Rituximab in Systemic Lupus Erythematosus and Lupus Nephritis

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**Abstract**
Treatment options for systemic lupus erythematosus (SLE) and lupus nephritis (LN) have high associated morbidity and mortality. Side effects, particularly from long-term corticosteroid usage, limit patient adherence, with subsequent impacts on treatment efficacy. In addition, a subset of patients with SLE/LN fails to respond to current standard immunotherapy. There is an urgent need to develop steroid-sparing treatment regimens as well as novel therapies for the management of refractory disease. Rituximab is a chimeric mouse/human monoclonal antibody directed against the B cell CD20 receptor. It has been used in the treatment of non-Hodgkin’s lymphoma for over 30 years and has an excellent safety profile. Recent work has demonstrated a role for B cell depletion therapy in the management of autoimmune disease, and the efficacy of rituximab in many observational studies in SLE and LN has been noted. Unfortunately, two large randomised controlled trials evaluating rituximab for the treatment of renal and non-renal lupus failed to meet their primary endpoints. Reasons for this have been discussed extensively within the medical community with a general consensus that trial design (steroid use, trial size and endpoints used) was the principal reason for the failures. Despite the lack of trial evidence, clinical experience means many physicians firmly believe in the value of rituximab in SLE/LN treatment and have continued to use it in their clinical practice. Recent work has demonstrated the efficacy of rituximab as a steroid-sparing agent and as an alternative therapeutic option for refractory SLE/LN. There are two further rituximab randomised controlled trials planned/started in LN – one using a steroid-minimising regimen with rituximab for induction and one evaluating rituximab for LN refractory to 6 months standard of care treatment. Rituximab remains a problematic drug in lupus and LN – it is a biologically plausible agent with a huge amount of supportive anecdotal clinical data. Yet the completed trials have been negative to date despite clinical experience strongly suggesting efficacy. It is hoped that the two new trials will determine the role for rituximab, at least in LN.

**Introduction**

B cells play a pivotal role in the development and maintenance of autoimmune disease [1]. Systematic lupus erythematosus (SLE) is a prototypic autoimmune disorder associated with a diverse array of pathogenic auto...
antibodies directed towards cytoplasmic and nuclear cell compartments. Multiple systems can be involved, with subsequent immune complex deposition driving complement activation, inflammation and end-organ damage. Between 40 and 70% of patients with SLE develop lupus nephritis (LN), and the consequences can be devastating [2]. Even with aggressive immunosuppressive therapy, rates of end-stage renal disease over 5–10 years are in the region of 10%, a figure that has disappointingly remained largely unchanged over the last 30 years [3, 4]. Despite the introduction of newer immunosuppressive agents such as mycophenolate mofetil (MMF), treatment of SLE and LN remains challenging. Current standard therapeutic regimens are associated with significant side effects and cumulative toxicity including premature ovarian failure, increased risk of future malignancies and teratogenicity. Prolonged corticosteroid use is associated with increased risk of premature cardiovascular disease and a 2- to 4-fold increased risk of coronary events in SLE [5]. In addition, cosmetic changes associated with prolonged steroid use may contribute to non-adherence, which is a recognised cause of treatment failure [6]. Consequently, there has been a strong desire amongst physicians to develop new and innovative treatment regimens to help improve prognosis and reduce the burden of iatrogenic morbidity [7]. Given the key role of B cells in the development of a dysregulated immune response, a strong argument exists for the use of B cell-depleting agents in the management of SLE and LN.

**Rituximab**

Rituximab is a chimeric mouse/human monoclonal antibody directed against the CD20 receptor of the B cell. CD20 is expressed on immature, mature and activated B cells, but not plasma cells, stem cells or pro-B cells. Rituximab acts via antibody-dependent cell-mediated cytolysis, complement-dependent cytotoxicity and apoptosis to effectively deplete B cells for 6–9 months in over 80% of patients [8]. Importantly, rituximab has been extensively used in the treatment of non-Hodgkin's lymphoma [9] and has an excellent safety record. Adverse events following rituximab use are minimal and include infusion-related reactions and increased risk of infection [7, 10]. Hence, there was confidence in transferring its use to autoimmune diseases, and rituximab has been successfully used in the treatment of rheumatoid arthritis, ANCA-associated systemic vasculitis and primary immune thrombocytopenic purpura [11–13].

