

Treatment options for lupus nephritis: what lessons have we learned from the LUNAR study?

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KEYWORDS: anti-B cell therapy ■ autoantibodies ■ chronic kidney disease ■ complement ■ glomerulonephritis

The LUNAR trial is a large, placebo-controlled randomized clinical study that compared rituximab versus placebo added to mycophenolate mofetil (MMF) and corticosteroids for the initial treatment of proliferative lupus nephritis (LN) [1]. Many in the lupus community anticipated that monoclonal antibody therapy targeting B cells would dramatically improve the treatment of LN. After all, a number of reports suggested rituximab was of benefit in refractory LN, although these were mainly small, uncontrolled nonrandomized trials or case series [2–5]. Excitement turned to disappointment when LUNAR did not show that rituximab did better than placebo. Despite these results, the LUNAR trial should not be viewed as the end of anti-B-cell therapies for LN, but as a tool to inform future LN trials.

The trial design of LUNAR has evoked considerable discussion in the lupus community. It has been criticized because it added rituximab to an already effective standard-of-care type therapy, was powered for improvement in complete but not partial remission, and was too short in duration [6]. It is possible to view these design aspects not as weaknesses, but as metrics for new trials. For example, achieving complete remissions in LN is of critical importance for the long-term preservation of kidney function, and prevention of chronic kidney disease and its associated cardiovascular morbidity. While it is certainly preferable to have a partial remission than no remission at all [7], setting the bar high by making complete remission the goal is laudable.

While MMF plus corticosteroids is considered an effective regimen for LN, the reality is that this therapy, and other current therapies, are only modestly successful and complete remission

rates are unacceptably low. Therefore, the addition of other agents to standard immunosuppressive regimens is a reasonable approach to try and increase success.

Similarly, although longer follow-up in LUNAR may have shown continued and possibly significant separation between rituximab and placebo groups, it can be argued that to preserve renal mass, minimize parenchymal fibrosis and avoid the development of chronic kidney disease, the inflammation of LN should be controlled as quickly as possible. The lupus community should not be content with waiting 1–2 years to achieve complete or partial remission.

In LUNAR, there was a trend toward increased partial remissions in black patients treated with rituximab. This finding is not unlike that seen in the ALMS study, where non-Caucasian non-Asian patients had a better response to MMF [8]. These favorable signals suggest that trials to compare rituximab (or other induction therapies) to conventional therapies in specific racial/ethnic populations are warranted.

Although increasing complete remissions of LN is important, the toxicity of our current therapies is also of significant concern. Reducing toxicity without compromising outcomes should be a goal in LN management. In particular, it would be of great benefit if the treatment of LN could proceed without prolonged use of corticosteroids. Rituximab is generally considered to have a relatively low side-effect profile and was well tolerated even when added to MMF and corticosteroids [1,9]. In an effort to attenuate toxicity without losing efficacy, rituximab has been tried as an LN induction therapy on its own, and not added on to a current standard-of-care regimen. Treatment was initiated with rituximab and a short course of pulse corticosteroid



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(methylprednisolone 500 mg × 2) at the treating physician’s discretion, and was followed by maintenance with MMF [10]. This approach showed promise, appeared to be relatively safe and was possibly steroid-sparing. Any new induction treatment of LN needs to not only demonstrate efficacy in the short term, but must also be shown to preserve kidney function as well as cyclophosphamide in the long term, something that is not yet clear even for MMF [11,12].

As mentioned earlier, the published experience of treating refractory LN off-label with rituximab has generally been positive [2-5]. These data are, however, difficult to interpret even beyond the fact that they were not derived from prospective randomized trials. Additional concerns include potential publication bias of positive outcomes, lack of a standard definition of refractory LN, variable rituximab dosing and variable use of other immunosuppressive drugs. Also, it is counterintuitive to expect rituximab to be beneficial in difficult to treat disease, when it provided no benefit beyond that of corticosteroids and MMF in the many incident disease patients who participated in LUNAR, and who might have been expected to be more responsive to therapy. The simplest explanation is that rituximab does not attack pathways of lupus activity that are not already attacked by MMF and corticosteroids.

