REVIEW

Management of refractory lupus nephritis: challenges and solutions

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Abstract: Refractory lupus nephritis, broadly defined as failure to attain clinical remission after appropriate induction immunosuppressive therapy, is associated with an increased risk of progression to end-stage kidney disease and mortality. This is a challenging issue in clinical practice, as modern induction therapy despite proven efficacy can still be associated with treatment failure. Moreover, newer therapies have failed in recent years to displace or even match existing protocols for effective induction of remission. Refractory disease is generally assessed on the basis of clinical parameters, which may be unreliable, and renal biopsy, which is often not performed in a standard or timely fashion. Persisting histological inflammation in 30%–50% of patients who have attained clinical remission highlights the disparity between clinical and immunological response to therapy. The lack of an international consensus regarding what constitutes refractory lupus nephritis compounds clinician indecision regarding optimal management for these patients. Moreover, non-adherence to prescribed therapy versus primary treatment failure can be challenging to discriminate, and the time point at which non-response becomes treatment failure is unclear. In this review, we assess the key published evidence for the treatment of refractory lupus nephritis and provide practical recommendations based around the use of adjunctive therapies. These agents include rituximab and calcineurin inhibitors, with evidence consisting largely of observational or uncontrolled studies, as well as some of the biologic therapies currently under investigation through prospective clinical trials. The poor prognosis of refractory lupus nephritis demands regular review of patient response and the flexibility to switch or augment therapy.

Keywords: lupus nephritis, refractory, management

Introduction

Lupus nephritis (LN) is a common severe complication of systemic lupus erythematosus (SLE) and a major determinant of morbidity and mortality.[1] Up to 60% of adult patients with SLE[2,3] develop renal disease of differing severity during the course of their illness. Despite the introduction of corticosteroids and other immunosuppressive agents which have profoundly changed the management of LN, namely cyclophosphamide (CYP) and mycophenolate mofetil (MMF), between 20% and 70% of patients with LN are reported to be refractory to standard immunosuppressive therapy.[4] The variable response rates reported in the literature are due to several factors including length of follow up, different definitions of clinical response used, and the ethnicity of the cohort being studied.

Patients with refractory LN have poorer outcomes. For example, in a study of 86 patients with diffuse proliferative LN, the patient survival at 10 years was 95% for

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complete remission, 76% for partial remission and 46% for no remission. Renal survival at 10 years was 94% for complete remission, 45% for partial remission and 19% for no remission.[5,6] Thus, even a partial remission in LN is associated with significantly better outcomes compared with no remission.

Long-term high dose immunosuppression is also associated with significant treatment toxicity. Novel alternative therapies that are currently available include "multitarget therapy" and various biologics that target B cells, T cells or cytokines, but to date, no new approaches to the treatment of LN have been shown to be superior to CYC or MMF plus corticosteroids.

The goals of this review are to address the key issues in the assessment and management of refractory LN, including the definition of complete response, the role of repeat renal biopsy to inform clinical decision-making, and the evidence for adjunctive therapies for patients with refractory disease.

Definition of refractory LN

A major challenge in determining the optimal treatment approach for refractory LN is the lack of a consensus definition for complete response following induction treatment. As a result, the reported incidence of "refractory" LN varies according to which of several definitions for complete remission is used. The European League Against Rheumatism (EULAR/ERA-EDTA) recommendations consider refractory LN as those patients who do not achieve a partial response after 6–12 months.[7] The guidelines from the American College of Rheumatology have defined refractory LN as worsening nephritis by 3 months or, treatment failure as assessed by the treatment physician by 6 months.[8]

Most criteria for complete or partial response are a composite of clinical indices including serum creatinine, proteinuria and urinary red blood cells. The Kidney Disease and Improving Global Outcomes (KDIGO) guideline on glomerulonephritis defines complete remission as return of serum creatinine to previous baseline and a decline in the urine protein creatinine ratio (UPCR) to <500 mg/mmol. Partial remission is defined by stabilization (±25%) or improvement of serum creatinine, but not to normal, and a >50% decrease in the UPCR.[9] In clinical practice, partial remission is expected at 3–6 months, and clinical parameters are usually assessed every 4 weeks in the first 6 months.

