PERSPECTIVE

Management of Lupus Nephritis in Children

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Lupus nephritis affects 50-75% of all children with systemic lupus erythematosus with a higher prevalence in Asians. It remains a major contributor to morbidity and mortality in childhood onset lupus. Proliferative lupus nephritis (class III and class IV) warrants aggressive treatment to prevent progression to end stage renal disease. Newer immunosuppressive agents available in the last decade offer more options to treat lupus nephritis. Despite guidelines from professional bodies, there remains a lack of consensus on the treatment of refractory disease and duration of maintenance therapy. We review the treatment options for pediatric patients with lupus nephritis based on studies and published guidelines in the last decade, and highlight opportunities for continued improvement in care.

Keywords: *Glomerulonephritis, Induction, Immunosuppression, Maintenance.*

Childhood-onset systemic lupus erythematosus (cSLE) has an incidence of 0.3 to 0.9 per 100,000 children-years and a prevalence of 3.3-8.8 per 100,000 children with higher prevalence rates in non-white populations including Asians [1]. About 10-20% of cases of SLE are diagnosed during childhood with a median age of onset of 11-12 years, and these patients have increased disease severity and lower survival rates [2]. Renal disease occurs in 50-75% of all cSLE patients, mostly within the first two years of diagnosis [2,3]. As per the American College of Rheumatology (ACR) criteria, lupus nephritis is defined as persistent proteinuria (>0.5 g/day or >3+ by dipstick) and/or cellular casts in the urine. A spot urine protein/creatinine ratio of >0.5 can be substituted for the 24-hour urine protein measurement and an 'active urinary sediment' (>5 RBC/high power field (hpf), >5 WBC/hpf in the absence of infection, or cellular casts limited to red blood cells or white blood cell casts) can be substituted for cellular casts [4]. Initial manifestations of renal disease range from minimal proteinuria and hematuria to nephrotic-range, rapidly progressive glomerulonephritis, severe hypertension, and acute kidney injury. The frequency of nephritis in patients with SLE is significantly higher in African Americans, Asians (40-82%) and Hispanics than in whites (29%) and is higher in men [5]. Nephritis is a major risk factor for morbidity and mortality in SLE and 10% of patients with lupus nephritis will develop end stage renal disease (ESRD) with a higher risk in patients with more severe histological classification (44% over 15 years) [5].

As there may be a lack of clinico-pathologic correlation, a renal biopsy is the gold standard for diagnosis. Histopathology is valuable in guiding treatment and a renal biopsy is strongly recommended for all patients with clinical evidence of lupus nephritis for classification of nephritis and evaluation of activity and chronicity [6,7]. The recommendations of the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) revised in 2018 are currently used as the basis for the classification of lupus nephritis [8,9]. In general, class I (minimal mesangial) and class II (mesangial proliferative) nephritis are mild lesions and require little to no targeted immunosuppressive treatment due to a favorable natural history. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines suggest that treatment for class I/II lupus nephritis be dictated by extra renal manifestations; except that patients with nephrotic range proteinuria receive steroid or calcineurin inhibitor (CNI) therapy [10]. Class III (focal proliferative) and class IV (diffuse proliferative) lesions are the most frequent and severe findings in childhood lupus nephritis [2,11]. Patients with proliferative lesions have the highest risk of ESRD and, thus, are treated with aggressive immunosuppression [2]. Combination of class III or IV with class V (membranous) lupus nephritis is prevalent and treatment strategies used for proliferative nephritis should be followed [10]. With current treatment regimens, the incidence of ESRD in patients with proliferative lupus nephritis has improved and the 5-year renal survival of children ranges from 77-93% [12].

Goals of Therapy

Therapeutic goals for the treatment of lupus nephritis include achieving prompt renal remission, avoiding flares, preventing chronic renal impairment, improving survival and quality of life, and minimizing iatrogenic effects. As short-term outcomes improve, more attention is needed on balancing the risks of long-term immunosuppressive exposure. However, it is important to remember that failure to achieve and maintain remission of nephritis reduces the rates of renal survival and overall survival.

The treatment of proliferative lupus nephritis is commonly divided into two distinct phases: induction and maintenance. The induction phase is composed of intense immunosuppression aimed at achieving remission with resolution of active inflammatory changes. Consensus renal response definitions in pediatric LN define substantial response (complete remission) as normalization of renal function, inactive urine sediment (<5 WBC/hpf, <5 RBC/hpf, and no casts), plus spot protein/creatinine ratio <0.2 [13]. Induction is followed by a longer maintenance phase, during which less intense immunosuppressive regimens are used to sustain remission while attempting to minimize side effects associated with medications. The widely used KDIGO practice guidelines are based on adult data, but suggest that pediatric providers follow the same treatment algorithms [10]. In the absence of robust clinical trial data in pediatric patients with proliferative LN, consensus treatment plans have been developed by CARRA (Childhood Arthritis and Rheumatology Research Alliance) for induction therapy based on available scientific evidence and pediatric rheumatology group experience with the goal of improving prognosis by standardizing treatment plans [13].

