MANAGEMENT OF REFRACTORY LUPUS NEPHRITIS

Antonis Fanouriakis,[1,2] *George Bertsias[1,2]

1. Department of Rheumatology, Clinical Immunology, and Allergy, University Hospital of Heraklion, Heraklion, Crete, Greece
2. Institute of Molecular Biology and Biotechnology, Foundation for Research & Technology - Hellas (FORTH), Heraklion, Crete, Greece
**Correspondence to gbert@med.uoc.gr*

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ABSTRACT

Despite the significant advances in the field, up to one-third of lupus nephritis (LN) patients still do not respond adequately to initial immunosuppressive treatment. This group of patients is heterogeneous in terms of clinical presentation (deterioration of glomerular filtration rate, variable degrees of persistent proteinuria, active urine sediment) and the potential for reversion (ongoing kidney inflammation versus irreversible damage due to scarring and fibrosis). A repeat kidney biopsy can be highly informative in this regard and should be strongly considered. High-quality evidence regarding the treatment of refractory LN is lacking, and management is largely based on observational studies and expert opinion. Options include switching between mycophenolate mofetil (MMF) and cyclophosphamide (CYC), using rituximab as monotherapy or add-on therapy, or combining MMF with a calcineurin inhibitor in cases of persistent proteinuria. Renal response can be maintained with MMF or prolonged pulses of intravenous CYC administered bimonthly or quarterly. The efficacy of novel biological agents and those under development in refractory forms of LN remains to be determined. Tight control of cardiovascular risk factors, use of hydroxychloroquine, immunisations, and osteoporosis prophylaxis are important adjunctive measures. For the future, we anticipate that research efforts for the identification of accurate biomarkers together with accumulating data from observational and controlled studies will assist therapeutic decisions and improve outcomes in patients with refractory LN.

Keywords: Autoimmune diseases, immunosuppressives, biologics, biopsy, biomarkers.

INTRODUCTION

Renal involvement constitutes one of the most severe manifestations of systemic lupus erythematosus (SLE) and is a major determinant of the overall morbidity and mortality associated with the disease.[1] In a recent single-centre study, life expectancy of SLE patients with renal disease and those with irreversible renal damage was reduced by an average of 15.1 years and 23.7 years, respectively, compared with the general population.[2] The current 'treatment paradigm' in lupus nephritis (LN) includes an initial induction phase, which aims to halt ongoing immunological injury and ideally put the disease into remission, followed by a maintenance phase, with the ultimate goal being to consolidate the response and prevent damage accrual.[3] The choice of therapeutic agents is based on risk stratification, according to renal pathology and patient demographic, and clinical and laboratory features.

The fundamental goal of treatment in LN is long-term preservation of renal function and improved survival. To this end, prevention of flares and avoidance of treatment-related harm is crucial. According to the recently published joint recommendations by the European League Against Rheumatism (EULAR) and the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA),[4] treatment should ideally aim at complete renal response (CRR), defined as a urine protein loss <0.5 g/24 h (urine protein:creatinine ratio [UPr] <50 mg/mmol) and at least near-normal glomerular

filtration rate (GFR) (i.e. within 10% of normal GFR if previously abnormal).[4] This is based on evidence that patients with proliferative or membranous LN who achieve CRR display favourable long-term renal outcome with low risk of developing end-stage renal disease.[5,6] Partial renal response (PRR), defined as ≥50% reduction in proteinuria to subnephrotic levels and normal or near-normal GFR, may be acceptable in certain circumstances; this should nevertheless preferably be achieved by 6 months and no later than 12 months following treatment initiation.

Given these widely accepted treatment goals, a considerable proportion of patients fail to achieve the target. This subset of patients has 'refractory LN', which represents a particularly challenging population for the treating physician and typically requires a multidisciplinary approach. In this review, we deal with the different definitions of this heterogeneous group of patients, scrutinise available data on therapeutic choices, and reflect on unmet needs and the future agenda in the field.