There are several problems with the focus on decline in proteinuria and creatinine as a marker of remission. Firstly,

emerging data on protocol repeat biopsies performed after complete clinical remission show continuing histologic activity in a significant number of patients.[10–13] Despite the discordance between histological and clinical metrics of disease activity, renal response definitions do not routinely include renal histology as a component of assessment. Stopping maintenance therapy based on clinical activity indices alone may theoretically put such patients at risk of a renal flare.

Secondly, there are other non-immunologic mechanisms of renal injury which may lead to changes in creatinine and proteinuria including thrombotic microangiopathy and secondary focal glomerulosclerosis. Moreover, all calcineurin inhibitors (CNI) therapy, potential therapy for LN, act directly on podocytes to reduce proteinuria, independent of its immunosuppressive effects. Thus, it is unclear whether disease remissions observed with CNI therapy result from "true" remission of the immunological disease processes or are the result of the antiproteinuric effects of CNIs.

Thirdly, the clinical intersection between what is sometimes termed "true" refractory LN, as opposed to non-adherence to therapy or inadequacy of the prescribed regimen, is somewhat blurred. Several studies suggest that problems with treatment adherence may directly influence clinical outcomes in patients with SLE.[14,15] Important barriers to adherence have been identified in focus groups and include financial problems, fear of side effects, difficulties navigating the health system and perceived treatment inefficacy.[16]

In practical terms, it can be extremely difficult to know whether a patient is non-adherent to treatment. This has significant implications for the intensification of therapy and accompanying drug toxicities, switching of therapy, and the monitoring of such patients. Pill counts, pharmacy records and measuring therapeutic levels of drugs (eg, MMF) may assist in the assessment of adherence but is no guarantee that the prescribed therapy has been taken. One exception may be in those patients receiving intravenous CYC, which is sometimes preferred as induction specifically because adherence is intrinsic.

Conversely, in an adherent patient failing to achieve remission, insufficient dosing of first line induction therapies should be considered. It is therefore important to review dosages of prescribed agents to ensure they conform with evidence-based guideline recommendations.[8,9,17] For example, if a patient is on MMF for induction of 2 g/day and has not achieved remission, we would recommend maximizing the dose to 3 g/day, as tolerated.

Nonetheless, therapeutic drug monitoring by assay of the 12 hour MMF area under the curve for dosage titration has shown some promise in LN.[18] A tailored approach such as this may be of use, for example, in Asian patients who are more susceptible to adverse effects of MMF at higher dosages prescribed on a per protocol basis.

In this review, we use the term refractory LN in reference to adherent patients who fail to achieve either a complete or partial response to initial standard immunosuppressive therapy, or whose renal function deteriorates on therapy, within a 6 to 12-month period. Long-term follow-up of patients in the Euro Lupus Nephritis Trial showed that the best predictor of good long-term renal outcomes is early (3–6 months) reduction in proteinuria by at least 50% or to <1 g/24 hours and decrease in creatinine,[19] a finding validated in subsequent studies.[20] Thus, clinical response to primary induction therapy after a 6-month interval represents an important checkpoint for the treating physician.

The role of the kidney biopsy in refractory LN

There are a number of key clinical circumstances, after initial histological diagnosis and staging of LN, at which repeat renal biopsy may provide useful information when considering a diagnosis of refractory LN.

A renal biopsy should be considered for patients on induction therapy presenting with worsening proteinuria and creatinine. Whilst immune complex-mediated LN is the most common cause of kidney disease in SLE, other mechanisms can result in renal injury that are not apparent by clinical data alone and require a different management approach. Examples include thrombotic microangiopathy, lupus podocytopathy, antiphospholipid antibody-induced vascular lesions, and tubulointerstitial nephritis.