So why would rituximab become effective in LN that has failed MMF (or cyclophosphamide) and corticosteroids? A clear mechanism has not surfaced. A potential explanation may be found in the efficacy of B-cell depletion by rituximab. Circulating B cells are more readily depleted than B cells that are in sequestered spaces such as germinal centers and marginal

zones [13]. Perhaps after several rounds of cytotoxic therapy these sequestered B cells become more susceptible to rituximab. If these cells are important in the pathogenesis of LN, rituximab may then have a bigger impact. Regardless of the mechanism, there is now such a prevailing belief in the efficacy of rituximab in refractory LN that a controlled trial of rituximab in patients who have been unresponsive to multiple courses of therapy and/or multiple treatment types should probably be undertaken.

One of the more difficult to explain results of LUNAR was the disassociation between serologic improvement in the rituximab-treated patients and renal and nonrenal systemic lupus erythematosus outcomes. Specifically, the rituximab-treated patients showed a significant increase in serum complement component C3 and C4 levels, and a significant fall in anti-double-stranded DNA autoantibody levels, but no increase in LN remissions [1]. This pattern was recapitulated in the EXPLORER trial, a study of rituximab versus placebo added to background immunosuppression in nonrenal systemic lupus erythematosus [14]. An important gap in the therapeutic targets of rituximab is the autoantibody-producing plasma cell. The LUNAR and EXPLORER results suggest that the plasma cells responsible for some autoantibodies in systemic lupus erythematosus, such as anti-double-stranded DNA, are short-lived and need to be replenished frequently by B cells, which are killed by rituximab. Autoantibodies from long-lived plasma cells, such as anti-SM and anti-RNP, are not readily affected by rituximab treatment [13], and may be responsible for continuing renal injury, even if anti-double-stranded DNA

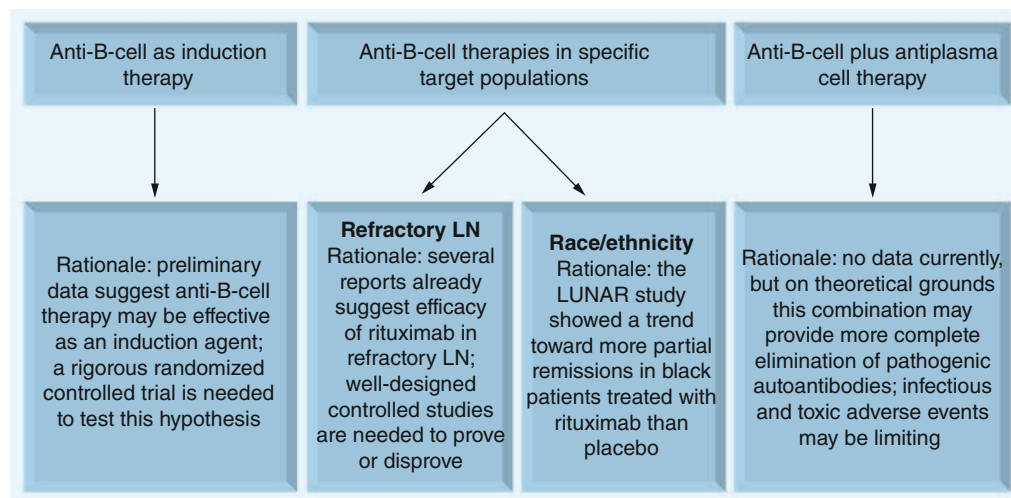


Figure 1. Suggested next steps for anti-B-cell therapies in lupus nephritis.
 LN: Lupus nephritis.

titers are low. Admittedly, this does not explain the discordant C3 and C4 results very well; perhaps serum complement levels are simply not sufficient to follow what is happening locally within the kidney [15]. Nonetheless, strategies to deplete autoreactive plasma cell precursors with rituximab, combined with a drug that depletes plasma cells, may be an effective approach to LN. One such agent is bortezomib, a proteasome inhibitor to which plasma cells appear to be sensitive [16].

In conclusion, the LUNAR design was high risk because its goal was complete, as opposed to any level of LN remission. Although the gamble did not work for LUNAR, the prize is so important it is definitely worth considering when designing future LN trials with new agents.

The discussion and controversies surrounding LUNAR have also provided the seeds for new ways to use anti-B-cell therapies in LN that need to be tested. This ample crop of ideas is summarized in FIGURE 1. Many of us are optimistic that anti-B cell therapies will be useful in LN, but we need to find the right niche for these therapies.

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