DEFINITIONS OF REFRACTORY LUPUS NEPHRITIS AND THE DIAGNOSTIC VALUE OF REPEAT KIDNEY BIOPSY AND BIOMARKERS

How is 'Refractory' Lupus Nephritis Defined?

A universally accepted definition of refractory LN is lacking.[5,7] The EULAR/ERA-EDTA recommendations consider refractory LN for the following groups of patients: i) those who fail to improve within 3-4 months (i.e. no reduction in UPr or deterioration of GFR), ii) those who do not achieve PRR after 6-12 months, and finally iii) those who do not reach CRR after 2 years of treatment. The respective guidelines from the American College of Rheumatology have adopted a more lenient definition; refractory disease is defined as a worsening of nephritis (i.e. >50% increase in UPr or serum creatinine [SCr]) by 3 months or generally, 'treatment failure' (judged by the treating physician) by 6 months.[8] It should be noted, however, that the aforementioned definitions have not been validated as treatment strategies in the context of controlled trials and therefore should not be treated as 'strict rules'. Nevertheless, they intend to guide physicians towards the optimisation of treatment. Using different definitions, the prevalence of LN patients not responding to conventional immunosuppressive therapy ranges between 14% and 33%.[5,9,10]

How Long Should We Wait Before Diagnosing Refractory Lupus Nephritis?

A critical question faced by physicians caring for patients with LN is when to label a patient as 'refractory'. The 'tempo' of response to immunosuppressive treatment in terms of proteinuria is helpful in this regard. The 'Euro-Lupus' trial showed that a good long-term renal outcome (SCr <1.4 mg/dl at 10 years) is predicted by an early (3-6 months) drop in proteinuria by at least 50% or to <1 g/24 h,[11,12] a finding that has been validated by subsequent studies.[13] Therefore, the 6-month timepoint from the initiation of induction therapy represents a critical checkpoint for determining the response to treatment. Nevertheless, complete resolution of proteinuria (UPr <0.5 g/24 h) may take longer, especially in patients with higher baseline UPr levels. In a recent retrospective study, the proportion of LN patients who achieved UPr <0.5 g/24 h increased from 28% in the first year to 74% at 5 years.[14] Taken together, these findings justify a 'hurry up and wait' approach, whereby intensified induction therapy should aim ideally for at least PRR at 6 months, followed by a watchful monitoring period of up to 2 years, when the highest rates of CRR are usually observed.

Is a Repeat Kidney Biopsy Necessary in Refractory Lupus Nephritis?

Its importance in LN notwithstanding, renal biopsy is an invasive procedure with potential, although uncommon, complications. Thus, a rational selection of patients that would benefit from repeat biopsy is desirable. Re-evaluation of renal histology will be considered valuable when it leads to optimisation of the therapeutic approach, to avoid both over and undertreatment of patients. Although no consensus currently exists, repeat biopsy may be considered in cases of inadequate renal response (PRR or no response) i.e. with residual proteinuria >1 g/24 h or GFR deterioration. In a significant proportion of these cases (up to 40% in partial responders and 60% in non-responders) histological transformation to more severe LN forms may be revealed, therefore justifying modification/intensification of immunosuppressive therapy.[15] However, at least one-third of patients with PR (and approximately 15% of non-responders) show an absence of active lesions on repeat biopsy[16] but an

increase in chronic, irreversible glomerular or tubulointerstitial lesions. In such cases, persistence of proteinuria does not justify more intense immunosuppression.

Repeat kidney biopsy may also be considered in severe nephritic or nephrotic renal flares.[17] Biopsy results will most often lead to a change in immunosuppressive treatment, especially in flares with nephrotic-range proteinuria, persistent deterioration of GFR, or in patients who were in remission for longer periods before they flared. Class switching to a proliferative LN type is most likely in patients who had no proliferative lesions in their original histology,[18] while scarring also tends to accrue over time.