For patients with worsening clinical parameters, refractory LN must be considered. We recommend repeat renal biopsy for patients who have not met the clinical criteria for complete or partial remission to first line induction immunosuppression within 6–12 months. Deciding when to repeat a biopsy for suspicion of refractory disease is challenging, and ultimately must be individualized to the patient and overall clinical assessment. For example, some clinicians may elect to wait 12 months or longer if creatinine is stable and proteinuria is progressively declining. Conversely, rapid decline of clinical parameters may necessitate an early repeat biopsy even before the 6 to 12-

month period. Our own practice is to consider repeat biopsy at 6 months if there has been no clear improvement, and earlier if renal function worsens on standard therapy over the first 3 months.

For patients with slowly rising serum creatinine or persistent proteinuria, a repeat renal biopsy is also helpful to distinguish active proliferative LN from advanced sclerosing LN which may allow for reduction in immunosuppression. Studies have demonstrated that increasing chronic damage on repeat biopsies performed after at least 6 months of immunosuppressive therapy is predictive of long-term renal outcomes.[10,12]

The role of protocol repeat kidney biopsies in LN is still debated and local preferences predominate. Emerging data suggests that serial biopsies may inform ongoing treatment decisions. After completing 6–8 months of immunosuppressive therapy, 30–50% of complete clinical renal responders still had histologic evidence of ongoing active inflammation, and 40–60% of patients with no histologic evidence of disease activity still had persistent high-grade proteinuria.[10,11] Despite several years of immunosuppressive therapy and at least 24 months of clinically quiescent disease, histologic activity was found in 30% of LN patients.[11]

A more comprehensive picture of kidney pathology has been examined through molecular imaging of the kidney biopsy. A recent study of intrarenal transcript expression profiles of the diagnostic kidney biopsy in patients with LN showed differing molecular profiles between patients who had a rapid clinical response to induction therapy and patients who did not.[21] The addition of molecular evaluation to histology has the potential to facilitate the individualization of LN treatment and identify those patients who would be refractory to conventional therapy.

The implications of refractory LN

The importance of achieving a complete or partial response was illustrated by the Lupus Nephritis Collaborative Study Group. Patients who achieved complete remission had better 10-year patient and renal survival rates (95% and 94%, respectively) as compared to those who attained partial remission (76% and 45%, respectively).[6] For patients who had no response to therapy, the 10-year patient and survival rate was 46% and 13% respectively.[5] Thus, even a partial response is better than no response in patients with proliferative LN.

Prognosis in LN is also influenced by the heterogenous demographic, clinical and histological variables of this disease. African American and Hispanic ethnicity were associated with

a shorter time-to-LN occurrence (HR=2.57, 95% CI 1.26–5.26; *p*=0.001 and HR 2.32, 95% CI 1.03–5.25; *p*=0.001 respectively) compared with Caucasians.[22] Indeed, African Americans with LN had the worst outcomes when compared to Hispanics and Caucasians, with the development of renal events or death being three times higher in African Americans and two times higher in Hispanics when compared to Caucasians.[23] Dooley[24] also reported a significantly poorer renal survival (free of ESRD) in African Americans compared to Caucasians treated with cyclophosphamide for LN, with a 5-year renal survival of 58% in African Americans as compared to 95% in Caucasians.[24] The reasons for these disparate outcomes remain controversial.

A higher incidence and more severe nephritis are also seen in male gender and juvenile onset SLE.[3] Other clinical factors include elevated serum creatinine at time of presentation, hypertension and tubulointerstitial inflammation.[23,25,26] Australian data on LN is scarce, with some studies suggesting that Asian Australians were more affected by SLE than non-Asian Australians in terms of disease severity and renal involvement.[27,28]

Therapeutic options for refractory LN

The management of patients with refractory disease varies with the first line agent used for induction therapy, clinical factors and local practices as outlined below. A suggested approach to the assessment and management of refractory LN is detailed in Figure 1.