INDUCTION THERAPY

The consensus treatment plans for induction therapy recommend either intravenous cyclophosphamide (IV-CYC) or mycophenolate mofetil (MMF) along with steroids for a duration of 6 months (***Table* I**). Consensus was reached to administer a total of 6 monthly IV-CYC dosages (starting with 500 mg/m^2 and increasing based on tolerance and WBC nadir to a maximum dosage of 1,500 mg). In the adult literature, this standard dosing regimen (designated the NIH regimen) has been compared to a low dose (or Euro-lupus) regimen which consists of 500 mg IV-CYC every 2 weeks for 6 treatments followed by initiation of maintenance therapy. These regimens have shown a similar efficacy in the populations studied and the ACR recommends this regimen for IV-CYC induction in patients who are white with European background [7]. The KDIGO guidelines also include option for oral cyclophosphamide (1.0-1.5 mg/kg/day, maximum 150 mg/day) for 2-4 months [10]. MMF is recommended at a dose of 600 mg/m^2/dose (maximum 1,500 mg) twice daily. This is similar to European pediatric consensus dosing regimens (1200 mg/m^2/day, maximum 2000 mg/day; when poor response option to increase to maximum of 1800 mg/m^2/day, maximum dose 3000 mg/day) [11]. African-Americans and Hispanics with lupus nephritis may respond less well to IV-CYC than patients of white or Asian races; thus, MMF is the preferred agent for these populations [7]. Observational studies and a recent single center trial from India suggest a comparable rate of response with either IV-CYC (both dosing regimens studied) or oral MMF [14–16]. However, one pediatric study in the Indian population detected better efficacy of MMF compared with IV-CYC induction [17].

Despite dramatic variability of glucocorticoid prescribing practices, CARRA consensus guidelines for induction provided three regimens (primarily oral, primarily IV, and mixed oral/IV) with the goal to achieve a daily dosage of oral glucocorticoids between 10 and 20 mg upon completion of induction therapy at 24 weeks [13]. High dose IV methylprednisolone pulses (30 mg/kg/dose IV for three consecutive days, maximum 1000 mg/dose), but not oral glucocorticoids, have the potential to eliminate the interferon–α gene expression signature in cSLE, by reducing the number of plasmacytoid dendritic cells and hence all regimen allow the use of this therapy, which is invariably used for severe disease [13]. Most studies in cSLE report the use of oral prednisone 1-2 mg/kg/day (maximum 60 mg/day) with tapering schedule by 10-20% at one- or two-week intervals based on clinical improvement [11].

Other immunosuppressive agents with some evidence for efficacy include azathioprine, abatacept (in conjunction with CYC), calcineurin inhibitors (CNI), (cyclosporine, tacrolimus), and rituximab. CNI-based regimens have been studied in Asia, and often combine MMF and steroids with a CNI ('multitarget therapy'). A large Chinese randomized trial reported improved rates of complete and partial renal remission at 24-weeks in patients treated with low-dose MMF, tacrolimus, and steroids compared to monthly IV-CYC and steroids for induction of proliferative LN [18].

Rituximab has generally been reserved as an adjunctive therapy in patients with relapsed or refractory disease. To date, prospective randomized controlled trials have failed to show a significant benefit in clinical outcomes with the addition of rituximab to standard of care induction therapy [19]. However, one study in pediatric