Biomarkers for Monitoring Lupus Nephritis

The quest to identify reliable biomarkers as surrogate markers of renal histology is ongoing.[19] A wide array of urine-excreted proteins have been evaluated for their potential association with histologic findings of LN, including neutrophil gelatinase-associated lipocalin, vascular cell adhesion molecule-1, and tumour necrosis factor-like weak inducer of apoptosis (TWEAK).[20-22] Although some of these molecules have shown promising results, they still lack firm validation and standardisation. Serological tests such as antibodies against C1q (anti-C1q Ab) are closer to clinical implementation. A recent meta-analysis of observational studies calculated an anti-C1q Ab sensitivity and specificity of 76% and 80%, respectively, to discriminate between active and inactive LN.[23]

THERAPEUTIC OPTIONS IN REFRACTORY LUPUS NEPHRITIS

Well-designed, randomised controlled trials (RCTs) are lacking in patients with refractory LN. Most data originate from observational studies performed in centres with expertise in the disease, and therapy is often individualised and based on expert opinion. Irrespective of the immunosuppressive or biological agent used, concomitant use of steroids is recommended, especially in the presence of significant histological activity in kidney biopsy. Although there are no data to support the use of high-dose steroids in refractory LN, we often advocate for three pulses of intravenous (IV) methylprednisolone (MP) followed by oral prednisolone 0.5-0.75 mg/kg/day with gradual tapering. Supplementing monthly IV cyclophosphamide (CYC) pulses with IV MP pulses is also an option.[24]

Switching from Mycophenolate Mofetil to Cyclophosphamide and Vice Versa

CYC and mycophenolate mofetil (MMF) are the two therapeutic agents most commonly used as induction therapy in LN. Consequently, it seems reasonable that failing to respond to one could justify switching to the other.[25] Rivera et al.[26] examined 85 patients with relapsing (n=50, who had experienced at least one relapse after having responded) or refractory (n=35, who had not responded after 6 months) LN (mean UPr: 2.5-3.1 g/24 h, 38% with GFR <60 ml/min), 86% of whom had previously received IV CYC.[26] All patients received MMF and at 24 months 87% of patients had responded (the majority within the first 6 months). Accordingly, both the EULAR/ERA-EDTA and the American College of Radiology (ACR) guidelines recommend switching from CYC to MMF in cases of LN not responding to the former.[4,8] The opposite approach (switch from MMF to CYC) is also proposed based on the good long-term efficacy data of CYC in LN, although this has not been formally tested.

Calcineurin Inhibitors and 'Multitarget Therapy'

Calcineurin inhibitors (cyclosporine A, tacrolimus) exert potent antiproteinuric effects and have been employed in difficult LN cases. Open-label studies have shown that both tacrolimus and cyclosporine, used as monotherapy, can be effective in reducing proteinuria in cases resistant to CYC with residual UPr >1 g/24 h. These data, although encouraging, should be cautiously interpreted due to the low numbers of patients included, the open-label, uncontrolled design of the studies, and the short follow-up period (12 months maximum).[27-29]

Both calcineurin inhibitors have been used in combination with MMF as part of a 'multitarget' approach. In a recent large RCT (n=362) in China, the combination of tacrolimus (4 mg/day) with MMF (1 g/day) was superior to monthly IV CYC (0.75 g/m^2) at 6 months (rates of CR: 45.9% versus 25.6%) as induction therapy.[30] Another observational study in 70 patients with proliferative LN not responding to MMF showed that the addition of tacrolimus led to an additional 70% of patients (12 out of 17) achieving clinical response after 24 months.[10] The combination has also shown better efficacy than IV CYC in an observational study of 40 patients with mixed Class V+III/IV LN

(UPr: 4.0-4.4 g/24 h, preserved renal function), 65% of whom had previously been treated with MMF or CYC.[31] These promising results should nevertheless be viewed with the limitation of short follow-up. Moreover, caution is needed when using calcineurin inhibitors in cases of reduced GFR (<60 ml/min), advanced chronic damage (fibrosis) in renal histology, or in the presence of arterial hypertension.[32] Diligent monitoring of SCr and blood pressure is mandatory.