Switching from CYC to MMF or vice versa

Switching to another first line induction agent is the recommended initial approach for patients with refractory LN and is recommended by both the EULAR/ERA-EDTA and American College of Rheumatology guidelines.[1,17] In general, CYC-resistant patients are treated with MMF and MMF-resistant patients with CYC. In addition to switching immunosuppressive agents, some accompany this with 3 days of intravenous pulses of glucocorticoids.[8]

The efficacy of MMF in patients with refractory LN[29–33] has been demonstrated in several open label studies. Rivera et al[34] examined 85 patients with relapsing (n=50) and refractory (n=35, who had not responded after 6 months of therapy) LN who were switched to MMF induction, of whom 87% had received initial induction therapy with IV CYC. Overall, 74 patients (87%) achieved a response (69% partial and 31% complete).[34]

Dooley et al[30] reported improvements in renal function and proteinuria in 12 patients given MMF who were either
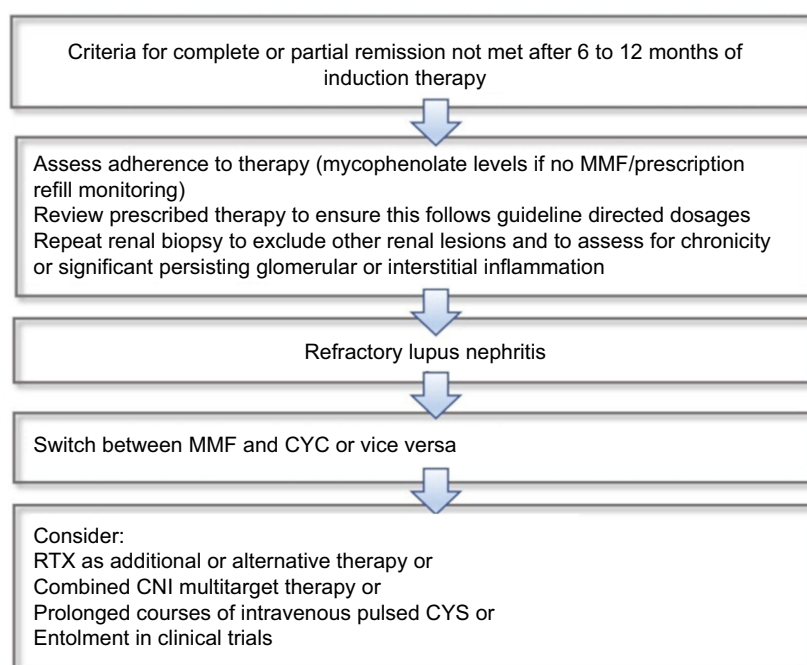

Figure 1 A suggested treatment algorithm for refractory lupus nephritis.
Abbreviations: MMF, mycophenolate; CYC, cyclophosphamide; CNI, calcineurin inhibitors; RTX, rituximab.

refractory or relapsed after treatment with CYC.[30] Four of the patients had declining renal function while receiving initial therapy with CYP and two patients had relapsing LN.

The opposite approach (switching from MMF to CYP) is also recommended[8,9,17] based on good long-term efficacy data of CYC in LN despite there being no data on outcomes of patients who have made this switch. Additionally, for a patient with suspected nonadherence to an induction regimen consisting of MMF or oral cyclophosphamide, switching to IV cyclophosphamide may be helpful.

