tacrolimus in induction treatment for lupus nephritis.

Leflunomide

A prospective observational study in 110 patients with biopsy-proven proliferative lupus nephritis reported that leflunomide (loading dose 1 mg/kg per day followed by 30 mg per day) was similarly effective to monthly cyclophosphamide pulses (0.5 g/m^2) as induction treatment (together with prednisone), both in terms of complete remission rate (21% versus 18%) and at least partial remission rate (52% versus 55%) at 6 months, with no differences in adverse event rates (including infections, alopecia and hypertension).[86] A study conducted in China reported that leflunomide therapy resulted in a significant reduction in the activity index on repeat biopsy and transformation to a less severe class of lupus nephritis occurred in 41.9% of patients.[87]

Mizoribine

In several small uncontrolled studies in patients with lupus nephritis (including diffuse proliferative lupus nephritis), mizoribine, an imidazole nucleoside that inhibits DNA synthesis in the S phase of the cell cycle, decreased proteinuria and significantly attenuated renal lesions on repeat biopsy.[88,89]

Fludarabine

Fludarabine is an adenosine analogue that is used in the treatment of hematological malignancies and is able to induce profound and prolonged depletion of both T cells and B cells. A small pilot study investigated use of this agent in patients with active proliferative lupus nephritis in combination with low-dose cyclophosphamide (monthly pulses at 0.5 g/m^2 for 6 months) and corticosteroids.[90] Treatment was effective (complete or partial response in 10 of 11 patients who received at least three cycles), but the study had to be prematurely terminated owing to bone marrow toxicity in several patients.

Agents investigated in experimental models

Several other agents have shown promising results in experimental models of lupus nephritis. The platelet-derived growth factor (PDGF) receptor antagonist

imatinib has been shown to ameliorate glomerulonephritis and prolong survival in MRL/lpr mice[91] and NZB/NZW F1 hybrid mice.[92] The topoisomerase I inhibitor irinotecan prevented onset of proteinuria, reversed established proteinuria and prolonged survival in experimental models of lupus nephritis (NZB/NZW F1 mice).[93] Administration of bortezomib, an inhibitor of the 26S proteasome, to MRL/lpr and NZB/NZW F1 mice resulted in depletion of long-lived B cells and plasma cells, almost complete disappearance of anti-double-stranded-DNA-producing B cells and the prevention or amelioration of established lupus nephritis with significantly prolonged survival.[94]

These drugs should be tested in pilot studies in patients with refractory lupus nephritis, but the translation of promising results from experimental studies into human disease may not be easy: their efficacy may be lower (very high doses are sometimes used in experimental studies) and safety issues are of particular concern.

Biologic treatments

A considerable proportion of patients with lupus nephritis become refractory to or do not tolerate treatment with corticosteroids, cyclophosphamide and MMF.[95] Targeted biologic treatments tested successfully in mice include soluble receptors that block T-cell co-stimulation (for example, abatacept and belatacept) and antibodies such as anti-interferon α, anti-interferon γ, anti-C5, anticytokine, or antichemokine antibodies.[96]

Intravenous immunoglobulins might ameliorate lupus activity by the suppression of autoreactive B cells (through signaling of FcγRIIB, idiotype-mediated inhibition of B-cell receptors and neutralization of cytokines such as the B-cell survival factors BAFF and APRIL).[97] A small randomized study showed that intravenous immunoglobulins were similarly effective to cyclophosphamide in maintaining proliferative lupus nephritis remission.[75] Treatment with intravenous immunoglobulins can, however, lead to osmotically induced acute kidney injury[98] and should therefore be used with caution only in patients refractory to other treatments.

B cells are believed to have an important role in the pathogenesis of lupus nephritis. As as result, researchers have investigated the potential therapeutic effect of B-cell-depleting monoclonal antibodies (for example, rituximab and epratuzumab) and monoclonal antibodies (for example, belimumab) and soluble receptors (for example, atacicept) for blocking BAFF in lupus nephritis.