Rituximab

Both the EULAR/ERA-EDTA and the ACR guidelines recommend the use of rituximab (RTX) either as add-on treatment or as monotherapy in cases of refractory LN.[4,8] This is despite the fact that the LUNAR trial failed to meet its primary endpoint in demonstrating the superiority of RTX over placebo in active Class III-IV LN.[33] However, this trial has received criticism for two main reasons: i) the use of high background immunosuppressive treatment (i.e. both arms received high-dose glucocorticoids and MMF 3 g/day) that might have diluted any effect attributable to RTX, and ii) the lack of adequate power to detect statistically significant differences in response rates (RR) between RTX and placebo. As a result, the 16% difference (31% versus 15%) in PRR favouring RTX over placebo did not reach statistical significance. To put this in perspective, a similar difference in RR (approximately 15%) between active drug and placebo arms in the larger BLISS trials led to the approval of belimumab in extrarenal SLE.[34]

Notwithstanding the above, advocacy for the use of RTX in LN is based primarily on positive experience with this agent, as well as a wealth of observational evidence, especially in cases with inadequate response to initial immuno suppression.[35-37] Pooled data from two different countries reported CRR or PRR in approximately two-thirds (67%) of 164 patients with LN treated with RTX, used mainly as a second-line option in refractory or flaring disease;[38] 76% of these patients received concomitant CYC or MMF. The presence of nephrotic syndrome or renal failure at the time of RTX administration was a predictor of poor prognosis and non-response. These predictors were confirmed in another systematic literature review of 300 patients treated with B cell depletion for variably defined refractory LN, who had previously received various immunosuppressive agents.[39] Similar to the previous study, RR reached a total of 74% (40% CRR and 34% PRR), reinforcing the notion that RTX is indeed efficacious in 'difficult' LN. Conversely, mixed forms of nephritis (Class V+III/IV) may respond less favourably to B cell depletion (CRR: 24%)[39] and a recent small observational study reported no efficacy of RTX in cases of rapidly progressive, crescentic glomerulonephritis.[40]

Plasma Exchange Therapy

Plasma exchange (plasmapheresis) has been successfully used in severe, life-threatening, or recalcitrant-to-immunosuppressive-agents SLE. In an open-label, non-randomised study in patients with steroid-resistant LN (mainly Class IV), plasma exchange (double filtration or immunoadsorption plasmapheresis) synchronised with monthly pulses of IV CYC was superior to either modality alone in inducing renal response and preventing flares.[41,42] Stummvoll et al.[42] have also reported favourable long-term (average 6.4 years) results with prolonged cycles of immunoadsorption combined with azathioprine or MMF in 11 patients with LN refractory to CYC. Notwithstanding these findings, immunoadsorption should be reserved for LN patients who have failed with multiple immunosuppressive and/or biologic agents, or in the presence of severe antiphospholipid antibody-associated nephropathy, and should be performed at experienced clinical centres.

Other Biologics and Novel Agents

Patients with severe LN were specifically excluded from the large RCTs that led to the approval of belimumab, an anti-B lymphocyte stimulating monoclonal antibody, for the treatment of SLE. This fact precludes any firm conclusions regarding the use of this agent in LN, including refractory forms of the disease. Nevertheless, a pooled post-hoc analysis of the BLISS trials evaluated 267 patients who had active renal involvement at baseline.[43] A trend towards reduction in the rate of renal flares (1.4% versus 3.0% in the placebo and belimumab 10 mg/kg arms, respectively) and level of proteinuria, as well as increased rates of renal remission (58.7% versus 70.5% in the placebo and belimumab 10 mg/kg arms, respectively), were observed in the belimumab groups over 52 weeks. Efficacy of belimumab was more pronounced in patients receiving MMF or those who were serologically active at baseline. A formal trial of belimumab in active LN is currently underway (NCT01639339).