**Rituximab in SLE**

SLE is an archetypal antibody-mediated disease and hence promoting B cell depletion appears to target a plausible critical pathophysiological pathway. Early case reports and then case series suggested benefit in the treatment of SLE (reviewed in [14]). This led to the development of the EXPLORER trial (a randomised, double-blind, placebo-controlled exploratory phase II/III SLE evaluation of rituximab) [15]. The EXPLORER trial recruited 257 patients aged 16–75 years with moderate and severe SLE who met four of the American College of Rheumatology (ACR) criteria for SLE including a positive test for antinuclear antibodies, active disease at screening [defined as ≥1 domain with a British Isles Lupus Assessment Group (BILAG) A score (severe activity) or ≥2 domains with a BILAG B score (moderate disease activity)], and stable use of one immunosuppressive drug at entry which was continued throughout the trial (methotrexate, azathioprine or MMF). 57% of participants were corticosteroid dependent. Exclusion criteria included severe central nervous system or organ-threatening lupus, any other active conditions requiring significant use of immunosuppressives, previous B cell depletion therapy, and deranged hepatic or haematological serum parameters. Patients were randomised at a 2:1 ratio to receive intravenous rituximab or placebo on days 1, 15, 168 and 182 (in addition to prednisolone and baseline immunosuppressive therapy). The primary endpoint was the effect of placebo versus rituximab in achieving and maintaining clinical response at week 52, assessed using the BILAG index organ system scores.

Unfortunately the EXPLORER trial failed to meet its primary endpoint. Potential reasons for this include inadequate trial size, concomitant background immunosuppressive/high-dose corticosteroid usage and apportion of endpoints which were unable to discriminate between minor disease fluctuations and meaningful clinical response [16]. However, on further examination, a post hoc analysis of this trial suggested rituximab reduced the risk of a subsequent first severe flare and lower mean severe flare rates [17]. In addition, efficacy signals were detected in subsets of patients including African Americans and Hispanics [15].

It is worth briefly reviewing the contrasting fate of the anti-BLys antibody, belimumab. B lymphocyte-stimulating factor (BLyS) is a cytokine produced predominantly by myeloid cells. BLyS is necessary for B cell maturation, survival and immunoglobulin production [16]. Belimumab, a soluble anti-BLys monoclonal antibody was...
shown to lead to superior results when added to standard of care, compared to standard of care alone, in two large randomised controlled trials in patients with active SLE (n = 865 and 819) [18, 19]. These results led to belimumab being granted regulatory approval for the treatment of patients with antibody-positive SLE with active disease despite treatment with standard drugs.

These trials were designed slightly differently to the EXPLORER trial; they used large numbers of patients and aimed for a smaller delta. A composite endpoint was used, the SLE Responder Index (SRI) response rate at week 52 [which is largely driven by the SLE Disease Activity Index (SLEDAI) score], and inclusion criteria were narrower – only seropositive patients were included and they had to have evidence of activity as judged by a SLEDAI score of at least 6. Key exclusions were central nervous system lupus or active LN. Participants were again continued on previous immunosuppressive therapy, but adjustments to background immunosuppressants were more strictly controlled and time limited, including increases to corticosteroid doses in the first 6 months and increases to other immunosuppressants in the first 16 weeks.

Interestingly, a post hoc analysis of the belimumab studies demonstrated that belimumab is most effective in the subset of patients with high disease activity (e.g. high titres of anti-dsDNA antibodies and low complement levels) [20]. Rituximab also reduces anti-dsDNA levels and increased complement levels [15, 21], suggesting that the problem might not be the drug, but instead the trial design.

