

Calcineurin Inhibitors in the Treatment of Lupus Nephritis: A Hare Versus Turtle Story?

Isabelle Ayoub and Brad H. Rovin

Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio

J Am Soc Nephrol 28: 3435–3437, 2017.

doi: <https://doi.org/10.1681/ASN.2017080830>

In this issue of the *Journal of the American Society of Nephrology*, we are given the eagerly anticipated follow-up of a large cohort of Chinese patients who took part in a randomized, controlled trial that compared multitarget therapy, a combination of a calcineurin inhibitor (CNI) plus mycophenolate mofetil (MMF), with standard of care for induction of remission in lupus nephritis (LN).¹ In the induction trial,² patients were randomized to 6 months of intravenous cyclophosphamide (0.5–1.0 g/m² body surface area per month) or tacrolimus (4 mg/d) plus MMF (1.0 g/d). All patients received pulse methylprednisolone (0.5 g/d) for 3 days followed by prednisone (0.6 mg/kg per day) tapered to a maintenance dose of 10 mg/d. After 6 months, 46% of the patients treated with the multitarget regimen were in complete remission compared with 26% of those treated with cyclophosphamide ($P < 0.001$). Patients who achieved a complete or partial remission (60% of the original cohort) were then recruited for the 18-month follow-up study. The cyclophosphamide group was converted to azathioprine (2 mg/kg per day) maintenance, and the multitarget group continued on reduced doses of tacrolimus (3 mg/d for 6 months and then 2 mg/d for the remaining 12 months) and MMF (750 mg/d for 6 months and then 500 mg/d for 12 months). Oral prednisone (10 mg/d) was continued in all patients. At the end of follow-up, there was no difference in cumulative LN flare rate between maintenance treatments. As expected, patients continued to go into complete remission over time during maintenance therapy.³ At 18 months, there was no difference in the proportion of complete responders in the multitarget and the cyclophosphamide-azathioprine groups.

The choice of azathioprine rather than MMF for maintenance in the control group is curious. Although azathioprine was found to be comparable with MMF for maintenance of LN remission in European cohorts,⁴ the Aspreva Lupus Management Study Maintenance Trial⁵ showed MMF to be superior to azathioprine in a large, multiethnic LN cohort that included a significant proportion of Asian subjects. Because

MMF was used in the experimental arm of this trial and azathioprine was used in the control arm, the two groups are not strictly comparable, and the outcome of the experimental arm could have been favorably influenced. Because there was no difference between the outcomes, this does not seem to have occurred. Furthermore, given the remarkably low relapse rates for each trial arm compared with historically reported relapse rates with MMF or azathioprine, it is unlikely that the control group would have done better than the test group if MMF had been used.

Although the induction trial showed that multitarget therapy induced complete (and partial) remissions more quickly than standard of care, the maintenance trial showed that standard of care caught up within 6 months and remained caught up for the duration of follow-up (Figure 3 and Supplemental Figure 2 in ref. 1). This raises the question of whether multitarget therapy is truly more effective than conventional treatment. The answer is maybe, because several studies suggest that an early therapeutic response in LN predicts good long-term kidney outcomes.^{6–8} In these retrospective studies, early responses included complete remissions, partial remissions, and declines in proteinuria of at least a 50% after 3–6 months of treatment. However, these studies did not compare the long-term outcomes of 6- and 12-month complete responders, and other studies have shown that a decline in proteinuria to about 800 mg/d after 12 months of therapy also predicts good long-term kidney health.^{4,9} Nonetheless, it is conceivable that, by increasing complete remissions at 6 months, multitarget therapy may preserve kidney function better than standard of care. This presumes that a clinical complete remission, which by and large means a reduction in proteinuria below a few hundred milligrams per day, reflects a concomitant resolution of renal inflammation and injury. Kidney biopsies after 6 months of standard of care LN treatment do not support this but instead, show a significant discordance between clinical and histologic complete remission.¹⁰ Basing LN remission mainly on proteinuria introduces even more uncertainty when treatment includes a CNI, because in addition to immune mechanisms, CNIs reduce proteinuria through nonimmune mechanisms. These include reduction of glomerular perfusion pressure and stabilization of the podocyte cytoskeleton.^{11,12} In a worst case scenario, CNIs could conceivably mask proteinuria in the face of ongoing inflammatory renal damage, leading to worse long-term outcomes.