Two RCTs were recently published comparing costimulation blockade with abatacept against standard of care in active LN. The ACCESS trial[44] found no difference in rates of CRR at 6 months when abatacept or placebo was added to low-dose CYC (Euro-Lupus regimen). In the second study, 298 patients were randomised to abatacept or placebo, both administered on background immunosuppression with MMF 2-3 g/day and oral prednisone.[45] After 12 months abatacept failed to increase the rates of CRR over placebo, although a greater reduction in proteinuria was observed in abatacept-treated patients with nephrotic syndrome at baseline. A post-hoc analysis showed that if less stringent outcome criteria were applied, CR rates would be higher and significant differences (reaching almost 18%) would be noted in favour of abatacept.[46] The use of abatacept in refractory forms of LN has not been tested.

A number of novel therapies are currently in the pipeline for assessment in LN, including interleukin-6 blockade (sirukumab), anti-TWEAK, anti-interferon α (sifalimumab, rontalizumab), and anti-fibrotic agents (fresolimumab), but a detailed review of their preliminary efficacy data is beyond the scope of this article. Figure 1 depicts a diagnostic and therapeutic algorithm for refractory LN.

Maintenance Therapy

Very scant data are available regarding therapeutic options for maintenance of renal response in refractory LN. The choice largely depends on physician experience, but also on the agent used for induction of response. In this regard, if MMF was used for induction and led to renal response, it seems reasonable to continue with it through the maintenance phase.