**Rituximab in LN**

Given the many case series and registry reports of use in refractory LN, it was reasonable to evaluate rituximab in a clinical trial setting for the treatment of LN. LN is classified according to the ISN/RPS criteria [22]. Treatment is generally reserved for those with proliferative LN (class III-a or a/c or class IV-S a or a/c or class IV-G a or a/c where a = active, c = chronic, S = segmental and G = Global – all referring to glomerular lesions), and some guidelines recommend treatment for class V LN only if associated with nephrotic range proteinuria [23]. Following the failure of the EXPLORER trial (non-renal SLE) to meet its primary endpoint of reduced clinical activity without subsequent flares [15], guidelines for steroid use in the LUNAR trial (Lupus Nephritis Assessment with Rituximab) were more stringent. However, rituximab was again used as an add-on to standard of care with MMF and corticosteroids. Unfortunately, the LUNAR trial also failed to meet its primary endpoint of 20% superiority in the proportion of patients achieving complete or partial remission at 52 weeks [21].

Trial design is again likely to have contributed to its lack of success. The use of corticosteroids as well as MMF as background in both the rituximab and control group may have masked any incremental benefit of rituximab. In addition, the LUNAR trial was powered for a composite endpoint of complete renal remission (CR) and partial renal remission (PR), but weighted towards a greater proportion of CR rather than PR (powered at 90% to detect a 20% increase in CR and a 5% increase in PR). This meant the study was underpowered to detect the 15% increase in the proportion of PR actually seen or doubling of the number of rituximab-treated patients who achieved a PR compared to standard therapy (31 vs. 15%). Ironically, the overall delta was 11%, which was larger than that seen in the belimumab trials but in a much smaller trial – so the difference was not significant. However, there are reasons to consider that the rituximab arm showed benefit. The data at 78 weeks of follow-up strongly suggest that rituximab was having a beneficial effect as there were significant differences in the proportion of patients who achieved proteinuric remission and who did not require additional immunosuppression (reviewed in [24]). Repeat renal biopsies, had they been done, might have demonstrated histological remission at 1 year which we have suggested may precede biochemical remission which can take a long time as suggested by these data. What is clinically important is that despite the failure of these two rituximab randomised controlled trials to achieve their primary endpoint, many clinicians continue to use rituximab in daily practice, based on their personal experience, the large case series and registry data, and the long-term outcome data in the LUNAR trial [1, 14, 25]. This contrasts with the clinical reality for belimumab, where despite the positive trial data there has been relatively slow uptake of use of this drug in lupus, possibly because of difficulty in knowing which patients would benefit most and due to the lack of data on use in LN.

We have developed an alternative way of using rituximab – we chose to use rituximab as an ‘instead of’ drug rather than an add-on and (more radically) opted to omit oral steroids. The rationale was based on experience in renal transplantation where the introduction of biological agents at induction has led to the development of steroid-avoiding regimens. Importantly, in transplantation such an approach has led to better outcomes both in
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3. Croca SC, Rodrigues T, Isenberg DA: Assessing a Goal, NCT01673295), another ongoing trial led by Houssiau and colleagues, is aiming to evaluate the addition of rituximab in patients who have had 6 months of standard of care but failed to achieve a complete remission. This trial will formally assess whether rituximab is effective in refractory LN.

So, several years after the first reports of rituximab as the new ‘wonder’ drug for lupus and LN, it remains unlicensed but quite widely used – in that respect it is no different from MMF, cyclophosphamide or azathioprine. Guidelines on the management of LN suggest it can be used (added in) where standard of care with MMF or cyclophosphamide has failed in the treatment of proliferative LN [29–31].

Conclusion

Whilst no randomised controlled trial presently exists demonstrating the efficacy of rituximab in treating SLE and LN, it is clear that clinicians and scientists have a strong belief in its potential role based on biological plausibility (the key role of B cells in lupus pathogenesis), the influence on serology and surrogate markers of disease activity, and numerous cohort and registry reports. Part of the drive to use rituximab is that it has a strong and long safety profile and that current treatment options have a high associated morbidity and mortality, and side effects experienced by patients limit adherence and treatment efficacy. There is an unmet need for both steroid-sparing treatment regimens and new novel therapies to treat refractory cases: rituximab is an exciting therapeutic option which has demonstrated success in both of the above. Further work is needed to elucidate the real value of B cell depletion through rituximab.