The effectiveness and safety of rituximab has been evaluated in a number of small uncontrolled observational studies of patients with SLE (including patients with lupus nephritis) who were either refractory or intolerant to previous treatment. Rituximab induced complete or partial remission in all patients with refractory SLE and lupus nephritis,[99] 78% of patients with class III, IV or V nephritis,[100] 77% of patients with active lupus nephritis[101] and 60% of patients with class IV or V nephritis (more than half of whom were refractory to standard treatment).[102] Complete or partial remission was achieved with rituximab combined with steroids and MMF in 80% of patients with biopsy-proven relapse of proliferative lupus nephritis[103] and in 64% of patients with lupus nephritis when rituximab was added to conventional immunosuppressive treatment.[104] In a study involving 50 patients with active SLE (34 of whom had lupus nephritis) nonresponsive or poorly responsive to conventional immunosuppression, the combination of rituximab and cyclophosphamide induced complete remission in 42% of patients and partial remission in 47% of patients.[105] A systematic review published in 2009 reported a therapeutic response to rituximab treatment in 91% of 103 patients with lupus nephritis.[106] Response of SLE and lupus nephritis to rituximab is strongly correlated with B-cell depletion[103] and an increase in $CD4^+$ regulatory T cells[107] and is better in patients with a short duration of nephritis and preserved renal function.[104] Relapses are common (64%[99] and 55%[105] reported in two studies) but respond to retreatment with rituximab.

Rituximab was generally well tolerated in patients with lupus nephritis: adverse events occurred in 23% of patients, most frequently infections, infusion reactions and skin rash. Anti-rituximab antibodies (human anti-chimeric antibodies) may, however, limit the effectiveness and tolerability of rituximab in retreated patients and the risk of life-threatening viral infections such as progressive multifocal leukoencephalopathy associated with this agent must be also taken into consideration.[108]

A small, randomized, open-label pilot study reported that rituximab alone induced a similar proportion of complete and partial responses to the combination of rituximab with intravenous cyclophosphamide.[109]

A larger, randomized controlled trial (LUNAR) investigated rituximab use in 144 patients with proliferative (class III or IV) lupus nephritis all being treated with corticosteroids and MMF who were randomized to receive either rituximab or placebo.[110] However, the primary end point for rituximab to increase the response rate by 30% was not met (complete or partial response occurred in 57% of rituximab-treated patients and 46% of controls).[110]

The discrepancy between the reported effectiveness of rituximab in retrospective studies in often refractory patients with lupus nephritis[105] and the lack of effect of rituximab in randomized controlled trials may partly be explained by ethnic differences: populations in the uncontrolled studies consisted mainly of white patients, but the LUNAR study population was more heterogeneous.[110] Compared with patients in the uncontrolled studies, the LUNAR study included patients with less-active disease (most of whom had no history of a lack of response to standard therapies), and patients in LUNAR were treated with high concomitant doses of corticosteroids and MMF, which may have masked any possible benefit of rituximab.[111] In addition, the duration of follow-up of LUNAR was short (and may not have been sufficient to demonstrate the efficacy of the biologic treatment) and the study may have been underpowered to demonstrate superiority of rituximab. Recent reports on the efficacy of the anti-BAFF antibody, belimumab,

confirm the potential utility of B-cell-targeted treatment in SLE.[112]

BELONG, another study of a fully humanized anti-CD20 antibody (ocrelizumab) in proliferative lupus nephritis was, however, prematurely halted because of a higher than expected rate of serious and opportunistic infections (some of them fatal) in lupus and rheumatoid arthritis trials.[113] If biologic treatments are to expand in the field of lupus, ensuring the safety of new treatments is of paramount importance.

On the basis of the available evidence, B-cell depletion cannot be recommended as a first-line treatment for patients with mild forms of SLE that responds well to the standard treatment; however, this strategy might be useful off-label in severe, refractory SLE, including lupus nephritis.[111] Further data from randomized controlled trials in patients with moderate to severe disease are needed.

Can we personalize treatment?