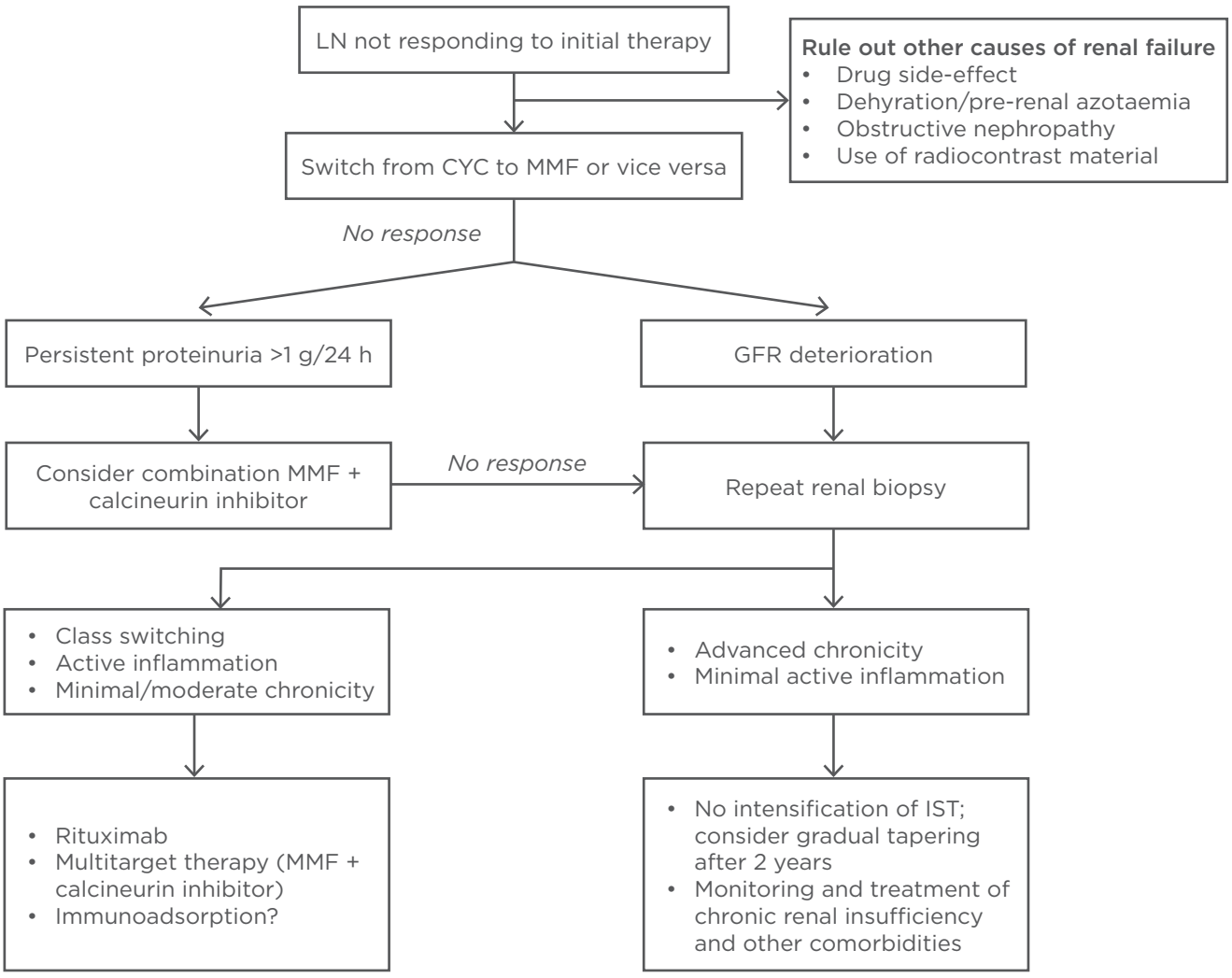

Figure 1: Diagnostic and therapeutic approach to refractory lupus nephritis.
LN: lupus nephritis; MMF: mycophenolate mofetil; GFR: glomerular filtration rate; CYC: cyclophosphamide; IST: immunosuppressive therapy.

In the study by Rivera et al.[26] that tested the efficacy of MMF after CYC failure, nearly 16% of patients (3/19) relapsed after discontinuing MMF. If CYC was used for induction, prolonged IV pulses (bimonthly or quarterly) can be used to consolidate the response. The pivotal initial studies from the National Institutes of Health have shown that prolonged IV CYC pulses are associated with beneficial renal outcomes in the very long term (10 years) with an acceptable safety profile; however, these studies did not specifically target patients with refractory LN.[24,47]

Adjunctive Therapy

The importance of adjunctive treatment in LN cannot be overemphasised. Tight control of hypertension and dyslipidaemia is recommended. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the agents of choice for the former, based on their antiproteinuric effects. Statins are recommended to treat dyslipidaemia (ideally low-density lipoprotein <100 mg/dl, as in other high-risk populations); a recent study suggested dyslipidaemia to be an independent risk factor for progression to chronic kidney disease in LN.[48] Hydroxychloroquine (HCQ) should be considered an essential component of LN therapy.[49] Thus, evidence suggests that inclusion of HCQ in the therapeutic armamentarium reduces the risk for nephritic flares and renal damage,[50,51] and it may also facilitate the successful withdrawal of immunosuppressives in patients with LN.[52] Finally, adherence to seasonal vaccination schedules and osteoporosis prophylaxis is of utmost importance.

UNMET NEEDS – CONCLUSION

Despite the advances in the field, LN continues to pose considerable therapeutic challenges, since a significant proportion of patients fail to respond to treatment and consequently carry an increased risk for developing chronic renal insufficiency and end-stage renal disease. Contradicting the accumulation of high-quality data in LN over the past decades, well-designed clinical trials have not yet been performed in refractory forms of the disease. The future research agenda will incorporate various issues, including but not limited to i) the identification of reliable surrogate markers to substitute for repeat renal biopsy in relapsing/refractory LN, ii) better clarification of any therapeutic gain from switching between different induction regimens in cases of treatment failure, iii) the precise role of adding calcineurin inhibitors, RTX, or belimumab to standard therapy in cases with residual disease, and iv) the testing of novel biologic agents currently under development. With all this in mind, we are looking forward to a fascinating period in the field.

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