Table I Summary of Common Treatment Regimens for Proliferative Lupus Nephritis

Induction therapy (choose one)		
Cyclophosphamide (CYC) IV (high dose, NIH regimen)	6 doses, given monthlyInitial dose 500 mg/m^2, increase as tolerated to 1000 mg/m^2 (maximum dose 1500 mg)	Adjust dose for renal insufficiency and low WBC nadir (7-10 d after dose)
Cyclophosphamide (CYC) IV (low dose, Euro-Lupus regimen)	6 doses of 500 mg/dose, given every 2 wks	
Mycophenolate mofetil (MMF)	600 mg/m^2/dose twice daily for 6 mo (maximum dose of 1500 mg twice daily)	May start lower dose and escalate to target dose within 4 wk, Consider maximum dose to 1000 mg twice daily in Asian population
Maintenance therapy (choose one)		
Mycophenolate mofetil (MMF)	600 mg/m^2/dose (maximum dose of 1,000 mg twice daily)	
Azathioprine (AZA)	2-3 mg/kg/day (maximum 150 mg/d)	
*Glucocorticoids**		
Induction 3 consensus regimens for induction from CARRA are summarized below – common goal is to achieve a daily dosage of oral glucocorticoids of 10-20 mg upon completion of induction therapy after 24 wks; all allow for the use of up to 3 high-dose methylprednisolone pulses (30 mg/kg/dose up to 1000 mg/dose) at the start of induction		
	>30 kg (oral regimen)	*<30 kg (oral regimen)*
Primarily oral Pulse 3× in wk 1 (*optional*)	60-80 mg daily for wks 1-4, decrease by ~10 mg daily every 2-4 wk	2 mg/kg/d for wk 1-6, decrease by ~5 mg daily every 2-4 wk
Primarily IV Pulse 3×in wk 1, 1-3×/wk in wk 2-7, 1×/month in wk 8-24	20 mg daily for wk 1-11, 15 mg daily for wk 12-18, 10 mg daily for wk 19-24	10 mg daily for wk 1-11, 7.5 mg daily for wk 12-18, 5 mg daily for wk 19-24
Mixed oral/IV Pulse 3× in wks 1, 1×/mo in wk 2-24	60 mg daily for wk 1-2, 50 mg daily for wk 3, 40 mg daily for wk 4, Decrease by 5 mg daily every 4 wk	1.5 mg/kg daily for wk 1-2, 1.2 mg/kg daily for wk 3, 1 mg/kg daily for wk 4, Decrease by 0.1 mg/kg daily every 4 wks
Maintenance[#]		
Continue to taper to 5-10 mg daily. Trials evaluating efficacy of maintenance therapies allowed up to 10 mg daily of steroid therapy.		

**Used throughout therapy in conjunction with above medication regimens, Often escalated for extra-renal causes or concern for LN flare, Wide variation in practice patterns. [#]If disease remains well-controlled, slowly decrease dose until steroid therapy is discontinued, No clear guidelines for timeline of taper or discontinuation.*

population demonstrated significantly improved flare-free survival in patients who received rituximab as induction therapy, as compared to patients treated with CYC or MMF [17]. Furthermore, a systematic review of studies that documented outcomes for patients with refractory lupus nephritis suggests that rituximab effectively induced remission in patients who had not achieved remission with standard therapies [20]. There are clinical trials underway which include children using rituximab as an induction agent. Additionally, there are several other B cell directed therapies which have recently shown promise in the treatment of LN including other B cell depletion agents targeting CD-20 (obinutuzumab, ocrelizumab), proteasome inhibitors (bortezomib, ixazomib) which particularly affect plasma cells, and B-cell activating factor (BAFF, also known as B-lymphocyte stimulator (BLyS)) antagonists (belimumab, tabalumab) [21].

ADJUNCTIVE THERAPY

The ACR and EULAR/ERA-EDTA recommend that all SLE patients with nephritis be treated with a background of hydroxychloroquine to improve outcomes by reducing renal flares and limiting the accrual of renal and cardiovascular damage [6,7]. Additionally, all patients with proteinuria >0.5 g/day (or >0.5 urine protein/creatinine ratio) should have blockade of the renin-angiotensin system to reduce intraglomerular pressure unless otherwise contraindicated [7,11]. Up to 80% of patients with SLE are treated with non-steroidal anti-inflammatory drugs (NSAIDs) for extra renal

manifestations, mainly arthritis and serositis. These medications can induce sodium retention and reduction in GFR, and lupus nephritis is a risk factor for hemodynamically mediated, NSAID-induced acute renal failure [22]. However, while a safe dosing and duration of NSAID use for extra renal manifestations in patients with lupus nephritis has not been established, it is reasonable for most patients to receive these medications if needed with close monitoring of renal function and re-evaluation for ongoing therapy on a regular basis.