Lupus nephritis is a very heterogeneous disease and treatment response is sometimes unsatisfactory. Personalized treatment could avoid both undertreatment (which can result in progression to irreversible damage) and overtreatment (which can lead to unnecessary severe adverse effects).[114]

Ideally, therapy should be modified to account for genetic variants of metabolic pathways that activate or inactivate drugs (for example, CYP polymorphisms affect the activation of cyclophosphamide and thiopurine methyltransferase polymorphisms influence the metabolism of azathioprine). Genetic or acquired variants of drug uptake and transport mechanisms and genetic or acquired variants of drug targets (for example, IgG Fc receptor polymorphisms that predict response to rituximab) should also be considered.[66]

As mentioned above, race and ethnicity are important predictors of outcome and treatment response in lupus nephritis. Data suggest that high-risk populations (for example, black and Hispanic patients) should not just be treated with higher doses of the same drug (for example, cyclophosphamide in the NIH studies), but possibly with different drugs (for example, MMF in ALMS[62]).

Renal function must also be taken into consideration. Owing to reduced cyclophosphamide clearance in patients with decreased creatinine clearance,[115] reduction of cyclophosphamide dose by 25% and 30–50%, respectively, is recommended in patients with creatinine clearance 25–50 ml/min and <25 ml/min. Experience with MMF in patients with lupus nephritis and reduced renal function is limited[62] and ciclosporin should be used with extreme caution even in patients with only slightly impaired renal function.[78]

Length and intensity of treatment should probably be tailored according to initial response of proteinuria (increasing intensity or switching to another treatment if proteinuria does not improve sufficiently during 3–6 months of treatment).[37]

In the future, treatment might be individually tailored based on the use of biomarkers that better reflect the activity and severity of the disease and predict its outcome more accurately than proteinuria, hematuria, or serum creatinine.[116–119] Anti-C1q antibodies strongly correlate with active renal disease and may be a useful predictor of renal flare[120] and antiphospholipid antibodies may predict the development of chronic renal insufficiency during long-term follow-up.[121]

Urinary messenger RNA (mRNA) might be another marker of active renal disease, but wide application of this method might not be feasible. The different roles of T-lymphocyte subpopulations and their prototypic cytokines in the pathogenesis of lupus nephritis seem to be reflected by the positive correlation of urinary mRNA expression of the T-helper-1 (T_H1)-specific transcription factor T-bet[122] and the T_H1-produced cytokine interferon γ[123] with histologic activity of lupus nephritis, and the negative correlation of urinary expression of the T_H2-specific transcription factor GATA-3[122] and the T_H17-specific transcription factor RORγ[124] with lupus nephritis activity.

Urinary TNF-like weak inducer of apoptosis (TWEAK)[125] and urinary hepcidin[126] have been shown to reflect renal disease activity and may predict renal flares and treatment response. Urinary TWEAK, hepcidin and other putative biomarkers (for example, urinary MCP-1, NGAL, transferrin and L-FABP)[119] should be validated in large SLE cohorts. Such biomarkers might be useful for modifying therapies on the basis of the risk of impending relapse or risk of progression to ESRD.

It is too early to clearly define the different subgroups that require different modes of treatment and the search continues for useful, widely available and generally applicable biomarkers to predict activity and outcome of lupus nephritis.

Conclusions

Although current treatments have considerably improved outcomes of patients with proliferative lupus nephritis, response to induction treatment is very slow, relapses on maintenance treatment are common, treatment is often complicated by severe adverse events and many patients still slowly progress to ESRD. Some new drugs are under investigation in lupus nephritis, and hopefully, at least some of them will show success in randomized controlled trials. Lupus nephritis treatment should become more personalized in the future as assessment of its activity and outcome improves and as the armamentarium of available drugs expands.

Review criteria

We searched PubMed (1964 to present) for studies investigating outcomes and treatments in lupus nephritis. The following search terms were used: "lupus nephritis", "proliferative lupus nephritis", "outcome", "treatment", "remission", "flare" and "biomarker". We concentrated on randomized controlled trials, but for newer drugs we also included some uncontrolled and observational studies. Case reports and small studies including fewer than five patients were deliberately omitted. We also considered recent reviews on this topic.

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