Several observations provide reassurance that the multitarget regimen is not actually fooling us into thinking that LN is better when it is really uncontrolled. After 6 months of induction with tacrolimus and MMF, 14 patients underwent a repeat kidney biopsy. The paired biopsies showed a decrease in activity index from a median of 11.5 pretreatment to 2 post-treatment ($P < 0.001$).² Furthermore, in both the induction and the long-term follow-up studies of multitarget therapy, other indicators of systemic autoimmune activity, such as serum complement levels, double-stranded DNA antibody titers, and systemic lupus erythematosus activity index scores, improved, suggesting that the multitarget approach is effective in controlling autoimmunity. This is

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Brad H. Rovin, Division of Nephrology, The Ohio State University Wexner Medical Center, 395 West 12th Avenue, Ground Floor, Columbus, OH 43210. Email: rovin.1@osu.edu

Copyright © 2017 by the American Society of Nephrology

not surprising, because CNIs suppress T cells, suppress IFN- γ expression, and restore intracellular glucocorticoid levels.^{13,14}

A variation of this multitarget approach to LN management was presented at the 2016 American Society of Nephrology meeting and the 2017 National Kidney Foundation meeting. In the phase 2 Aurinia Urine Protein Reduction in Active Lupus Nephritis Study (AURA-LV), a multiethnic cohort was treated with the novel CNI voclosporin combined with MMF or MMF alone. Both groups received an abbreviated course of corticosteroids. Consistent with the Chinese multitarget trial, the AURA-LV Trial preliminary data showed that patients treated with voclosporin (23.7 mg twice daily) plus MMF (2 g/d) had significantly more complete remissions at 6 months than the controls (32.6% versus 19.3%; $P=0.05$). However, in contrast to tacrolimus plus MMF, this difference in complete remissions was maintained when the trial was continued for an additional 6 months (voclosporin plus MMF: 49% versus MMF: 24%; $P<0.001$). The reasons for this discrepancy are not immediately clear but may be due, in part, to the higher dose of MMF in the AURA-LV Trial or differences in potency or efficacy between the CNIs used. Alternatively, the control group did not show the expected rate of increase in complete remissions during the maintenance phase of the AURA-LV Trial.

An important consideration for LN therapies is safety. Although the multitarget maintenance trial showed fewer adverse events and withdrawals in the multitarget group, a more clinically useful assessment of the adverse event profile may be had by looking at the induction and maintenance phases together. In Supplemental Table 5 in ref. 1, aggregate data on adverse events from both phases are provided. Despite the very low doses of tacrolimus and MMF used, the multitarget approach had a fairly similar overall adverse event profile as standard of care, but it was superior in terms of gastrointestinal side effects, leukopenia, and liver dysfunction. During the induction phase, ten patients withdrew from the multitarget group and three patients withdrew from the cyclophosphamide group due to adverse events, whereas in the maintenance phase, two patients withdrew from the multitarget group and eight patients withdrew from the azathioprine group due to adverse events. During maintenance, only one instance of leukopenia was associated with an infection. Finally, if a CNI is to be considered for the induction and maintenance therapy of LN, it will be important to histologically assess the incidence of CNI-induced nephrotoxicity in patients on chronic multitarget therapy to provide a complete picture of the regimen's risk.

In summary, the multitarget approach to LN induction therapy offers a theoretical advantage over standard of care approaches, because complete remissions occur much more rapidly. However, like the proverbial race between the tortoise and the hare, over time, standard of care catches up and seems to be similarly effective in LN management. Furthermore, short-term safety signals do not overwhelmingly favor one approach over the other. These trials also underscore the limitations of using mainly proteinuria to assess response in LN. Whether jumping off to an early start toward remission with a CNI im-

proves long-term (years) kidney health remains to be seen. Other than renal survival data from extended studies, a reassuring indicator that these early responders may do better in the long run than later responders would be concordance of the clinical and histologic responses as assessed by repeat biopsy after treatment.

DISCLOSURES

B.H.R. is a medical advisor for Aurinia Pharmaceuticals and was an investigator in the AURA-LV trial.