Prolonged courses of cyclophosphamide

Extended therapy with CYC can be considered for patients who fail to meet remission criteria by 6 months. Mok et al[35] demonstrated in a cohort of Chinese patients with LN that cumulative doses, determined the initial treatment response.[35] However, the significant treatment toxicities of CYC, such as infertility, urotoxicity and oncogenicity, which are particularly relevant as most patients are of childbearing age, is a major limitation to this. Ovarian reserve is inversely related to the cumulative doses of CYC received and concomitant use of gonadotropin-releasing hormone (GnRH) analogues should be considered.[36,37]

B cell therapies

B cells play a principal role in the pathogenesis of LN and are therefore attractive therapeutic targets. Rituximab (RTX) is a chimeric mouse-human monoclonal antibody directed against the B-cell surface molecule CD20. Several uncontrolled studies reported efficacy of RTX in patients with refractory LN.[38–45] However, RTX failed to show any benefit in the Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial which excluded patients with severe active LN.[46] Additionally, the single randomized, double-blind placebo-controlled trial (LUNAR) comparing RTX with placebo when added to standard of care with prednisolone and MMF in incident LN, also failed to demonstrate any significant therapeutic efficacy.[47]

Interpretation of these results needs to be balanced with the concerns raised about the LUNAR trial's design. All patients received intense background immunosuppression with regular infusions of 1 g methylprednisolone and high dose oral MMF which may explain the minimal additional benefit seen with the addition of RTX at week 52 follow up. In addition, the LUNAR trial included only incident LN patients, whereas most previous uncontrolled studies describe efficacy in a cohort of patients with refractory LN

who had failed CYC or MMF and had RTX as an alternative, not an add-on therapy.[48]

Additionally, a higher complete response rate was seen with respect to proteinuria in patients who received RTX (32 vs 9%). This reduction in proteinuria persisted through to 78 weeks, raising the possibility that a longer period of follow up may have yielded a significant difference. The study also found higher partial response rates in the RTX group for all patients and in the prespecified subgroup of African-American patients, however, the trial was not powered to detect differences in partial response rates.[47]

Gomez-Mendez et al[49] recently demonstrated in a post hoc analysis of the LUNAR trial that there was substantial variability in peripheral blood B cell depletion in patients with LN treated with RTX. Achievement of complete peripheral depletion (peripheral B cells 0 cells/µL) as well as the rapidity and duration of complete peripheral depletion were associated with complete response at week 78.[49] Reasons for this have been hypothesized to include autoreactive pathogenic B cells persisting within lymphoid structures and the kidney tubulointerstitium.[50,51]

Despite the failure of the LUNAR trial to meet its primary endpoint, advocacy for the use of RTX in refractory LN continues and is primarily based on observational evidence, especially in patients who have an inadequate response to first line induction regimens. In a systematic review of published case reports and case series on the efficacy of RTX in patients with refractory LN, 300 patients who were followed up for 60 weeks had sustained complete and partial response rates in 87, 76, 67 and 76% of patients with class III, IV, V and mixed class respectively.[48]

A few cases of progressive multifocal leukoencephalopathy caused by reactivation of polyoma virus have been reported in patients with rheumatologic disease treated with RTX.[52] Many of these patients were also on other immunosuppressive agents, and it is possible that reactivation risk is determined by total immunosuppression rather than by any specific drug alone.

The exact role of RTX in the treatment paradigm of LN remains to be determined with open label evidence suggestive of a role in the treatment of refractory LN. RTX is a reasonable alternative therapy that could be considered for patients with refractory disease.

Calcineurin inhibitors
The calcineurin inhibitors (CNIs) cyclosporine A (CSA) and tacrolimus have been studied extensively in LN,

especially in Asia, with emerging evidence for its efficacy in refractory LN.

CSA binds to its cytoplasmic receptor, cyclophyllin, and the resultant drug-receptor complex binds to calcineurin and interferes with IL-2 production, thus leading to selective and reversible inhibition of T cell-mediated immune response. In addition to its potent immunosuppressive action, CSA has been shown to have direct antiproteinuric effects. The mechanism is related to stabilization of actin in podocytes.[53] Tacrolimus binds to a different cytoplasmic receptor, the FK-binding protein-12, which then interacts with calcineurin.