MAINTENANCE THERAPY

The goal of maintenance therapy is to prevent relapse and control the disease by limiting inflammation and damage. Up to 50% of patients with proliferative lupus nephritis relapse following reduction/cessation of immunosuppressive therapy. In the adult population, the relapse rates range from 5 to 15 per 100 patient-years for the first five years of follow up [22]. Incidence of flares in the Indian pediatric population has been reported to be about 0.16 episodes/person/year with median duration to onset of first flare of 29 months [23]. The ACR recommends either MMF (1-2 g/day) or azathioprine (AZA) (2 mg/kg/day) and low dose steroid for the maintenance phase of treatment [7]. European evidence-based recommen-dations for treatment of childhood-onset lupus nephritis also advise use of MMF or AZA as maintenance therapy [11]. The KDIGO guidelines additionally suggest that a CNI be used for maintenance therapy in a patient intolerant of MMF or AZA [10]. Low dose oral prednisone is continued to attain the minimum dose required for control of extrarenal symptoms. Across different trials, the maintenance prednisone dose ranged from 0 to 0.2 mg/kg/day [24-26]. Two recent meta-analyses evaluating treatment for proliferative lupus nephritis found that MMF was the best therapy for maintaining remission and preventing kidney failure during maintenance treatment [27,28]. AZA should be used when MMF is contraindicated or following failure of MMF therapy. Additionally, patients maintained on multitarget therapy (tacrolimus and MMF) had similar rates of relapse to the group that had received IV-CYC who were then maintained on AZA therapy [29].

The ideal length of this therapy phase is unknown, and regimens reported in the literature vary from one to five years. In older literature, stopping cyclophosphamide abruptly was associated with a rapid deterioration of renal function [30], but evidence supporting timeline and withdrawal of currently accepted maintenance regimens remains limited. The majority of patients in trials were adults and the duration of the maintenance phase varied widely, with a mean follow-up time ranging from 18-36 months. The usual extended therapy dose of MMF in adult patients is 1000 mg twice daily (or 1200 mg/m^2/day with a maximum dose of 1000 mg twice daily) [6,7,11]. The dose may be tapered in stable patients, but there are no specific guidelines on the timeline of this taper.

Common end points of trials evaluating maintenance therapy include time to disease flare, doubling of serum creatinine, or development of ESRD, and these studies are designed to compare medication regimens. There are no published randomized controlled trials designed to prospectively evaluate duration of maintenance therapy; however, a randomized clinical trial is underway to address this specific question (Clinicaltrials.gov identifier NCT01946880). Relatively small retrospective studies have shown that some patients with proliferative lupus nephritis who enter stable remission can be maintained without immunosuppressive treatment for years [22,25]. One of the larger studies to date evaluating duration of maintenance therapy included 32 patients in whom therapy was successfully withdrawn with a subsequent median follow up period of 203 months. This study found that longer median duration of treatment (57 months *vs* 30 months) and longer duration of remission before withdrawal of therapy (median 24 months *vs* 12 months) were associated with decreased risk of disease flare [25]. Thus, these authors recommended at least five years of treatment prior to withdrawal of therapy. However, when the decision to stop therapy was made, four patients were receiving only low dose AZA (25-50 mg/day) and the other 28 were taking only low dose prednisone, which is less therapy than the standard maintenance regimens at this time.

In the most recent ACR guidelines, the task force panel did not vote on the rate of medication taper during the maintenance phase given the lack of adequate data [7]. Consensus documents have indicated a minimum duration of three years [6,11]. Beyond this time period, there is little data to guide treatment and consensus statements suggest that continuing treatment for longer should be individualized with an effort first to withdrawal glucocorticoids [6]. A re-biopsy has been suggested in those patients with sustained remission to verify histologic remission prior to discontinuing immunosuppression [5]. Most of the published studies in which immunosuppression was either minimized or stopped originated in Europe, therefore these findings cannot necessarily be extrapolated to patient groups with different ethnic backgrounds [22].

CONCLUSION

Advances in immunosuppressive medications have resulted in improved renal survival and quality of life in

pediatric patients with lupus nephritis. Newer agents such as MMF are effective as induction therapy, though with variation amongst different ethnic groups. The duration of maintenance therapy is a particularly important question in pediatric onset lupus nephritis given the potential for cumulative immunosuppressive medication exposure over time. Currently, there is little data to guide duration of treatment beyond three years in patients with well-controlled disease. Consensus statements support tapering medication around this time point with the initial goal of withdrawal of glucocorticoids. Although reducing rates of renal flares is important in preventing disease-related morbidity and mortality in patients with cSLE and lupus nephritis, a period without corticosteroids and immunosuppressive therapy could be particularly useful for preventing iatrogenic morbidity.