REFERENCES

- Zhang H, Liu Z, Zhou M, Liu Z, Chen J, Xing C, Lin H, Ni Z, Fu P, Liu F, Chen N, He Y, Liu J, Zeng C, Liu Z: Multitarget therapy for maintenance treatment of lupus nephritis. *J Am Soc Nephrol* 28: 3671–3678, 2017
- Liu Z, Zhang H, Liu Z, Xing C, Fu P, Ni Z, Chen J, Lin H, Liu F, He Y, He Y, Miao L, Chen N, Li Y, Gu Y, Shi W, Hu W, Liu Z, Bao H, Zeng C, Zhou M: Multitarget therapy for induction treatment of lupus nephritis: A randomized trial. *Ann Intern Med* 162: 18–26, 2015
- McKinley A, Park E, Spetie D, Hackshaw KV, Nagaraja S, Hebert LA, Rovin BH: Oral cyclophosphamide for lupus glomerulonephritis: An underused therapeutic option. *Clin J Am Soc Nephrol* 4: 1754–1760, 2009
- Tamirou F, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Fiehn C, Ayala Gutierrez MM, Gilboe IM, Tektonidou M, Blockmans D, Ravelingien I, le Guem V, Depresseux G, Guillemin L, Cervera R, Houssiau FA; MAINTAIN Nephritis Trial Group: Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. *Ann Rheum Dis* 75: 526–531, 2016
- Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, Eitner F, Appel GB, Contreras G, Lisk L, Solomons N; ALMS Group: Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 365: 1886–1895, 2011
- Herath N, Ratnatunga N, Weerakoon K, Wazil A, Nanayakkara N: Clinicopathological findings, treatment response and predictors of long-term outcome in a cohort of lupus nephritis patients managed according to the Euro-lupus regime: A retrospective analysis in Sri Lanka. *BMC Res Notes* 10: 80, 2017
- Hanaoka H, Yamada H, Kiyokawa T, Iida H, Suzuki T, Yamasaki Y, Ooka S, Nagafuchi H, Okazaki T, Ichikawa D, Shirai S, Shibagaki Y, Koike J, Ozaki S: Lack of partial renal response by 12 weeks after induction therapy predicts poor renal response and systemic damage accrual in lupus nephritis class III or IV. *Arthritis Res Ther* 19: 4, 2017
- Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, Abramovicz D, Blockmans D, Cauli A, Direskeneli H, Galeazzi M, Gül A, Levy Y, Petera P, Popovic R, Petrovic R, Sinico RA, Cattaneo R, Font J, Depresseux G, Cosyns JP, Cervera R: The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis* 69: 61–64, 2010
- Dall'Era M, Cisternas MG, Smilek DE, Straub L, Houssiau FA, Cervera R, Rovin BH, Mackay M: Predictors of long-term renal outcome in lupus nephritis trials: Lessons learned from the Euro-Lupus Nephritis cohort. *Arthritis Rheumatol* 67: 1305–1313, 2015
- Parikh SV, Alvarado A, Malvar A, Rovin BH: The kidney biopsy in Lupus Nephritis: Past, present, and future. *Semin Nephrol* 35: 465–477, 2015
- Liao R, Liu Q, Zheng Z, Fan J, Peng W, Kong Q, He H, Yang S, Chen W, Tang X, Yu X: Tacrolimus protects podocytes from injury in Lupus

- Nephritis partly by stabilizing the cytoskeleton and inhibiting podocyte apoptosis. *PLoS One* 10: e0132724, 2015
12. Faul C, Donnelly M, Merscher-Gomez S, Chang YH, Franz S, Delfgaauw J, Chang JM, Choi HY, Campbell KN, Kim K, Reiser J, Mundel P: The actin cytoskeleton of kidney podocytes is a direct target of the anti-proteinuric effect of cyclosporine A. *Nat Med* 14: 931–938, 2008
 13. Ikezumi Y, Kanno K, Koike H, Tomita M, Uchiyama M, Shimizu F, Kawachi H: FK506 ameliorates proteinuria and glomerular lesions induced by anti-Thy 1.1 monoclonal antibody 1-22-3. *Kidney Int* 61: 1339–1350, 2002
 14. Suzuki K, Kameda H, Amano K, Nagasawa H, Takei H, Nishi E, Okuyama A, Tsuzaka K, Takeuchi T: Single center prospective study of tacrolimus efficacy and safety in the treatment of various manifestations in systemic lupus erythematosus. *Rheumatol Int* 31: 757–763, 2011
-
- See related article, “Multitarget Therapy for Maintenance Treatment of Lupus Nephritis,” on pages 3671–3678.