Lupus Nephritis: How Far Have We Come, and Where Are We Headed?

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Of all the organ domains involved in systemic lupus erythematosus (SLE), renal disease is associated with the greatest morbidity and mortality. Relative age-adjusted mortality in SLE patients with renal disease compared to those without is greater at every level of renal involvement and stage of CKD.[1,2] Recent data show decreased trends in the burden of end-stage renal disease (ESRD) due to lupus nephritis (LN) in the United States. However, greater than 50% of SLE patients will develop LN and an unacceptably high number (up to 44% of patients with class III or IV LN) progress to ESRD by 15 years requiring renal replacement therapy in the form of dialysis or kidney transplant.[3,4] Continued efforts to elucidate the pathogenesis of LN have not yet resulted in new therapies that can replace the standard-of-care regimens of cyclophosphamide or mycophenolate mofetil plus high-dose corticosteroids. Despite aggressive therapy, the majority of patients will not achieve remission at 6 months, and 30% will continue to have signs of ongoing activity at 1 year.[5,6] In addition, severe side effects from these regimens accrue as therapy becomes prolonged or repeated due to inadequate responses. In this issue of *Advances in Chronic Kidney Disease*, our group of experts touch on important as well as less frequently reviewed topics in LN, emphasizing the ongoing issues and future direction of managing renal disease in lupus patients.

As Drs. Wong and Goral (pp 313-322) point out in their review of LN and kidney transplantation, transplant data provide some welcome relief in that studies demonstrate rare recurrence of clinically significant LN and equivalent patient and allograft survival in SLE transplant recipients.[7] Given the mortality benefit of renal transplantation and better outcomes with pre-emptive transplantation, it is imperative that we address disparities in resources and practices that may prevent SLE patients from early access to transplantation.[8,9] African Americans with ESRD from LN are less likely to undergo transplantation and more likely to die prematurely.[3] The idea that it is better to wait for SLE to "burn out" while remaining on dialysis may be tempered by the knowledge of the recent success of a phase II trial utilizing the multitarget regimen for active LN.[10] Given that multitarget therapy is akin to the kidney transplant maintenance regimen, the decision to wait rather than proceed with transplantation in many cases may be unnecessary.

Currently, we remain far from knowing which therapies may be the most successful or should replace current standard of care. Dr. Hobeika and colleagues (pp 338-350) highlight the potential for biologic therapies given basic and translational research data supporting their role. Many different immunologic pathways have been shown to be significant drivers of disease in LN. The development and testing of biologics to target these key immunologic pathways are ongoing, but none to date have proven efficacy above standard of care. Success of future therapies will hinge on several factors that require ongoing and intensive study. The properties of biologics targeting the same pathway can differ largely in how and to what extent a specific biologic modulates an expected immunologic response. Therefore, continued testing of several biologics directed at the same target will be necessary. For biologics, one size may not fit all, and therapy may need to be individualized based on a patient's immunologic profile. Further knowledge of how biologics modulate the immune system in vivo are relevant for understanding their success or failure. It may be necessary to address several key pathways at once, or in combination, to have significant impact on remission of disease. Challenges with clinical trial design may be limiting progress in identifying new therapies for LN. Addressing these design flaws will lead to greater success in LN clinical trials and more favorable outcomes for our patients with LN.[11]

Immunosuppressive management requires special consideration both in the short- and long-term course of disease in patients with LN. Dr. Maynard and colleagues (pp 330-337) discuss how hormonal and immunologic changes during pregnancy impact lupus disease activity and how different immunosuppressive regimens may be required to promote favorable maternal and fetal outcomes. In the long term, the risks and benefits of continued immunosuppression need to be considered. The cumulative burden of immunosuppression is particularly relevant for our patients with a history of LN. In principle, weaning immunosuppression is a worthy goal; however, Drs. Heinlen and Chakravarty (pp 387-392) highlight the scarcity of data available to inform us what to do in practice. In a National Institutes of Health–sponsored multicenter trial, Dr. Chakravarty and others are studying the extent to which patients need to remain on long-term immunosuppression.

Despite the numerous side effects of high-dose and chronic steroid use, the difficulties in eliminating steroids from treatment regimens continue to remain clinically and theoretically problematic. The clinical benefit of immediately impacting gross inflammation in LN with steroids is clearly driven by the profound ability of steroids to dampen signals and impact a large number of transcription factors operative in multiple cell types of both the innate and adaptive immune system.[12] No single agent to date has such broad effects on different arms of the immune response. Additional agents nonetheless are still required to treat active disease. However, a few recent studies demonstrate the potential for regimens requiring none or far less steroid dosing than ever previously considered.[10,13]

For patients with a history of LN, it would be naïve to attribute progressive kidney disease to failed therapies alone. In part, progressive disease is mediated by not knowing when to act, and how much to do for an individual patient during the course and history of their lupus renal disease. Preventing progression requires a form of vigilance plagued by inadequate tools to instruct physicians on the status and endangerment of kidney tissue at stake. In this regard, Drs. Caster and Powell (pp 351-359) provide the current and future status of LN biomarkers. As many of us caring for patients with LN already know, our current clinical biomarkers fail to adequately

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differentiate active from chronic disease. Patients who attain remission by current clinical trial definitions have no guarantee of quiescent disease activity in the kidney. The level of proteinuria and the absence of active sediment do not guarantee freedom from active class III or IV lesions in LN. Serologic markers such as complement and anti-double-stranded DNA (anti-dsDNA) antibodies can be equally problematic in predicting active disease. Likewise, a normal creatinine may provide assurance about disease progression, but can be deceptive. The surprising degree of renal fibrosis observed on biopsy in some patients with relatively normal creatinine is likely a direct result of undetected ongoing subclinical inflammation and/or repeated flares of disease. As Drs. Stokes and D'Agati (pp 323-329) point out, histologic findings on biopsy have clinical limitations. In their review, they discuss newer approaches to augment pathologic diagnosis and prognostication.

