

Dialogue: Early predictors of long-term lupus nephritis outcomes: looking into the future

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Patients with lupus nephritis (LN) remain difficult to treat, and any patient characteristics that allow physicians to better predict outcomes are likely to improve patient care. Clinical and serological factors that present early in the course of treatment can predict long-term outcomes, and are, therefore, important to identify. The current study by Dall'Era *et al*¹ adds to a growing literature regarding the early predictors of long-term outcomes in patients with LN.

The study analysed data from Aspreva Lupus Management Study (ALMS) extending to 36 months post induction to assess those factors determining either complete renal remission (CR) or treatment failure (TF). They assess features at the time of trial entry and end of induction, and response to therapy during induction. Complete response could occur at any time during the maintenance phase.

Among the 370 subjects who entered the trial, only non-Hispanic ethnicity was associated with a higher likelihood of CR. Several factors related to induction were independently associated with a greater likelihood of TF, including the positive anti-dsDNA at trial entry, failure to reduce anti-dsDNA within 8 weeks, failure to reduce urine protein:creatinine ratio (UP/C) by >25% within 8 weeks.

Among the 227 subjects who entered the maintenance phase, baseline eGFR >90 mL/min/1.73 m² was associated with CR, and perhaps not surprisingly, UP/C>1 g/g at the end of induction was associated with a lower likelihood of CR. Interestingly, induction treatment with intravenous cyclophosphamide (IVC)—versus mycophenolate mofetil (MMF)—was associated with a lower likelihood of TF. Lack of treatment with antimalarials, positive anti-DNA at the end of induction and, as with the starting cohort, failure to reduce anti-dsDNA or UP/C during the first 8 weeks of induction were independently associated with a greater likelihood of TF.

The finding of non-Hispanic ethnicity predicting CR at trial entry, but not at entry into the maintenance phase, is difficult to interpret. It may suggest that those who did not respond in induction may have responded later, but they were not followed beyond the induction phase. It is possible that medications may take longer to work in the Hispanic population; this requires further study.

The current study builds on our understanding of longer-term outcomes in LN. The long-term follow-up of the Euro-Lupus Nephritis Trial²⁻³ and MAINTAIN trial⁴ also notes that reduction in proteinuria is the most significant predictor. In Euro-Lupus patients, proteinuria dropped significantly at 3 and 6 months compared with baseline in only patients with good 10-year outcome (defined as creatinine \leq 1.4).² The same was demonstrated in a shorter outcome study of the same patients, where proteinuria of <0.8 g/day was the single best predictor of good long-term renal outcomes at 7-year follow-up (sensitivity 81%, specificity 78%), and where neither creatinine nor haematuria improved prediction.³

Study of 10-year outcomes in the European MAINTAIN Nephritis Trial, which failed to show any difference between MMF and Azathioprine (AZA) as maintenance drugs after IVC induction by the Euro-Lupus protocol, identified a 'prompt and dramatically' reduced proteinuria as the only factor predictive of good long-term renal outcome (defined as last serum creatinine \leq 120% of baseline). The positive predictive value of a reduction in proteinuria to \leq 0.5 g/day at 3, 6 and 12 months was 89%, 90% and 92%, respectively. Notably, the negative predictive value of proteinuria >0.5 g/d at these time points was low. This suggests that even in those who did not reduce their proteinuria in this European (mainly Caucasian) population, long term outcomes were good at 10 years.



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In addition to the corroborative findings regarding proteinuria, the current study has other interesting results pertaining to long-term outcomes. It raises the question whether those who respond to induction therapy with IVC might have better long-term outcomes compared with MMF. As the authors note, IVC induction showed a trend to improved efficacy and reduced TF in the ALMS maintenance study.⁵ Unfortunately, the relative role of the maintenance agents are not assessed. This is a major limitation of this study, which is particularly relevant in light of the greater effectiveness of MMF over AZA in ALMS. The authors state that they were most interested in preinduction and end-of-induction factors as predictors, but we cannot discount the effect of drugs used during the maintenance phase of the study. This study also supports the contention that antimalarials are important in the management of patients with lupus, particularly those with LN.^{6–8}

What does this mean to the practising clinician? As the authors note, for those who have a robust early response, reassurance can be given to these patients. In those who do not respond early, one may be more justified in considering a change in therapy. These findings also have implications regarding future trial design. One may ask whether or not a reduction in a surrogate marker predicts better long-term outcomes. For example, though the Lupus Nephritis Assessment with Rituximab (LUNAR) trial did not show a benefit in the primary outcome of a rituximab-based regimen, those who received rituximab did have greater reduction in their anti-DNA antibody levels,⁹ a finding associated with lower TF in the current study. It will be interesting to see if longer-term follow-up of the LUNAR patients suggests similar findings to the current study.

In conclusion, it is likely that studies like the current one will provide us with expanding evidence that will help the physician make clinical judgements. In turn,

this may allow for the optimisation of long-term treatments for this patient population, one which so frequently has limited options.

Competing interests None declared.

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