References


10 Turner-Stokes T, et al: The efficacy of repeat-
ed treatment with B-cell depletion therapy in
systemic lupus erythematosus: an evaluation.
therapy with rituximab in patients with rheu-
matoid arthritis. N Engl J Med 2004;350:
2572–2581.
12 Ferraro AJ, et al: Effective therapeutic use of
rituximab in refractory Wegener’s granulo-
matosis. Nephrol Dial Transplant 2005;20:
623–625.
13 Patel VL, et al: Outcomes 5 years after re-
response to rituximab therapy in children and
adults with immune thrombocytopenia.
14 Favas C, Isenberg DA: B-cell-depletion ther-
apy in SLE – what are the current prospects for
its acceptance? Nat Rev Rheumatol 2009;5:
711–716.
15 Merrill JT, et al: Efficacy and safety of ritux-
imab in moderately-to-severely active sys-
 temic lupus erythematosus: the randomized,
double-blind, phase II/III systemic lupus ery-
thematosus evaluation of rituximab trial. Ar-
16 Thanou A, Merrill JT: Treatment of systemic
lupus erythematosus: new therapeutic ave-
nues and blind alleys. Nat Rev Rheumatol
17 Merrill J, et al: Assessment of flares in lupus
patients enrolled in a phase II/III study of
rituximab (EXPLORER). Lupus 2011;20:709–
716.
18 Furie R, et al: A phase III, randomized, place-
bo-controlled study of belimumab, a mono-
clonal antibody that inhibits B lymphocyte
stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum 2011;63:
3918–3930.
19 Navarra SV, et al: Efficacy and safety of beli-
mumab in patients with active systemic lupus
erythematosus: a randomised, placebo-con-
trolled, phase 3 trial. Lancet 2011;377:721–
731.
20 van Vollenhoven RF, et al: Belimumab in the
treatment of systemic lupus erythematosus:
high disease activity predictors of response.
21 Rovin BH, et al: Efficacy and safety of ritux-
imab in patients with active proliferative lu-
pus nephritis: the Lupus Nephritis Assess-
ment with Rituximab study. Arthritis Rheum
2012;64:1215–1226.
22 Weening JJ, et al: The classification of glomer-
ulonephritis in systemic lupus erythematosus
23 Radhakrishnan J, Cattrán DC: The KDIGO
practice guideline on glomerulonephritis:
reading between the (guide)lines – applica-
tion to the individual patient. Kidney Int
2012;82:840–856.
24 Lightstone L: The landscape after LUNAR:
rituximab’s crater-filled path. Arthritis Rheum
2012;64:962–965.
25 Gunnarsson I, Jonsdottir T: Rituximab treat-
ment in lupus nephritis – where do we stand?
26 Lightstone L: Minimising steroids in lupus
nephritis – will B cell depletion pave the way?
27 Condon MB, et al: Prospective observational
single-centre cohort study to evaluate the ef-
ectiveness of treating lupus nephritis with
rituximab and mycophenolate mofetil but no
1286.
28 Ezeonyeji AN, Isenberg DA: Early treatment
with rituximab in newly diagnosed systemic
lupus erythematosus patients: a steroid-sparing
regimen. Rheumatology (Oxford) 2012;
51:476–481.
29 Bertsias GK, et al: Joint European League
against Rheumatism and European Renal As-
sociation-European Dialysis and Transplant
Association (EULAR/ERA-EDTA) recom-
endations for the management of adult and
paediatric lupus nephritis. Ann Rheum Dis
30 Hahn BH, et al: American College of Rheu-
matology guidelines for screening, treatment,
and management of lupus nephritis. Arthritis
Care Res (Hoboken) 2012;64:797–808.
31 Kidney Disease: Improving Global Out-
comes (KDIGO) Glomerulonephritis Work-
232.