The lack of consistent and reliable noninvasive tests to indicate whether there is active and ongoing inflammation in the kidney has required a more aggressive management approach that includes more frequent renal biopsies. Drs. Ayoub and colleagues (pp 360-368) discuss the "view of the past and the vision of the future" for kidney biopsy in LN. Although impractical, biopsies performed at different time points during the course or history of LN have been quite informative. Recent biopsy studies demonstrate the significant discordance between intrarenal inflammation, active and chronic injury, and our current clinical and laboratory biomarkers for disease.[14,15] Even in patients deemed candidates for immunosuppression withdrawal, studies have demonstrated active lesions upon biopsy.[16] We must remain aware that renal biopsy findings may invoke a complete change in management. Drs. Almaani and Parikh (pp 393-403) point out in their review of Membranous LN that conversion to class V from a proliferative class of LN can occur, and biopsy in these instances may help avoid an escalation in therapy. Drs. Kotzen and colleagues (pp 376-386) discuss the impact of thrombotic microangiopathies and antiphospholipid antibody in lupus renal disease, and Dr. Oliva-Damaso and colleagues (pp 369-375) review lupus podocytopathy. These diseases result in different biopsy findings that require specific therapies that differ from standard of care therapies for LN. Notably, all of these lupus biopsy findings currently remain separate from the International Society of Nephrology and Renal Pathology Society classification of LN.

Novel noninvasive biomarkers of renal response that can instruct on when to intervene, and alter the course of management, are in dire need. The less than perfect performance of our current clinical and laboratory biomarkers tells us that for now we should consider including tissue endpoints in our assessment of response to therapies both for practice and for clinical trials. For clinical trials, testing of various tissues for novel markers and/or indicators of disease and response can only help improve management of lupus kidney disease and help limit progressive kidney damage in the future.

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REFERENCES

1. Danila MI, Pons-Estel GJ, Zhang J, Vila LM, Reveille JD, Alarcon GS. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. *Rheumatology (Oxford).* 2009;48(5):542-545.
2. Mok CC, Kwok RC, Yip PS. Effect of renal disease on the standardized mortality ratio and life expectancy of patients with systemic lupus erythematosus. *Arthritis Rheum.* 2013;65(8):2154-2160.
3. Sexton DJ, Reule S, Solid C, et al. ESRD from lupus nephritis in the United States, 1995–2010. *Clin J Am Soc Nephrol.* 2015;10(2):251-259.
4. Costenbader KH, Desai A, Alarcon GS, et al. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995 to 2006. *Arthritis Rheum.* 2011;63(6):1681-1688.
5. Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971-2015: a systematic review and Bayesian meta-analysis. *Arthritis Rheumatol.* 2016;68(6):1432-1441.
6. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. *Clin J Am Soc Nephrol.* 2017;12(5):825-835.
7. Parikh SV, Rovin BH. Current and emerging therapies for lupus nephritis. *J Am Soc Nephrol.* 2016;27(10):2929-2939.
8. Jorge A, Wallace ZS, Lu N, Zhang Y, Choi HK. Renal transplantation and survival among patients with lupus nephritis: a cohort study. *Ann Intern Med.* 2019;170(4):240-247.
9. Sabucedo AJ, Contreras G. ESKD, transplantation, and dialysis in lupus nephritis. *Semin Nephrol.* 2015;35(5):500-508.
10. Rovin B, Solomons N, Pendergraft WF, et al, AURA-LV Study Group. A randomized, controlled, double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int.* 2019;95(1):219-231.
11. Merrill JT, Manzi S, Aranow C, et al. Lupus community panel proposals of optimising clinical trials: 2018. *Lupus Sci Med.* 2018;5(1):e000258.
12. Cain DW, Cilowski JA. Immune regulation by glucocorticoids. *Nat Rev Nephrol.* 2017;17(4):233-247.
13. Ashby D, Pepper RJ, Cook HT, et al. Prospective observational single-center cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. *Ann Rheum Dis.* 2013;72(8):1280-1286.
14. Malvar A, Pirruccio P, Alberton V, et al. Histologic versus clinical remission in proliferative lupus nephritis. *Nephrol Dial Transpl.* 2017;32(8):1338-1344.
15. Alvarado AS, Malvar A, Lococo B, et al. The value of repeat kidney biopsy in quiescent Argentinian lupus nephritis patients. *Lupus.* 2014;23(8):840-847.
16. De Rosa M, Azzato F, Toblli JE, et al. A prospective observational cohort study highlights kidney biopsy findings of lupus nephritis patients in remission who flare following withdrawal of maintenance therapy. *Kidney Int.* 2018;94(4):788-794.