EDITORIAL

Childhood Lupus Nephritis: Achieving and Maintaining Remission Seems Critical for Renal Survival

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Nephritis is an ominous manifestation of systemic lupus erythematosus (SLE) that is associated with increased morbidity and mortality [1]. Treatment modality to be adopted is governed by the classification of disease based on renal biopsy. Proliferative disease carries the greatest risk of progression to end-stage renal disease, and is therefore treated with immunosuppression, usually in two phases: induction and maintenance. Intravenous cyclophosphamide (IVCP) in low dose was found equivalent to the same in high dose for the critical outcomes of death and end-stage renal disease [2]; hence, IVCP with systemic corticosteroids for the first 3-6 months became the conventional induction therapy regimen. Mycofenolate mofetil (MMF) has emerged as an alternate to low-dose IVCP in inducing remission due to similar efficacy and safety [3]; however, lack of long-term data and higher cost are barriers to its usage. An antimetabolite with continued oral corticosteroids in lower doses is standard maintenance therapy; however, MMF was found more effective than azathioprine in maintaining a renal response to therapy in terms of time to treatment failure as well as renal flares [4].

Treatment in lupus nephritis is usually individualized; age and ethnicity are important factors. Overall, renal involvement in SLE is more common in children, with greater numbers of children showing active urinary segment and proteinuria as compared to adults [5]. Treatment of lupus nephritis may therefore need to be more aggressive in this age group. Ethnicity also has important connotations. For instance, the dose of MMF that balances safety and efficacy is believed to be lower in Chinese patients than Caucasians [6]. There is limited long-term data on pediatric lupus nephritis in South Asian patients. In this issue of *Indian Pediatrics*, George, *et al.* [7] evaluate the incidence of renal flares and treatment resistance in patients with childhood lupus nephritis in 34 patients of Indian ethnicity with median follow up of 7 years. Thirty-two patients achieved either complete or partial response at the end of 6-months' induction therapy. However, 14 patients experienced at least one episode of renal flare, an incidence of about 0.16 episodes/person/year. Eight patients had refractory illness; of these, 2 were noted to have no response to induction therapy while 6 failed to respond following a flare. Thus, refractory disease was more common after a flare than at onset. Refractory illness and occurrence of multiple flares were associated with adverse renal outcome. Despite being a small retrospective case series, the importance of prevention or at least early identification and treatment of renal flares is reinforced in this paper, as is the seriousness of refractory disease.

While the best strategy to treat refractory lupus nephritis and prevent renal flares remains a dilemma, therapeutic options seem to be emerging. For refractory disease, rituximab may be a rescue agent of value despite lack of demonstrable superiority in the LUNAR trial. In a systemic analysis of 26 reports and 300 patients with refractory lupus nephritis, at least partial response was noted in 87%, 76% and 67% of patients with class III, IV and V lupus nephritis, respectively [8]. Multitarget therapy with tacrolimus and MMF may be an attractive alternative. For induction of remission as compared to IVCP, a network meta-analysis of randomized controlled trials reported an odds ratio of 2.69 (95% CI 1.74, 4.16) [9]. Plasma exchange and intravenous immunoglobin have been used but with only anecdotal benefit [10]. A large number of biological agents targeting various limbs of the acquired immune system show promise but are yet to find support in clinical studies related to lupus nephritis [11]. These agents may play a role in induction of remission as well as maintenance therapy for prevention of renal flares.Early detection or prediction of renal flares will enable timely therapy and improve renal outcome. Close follow-up with careful monitoring of blood pressure, renal function, proteinuria, and urinary sediment for prompt detection of renal flare is good practice. However, appearance of cellular casts, a rise in

titers of antibodies to dsDNA and/or complement C1q and other biomarkers may predict a renal flare. In addition, other biomarkers such as NGAL may find a place in future. In situations of ambiguity, a renal biopsy may be required [12].

Given a state of remission, how does one minimize adverse effects of therapy? The time-tested practices of appropriate vaccination, monitoring for drug toxicities with attention to growth and prevention or at least timely management of opportunistic infections, osteoporosis and cardiovascular complications should continue. Systemic corticosteroids are conventionally administered for prolonged duration with multiple adverse effects. For this reason, steroid-free regimens are being contemplated. In the RITUXILUP cohort of 50 patients, 45 patients attained at least partial remission by a median time of 37 weeks. Over a median follow-up period of 163 weeks, 11 (22%) patients experienced renal flares [13]. Thus, short- and medium-term results are encouraging; however, these results should be interpreted cautiously.

Lupus nephritis is a condition with complex pathogenesis and often poses therapeutic dilemmas. In this background, the study by George, *et al*. [7] puts forth a simple message: achievement and maintenance of renal remission is the aim behind therapy, irrespective of the regimen used. Renal remission, therefore, also marks the point beyond which minimization of the adverse effects of immunosuppression becomes an important objective.

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REFERENCES

1. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12:825-35.
2. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido E de R, Danieli MG, *et al*. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis. 2010;69:61-4.
3. Rathi M, Goyal A, Jaryal A, Sharma A, Gupta PK, Ramachandran R, *et al*. Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis. Kidney Int. 2016;89:235-42.
4. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, *et al*. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011;365:1886-95.
5. Livingston B, Bonner A, Pope J. Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: a meta-analysis. Lupus. 2011;20:1345-55.
6. Yap DYH, Chan TM. Treatment of lupus nephritis: practical issues in Asian countries. Int J Rheum Dis. 2015;18:138-45.
7. George J, Sankaramangalam KP, Sinha A, Hari P, Dinda A, Bagga A. Lupus nephritis in Indian children: flares and refractory illness. Indian Pediatr. 2018;55:478-81.
8. Weidenbusch M, Römmele C, Schröttle A, Anders H-J. Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis. Nephrol Dial Transplant. 2013;28:106-11.
9. Palmer SC, Tunnicliffe DJ, Singh-Grewal D, Mavridis D, Tonelli M, Johnson DW, *et al*. Induction and maintenance immunosuppression treatment of proliferative lupus nephritis: a network meta-analysis of randomized trials. Am J Kidney Dis. 2017;70:324-36.
10. Mok CC. Therapeutic options for resistant lupus nephritis. Semin Arthritis Rheum. 2006;36:71-81.
11. Narain S, Furie R. Update on clinical trials in systemic lupus erythematosus: Curr Opin Rheumatol. 2016;28:477-87.
12. Sprangers B, Monahan M, Appel GB. Diagnosis and treatment of lupus nephritis flares-an update. Nat Rev Nephrol. 2012;8:709-17.
13. Condon MB, Ashby D, Pepper RJ, Cook HT, Levy JB, Griffith M, *et al*. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis. 2013;72:1280-6.