The CNIs have shown encouraging results in open label trials and are a potential less toxic alternative to conventional therapy. An early trial of 18 patients with proliferative LN refractory to conventional therapy who were administered CSA at 5 mg/kg/day had reduced proteinuria, improved renal function and decreased requirement for corticosteroids.[54] Dostal et al[55] demonstrated the efficacy of CSA administered for 1 year to eleven patients with LN (eight with LN refractory or intolerant to CYC or azathioprine).[55] There was a significant improvement in disease activity scores, degree of proteinuria, dsDNA titres and histological activity. In a small open label prospective study, nine Japanese patients with LN refractory to conventional therapy received low dose CSA (2.5 mg/kg/day) and were followed up for 30 weeks. Two patients achieved complete remission and four went into partial remission with improved proteinuria and reduced corticosteroid dependence.[56]

CNIs have been used as part of a multitarget approach to treat LN, added to a regimen of MMF and corticosteroids. Combining immunosuppressive agents for a synergistic effect has long been utilized in organ transplantation to minimize the risk of rejection. Multitarget therapy comprising corticosteroids, tacrolimus and MMF has been investigated in a prospective randomized open label trial for the induction treatment of LN and has been shown to be superior to intravenous CYC in induction of remission at 6 months.[57] Interestingly, there were more patient withdrawals due to adverse events in the CNI arm than the CYC arm, though the overall rate of adverse events did not differ between the two groups. These results need to be interpreted cautiously as reduction in proteinuria is the major clinical determinant of renal remission in these trials and CNIs can attenuate proteinuria through immune and nonimmune mechanisms. Indeed, upon cessation of these agents, the antiproteinuric affects are often reversed. Thus, proteinuria may not be an appropriate end point in LN patients treated with a CNI, and post-treatment kidney biopsy should be performed to ensure resolution of immune injury. Finally, long-term preservation of kidney function and applicability of CNIs to non-Asian cohorts need to be verified.

Plasma exchange and immunoadsorption

The evidence for extracorporeal treatments such as plasma exchange and immunoadsorption in refractory LN is minimal, based mainly on single case reports and observational studies. A randomized, controlled trial conducted by the Lupus Nephritis Collaborative Study Group examining the efficacy of plasma exchange when added to standard therapy in patients with severe LN failed to show improvement in clinical outcomes.[58] In a study of eight patients with refractory disease who underwent immunoadsorption and had concomitant CYC, all patients had reductions in creatinine and urinary protein excretion.[59]

Several studies have reported that plasma exchange in antiphospholipid syndrome and its associated complications may be of benefit.[60,61] Extracorporeal therapies have sometimes been considered for patients with contraindications to standard therapy including severe infection risk and significant leucopenia as well as other indications such as pulmonary hemorrhage.[60]

Investigational biologic therapies

A number of clinical trials on the efficacy and safety of emerging novel biologic therapies are under way. Access to such agents are limited to trials at this stage and consideration of trial therapy may be a therapeutic option for those patients with refractory LN who have failed to respond to or are intolerant of the above regimens. It should be noted that the efficacy of these novel biologic agents has not been studied in a cohort of patients with refractory disease.

B cell survival factors

B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL) are key survival cytokines for B cell survival and development. They bind to three different receptors: transmembrane activator and calcium-modulating cytophilin ligand interactor (TACI), the B cell maturation antigen (BCMA) and the BAFF receptor (BAFF-R).[62]

Overexpression of BLyS promotes survival of B cells (including autoreactive B cells), whereas inhibition of BLyS results in autoreactive B cell apoptosis. Elevated circulating BLyS and APRIL levels are seen in SLE and

correlate with increased SLE disease activity and elevated anti-double stranded DNA (anti-dsDNA) antibody concentrations.[63,64]