REFERENCES

1. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol. 2010;6:538-46.
2. Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. Pediatr Clin North Am. 2012;59:345-64.
3. Hiraki LT, Benseler SM, Tyrrell PN, Hebert D, Harvey E, Silverman ED. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: A longitudinal study. J Pediatr. 2008; 152:550-6.
4. Dooley MA, Aranow C, Ginzler EM. Review of ACR renal criteria in systemic lupus erythematosus. Lupus. 2004; 13:857-60.
5. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017; 12:825-35.
6. Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JHM, *et al*. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) Recommendations for the Management of Adult and Paediatric Lupus Nephritis. Ann Rheum Dis. 2012;71:1771-82.
7. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, *et al*. American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis. Arthritis Care Res. 2012; 64:797-808.
8. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, *et al*. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int. 2004; 65:521-30.
9. Bajema IM, Wilhelmus S, Alpers CE, Bruijn JA, Colvin RB, Cook HT, *et al*. Revision of the International Society of Nephrology/Renal Pathology Society Classification for Lupus Nephritis: Clarification of Definitions, and Modified National Institutes of Health Activity and Chronicity Indices. Kidney Int. 2018;93:789-96.
10. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int Suppl. 2012; 2:139-274.
11. Groot N, de Graeff N, Marks SD, Brogan P, Avcin T, Bader-Meunier B, *et al*. European Evidence-based Recommendations for the Diagnosis and Treatment of Childhood-onset Lupus Nephritis: the SHARE Initiative. Ann Rheum Dis. 2017; 76:1965-73.
12. Bennett M, Brunner HI. Biomarkers and updates on pediatrics lupus nephritis. Rheum Dis Clin North Am. 2013;39:833-53.
13. Mina R, von Scheven E, Ardoin SP, Eberhard BA, Punaro M, Ilowite N, *et al*. Consensus Treatment Plans for Induction Therapy of Newly Diagnosed Proliferative Lupus Nephritis in Juvenile Systemic Lupus Erythematosus. Arthritis Care Res. 2012; 64: 375-83.
14. Mendonca S, Gupta D, Ali S, Gupta P. Mycophenolate mofetil or cyclophosphamide in indian patients with lupus nephritis: Which is better? A single-center experience. Saudi J Kidney Dis Transplant. 2017;28:1069-77.
15. Sahay M, Saivani Y, Ismal K, Vali PS. Mycophenolate versus clophosphamide for lupus nephritis. Indian J Nephrol. 2018;28:35-40.
16. Rathi M, Sharma A. Mycophenolate or cyclophosphamide in lupus nephritis: Which one to use in Indian patients? Indian J Nephrol. 2018;28:99-100.
17. Basu B, Roy B, Babu BG. Efficacy and safety of rituximab in comparison with common induction therapies in pediatric active lupus nephritis. Pediatr Nephrol. 2017; 32:1013-21.
18. Liu Z, Zhang H, Liu Z, Xing C, Fu P, Ni Z, *et al*. Multitarget therapy for induction treatment of lupus nephritis: A randomized trial. Ann Intern Med. 2015;162:18-26.
19. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, *et al*. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum. 2012; 64:1215-26.
20. 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.
21. Almaani S, Rovin BH. B-cell therapy in lupus nephritis: An overview. Nephrol Dial Transplant. 2019;34:22-9.
22. Ostensen M, Villiger PM. Nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus. Lupus. 2001;10: 135-9.
23. Grootscholten C, Berden JHM. Discontinuation of immunosuppression in proliferative lupus nephritis: Is it possible? Nephrol Dial Transplant. 2006;21:1465-9.
24. George J, Sankaramangalam KP, Sinha A, Hari P, Dinda AK, Bagga A. Lupus nephritis in Indian children: Flares and refractory illness. Indian Pediatr. 2018; 55:478-81.
25. Contreras G, Victoriano P, Baudouin L, Oliver L, Elaine T, Patricia O, *et al*. Sequential therapies for proliferative lupus nephritis. N Engl J Med. 2004;350:971-980.
26. Moroni G, Gallelli B, Quaglini S, Banfi G, Rivolta E, Messa

P, *et al*. Withdrawal of therapy in patients with proliferative lupus nephritis: long-term follow-up. Nephrol Dial Transplant. 2006;21:1541-8.
27. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, *et al*. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: Results from the MAINTAIN nephritis trial. Ann Rheum Dis. 2010;69:2083-9.
28. Tian SY, Feldman BM, Beyene J, Brown PE, Uleryk EM, Silverman ED. Immunosuppressive therapies for the maintenance treatment of proliferative lupus nephritis: A systematic review and network metaanalysis. J Rheumatol. 2015; 42:1392-400.
29. 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.
30. Zhang H, Liu Z, Zhou M, Liu Z, Chen J, Xing C, *et al*. Multitarget therapy for maintenance treatment of lupus nephritis. J Am Soc Nephrol. 2017;28:3671-8.
31. Aptekar RG, Decker JL, Steinberg AD. Exacerbation of SLE nephritis after cyclophosphamide withdrawal. N Engl J Med. 1972;286:1159-60.