Belimumab is the first new drug approved by both the Food and Drug Administration (FDA) and by the European Medicines Agency for antibody-positive SLE in decades. Belimumab is a human monoclonal IgG1 antibody that binds to and inhibits soluble B-lymphocyte stimulator protein. It was found to be superior compared with placebo in two Phase III placebo-controlled trials, BLISS-52 and BLISS-76 in addition to standard therapy in 1684 serologically positive SLE patients.[65,66]

Although patients with severe LN were excluded from this study, a pooled post-hoc analysis of the cohort indicated that over 52 weeks there was a significant reduction in the frequency of renal flares and a tendency for greater reduction in proteinuria.[67] A phase 3 randomized controlled trial is currently underway to evaluate the efficacy of belimumab in LN (NCT01639339).

Co-stimulation blockade

Abatacept is a soluble Fc CTLA-4 fusion protein that prevents T cell activation by competing with CD28 for binding to CD80-86, a costimulatory signal required for T cell activation.

Evidence from the Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis (ACCESS) trial, failed to demonstrate any benefit of abatacept plus low dose CYC compared to placebo plus low dose CYC.[68] Interestingly, patients on the abatacept arm who reached complete renal remission at 6 months were followed for another 6 months without any maintenance immunosuppressive therapy. At 12 months, the patients in the abatacept arm had fewer renal flares. Whilst the study was not powered to test abatacept for maintenance of remission, these results suggest abatacept may be worth investigating as a maintenance agent for flare minimization.

Recently completed, the largest randomized controlled trial in LN (NCT01714817) had 405 participants and sought to compare abatacept to placebo when added to standard of care therapy consisting of mycophenolate and steroids. Disappointingly, there was no difference in the primary end point of complete renal remission at week 52 (abatacept 35% and placebo 33%, p=0.73).[69]

Epratuzumab

Epratuzumab is a humanized monoclonal antibody of the IgG1 class that targets CD22 on B cells, disrupting the B cell receptor signaling complex and resulting in modulation of B cell activity without substantial reductions in the number of peripheral B cells.[70] The EMBODY 1 and EMBODY 2 phase III multicenter randomized placebo-controlled double-blinded trial was conducted in patients with moderately to severely active SLE, though excluded patients with LN.[71] Treatment with epratuzumab in conjunction with standard therapy did not result in improved outcomes at week 48 when compared to placebo. Phase III trials in LN have yet to be conducted.

Atacicept

Atacicept is a recombinant fusion protein comprising the extracellular domain of the TACI receptor joined to a human IgG1 Fc domain.[62] Atacicept blocks B cell stimulation by both BLyS and APRIL pathways. In 306 patients with active, autoantibody positive non-renal SLE receiving standard of care, there was a trend towards efficacy when compared to placebo.[72]

Anifrolumab

Interferon-alpha appears to have a central regulatory role in SLE and LN and is therefore a potential treatment target. Recent phase III clinical trial, the TULIP-1 study, examined the efficacy of anifrolumab, a monoclonal antibody against IFN-alpha receptor 1, versus placebo in patients with moderately-severely active auto-antibody-positive non-LN SLE and, failed to meet the primary endpoint of a reduction of disease activity as measured by the SLE Responder Index (NCT02446899). The TULIP-2 trial and TULIP-LN1 trial, examining the efficacy of anifrolumab in active proliferative LN, is ongoing (NCT02446912, NCT02547922).

In summary, LN that is refractory to first line induction therapies is associated with worse long-term renal and patient outcomes. The traditional clinical parameters used to assess clinical response cannot reliably distinguish immunological activity from persistent damage and scarring. A number of therapeutic strategies may be tried for patients with refractory disease, including using alternative first line induction agents, rituximab, calcineurin inhibitors or enrolment in clinical trials of new targeted therapeutics. Further evidence is needed to advance this topic forward from opinion-based to evidence-based recommendations. Only then can the significant clinician uncertainty that dominates the management of refractory LN be adequately addressed.

Disclosure

The authors report no conflicts of interest in this work.

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