Introduction

About 10% to 20% of SLE cases are diagnosed during childhood which uses 18 years as the upper cutoff age in most of the studies [1]. The kidney involvement i.e. lupus nephritis (LN) is a serious component of SLE which presents with proteinuria, microscopic hematuria and renal dysfunction thereby exerting adverse impact on long-term renal and patient survival. African-Americans (AA), Hispanics, Asians, and non-Caucasians are high-risk populations with higher prevalence and severe disease. Despite the similarities in adults, childhood-onset LN tends to have more active onset and severe disease activity requiring timely recognition and proper treatment. Over the past 2 decades, huge progress has been made in the treatment of childhood LN. Ethnicity has a quite well-defined effect on the response to treatment for which special considerations must be taken in treatment strategy. This review will discuss the current therapies of LN in clinical practice and shows a comparison of treatment responses in different ethnicities.

Keywords: Lupus Nephritis; Systemic Lupus Erythematosus; Pediatric; Ethnicity; Immunosuppressive Treatment

Abbreviations: SLE: Systemic Lupus Erythematosus; LN: Lupus Nephritis; AA: African-Americans; CYC: Cyclophosphamide; NIH: National Institutes of Health; IV: Intravenous; ELNT: Euro-Lupus Nephritis Trial; MMF: Mycophenolate Mofetil; RCT: Randomized Controlled Trial; ALMS: Asperva Lupus Management Study; AZA: Azathioprine; CNI: Calcineurin Inhibitors (CNIs); RTX: Rituximab; HCQ: Hydroxychloroquine; ACR: American College of Rheumatology; KDIGO: Kidney Disease Improving Global Outcomes; EULAR: European League Against Rheumatism

Historically, patients with LN were treated with low-dose steroids alone. Before the initiation of immunosuppressive regimens, a study showed that a two-year survival rate was less than 10% in patients with diffuse proliferative glomerulonephritis [9]. The standard treatment regimens for pediatric LN have been mostly derived from the studies in adults which has progressed over the few past decades with the usage of corticosteroids alone to the combination of different immunosuppressant drugs resulting improvements in overall patients and renal survival. The early treatment of acute lesions greatly contributes to delay disease progression and reduces the risk of chronic kidney disease.
progression and achieve remission hence improving the survival rates of patients with LN [10]. The treatment of lupus nephritis involves two phases: an induction phase, in order to reverse the immune-mediated inflammatory processes with the use of potent immunosuppressive medications. This is followed by a maintenance phase, in which a longer period of lower dose immunosuppressive medications is used in order to maintain a stable state and prevent recurrences.

**Cyclophosphamide (CYC)**

With the advent of CYC in the treatment of LN in children, renal survival at 5 and 10-year was significantly better [11]. The landmark National Institutes of Health (NIH) study led to the routine use of high dose intravenous (IV) CYC plus prednisolone as induction therapy which was superior to the pulse steroids alone and it became the ‘standard of care’ [12]. Several studies with the use of high dose CYC in children with different ethnicities showed good outcome [13-16]. Despite the good outcome, IV CYC treatment is associated with short- and long-term side effects, such as infections, alopecia, nausea, amenorrhea, infertility and hemorrhagic cystitis. In order to reduce the CYC toxicity, low-dose intermittent IV CYC was investigated. The Euro-Lupus Nephritis Trial (ELNT) on adult population compared a high dose NIH regimen of IV CYC (six monthly pulses at a dose of 0.5-1 mg/m² followed by two quarterly pulses) with the Euro-Lupus low dose regimen (six pulses of IV CYC every two weeks at a fixed dose of 500 mg). ELNT with reduced CYC dose has been shown to be as effective as the standard dose CYC regimen when used in 85% of the patient being Caucasians with less severe proliferative LN and it was associated with fewer side effects [17]. A little data has been reported on the efficacy of the Euro-Lupus regimen in Asians and non-Caucasians. So, there still needs to be demonstrated that a low-dose CYC regimen can be effectively used in patients with other ethnicities including AA, Hispanics, and Asians.

**Mycophenolate Mofetil (MMF)**

Based on the studies reported in adult patients, from the beginning of the 21st century the use of MMF as induction therapy and maintenance therapy is increasing in children and signifies a major progress in the immunosuppressive therapy for severe LN. The first randomized controlled trial (RCT) done in an adult Chinese population with diffuse proliferative LN comparing oral CYC (2.5 mg/kg/day) with MMF (1 gm twice daily) as induction therapy showed equivocal improvement in complete renal and relapse rates. Furthermore, patients treated with MMF had fewer adverse events including infections, alopecia, and amenorrhea as compared with CYC [18]. Likewise, several data on Asian children show no significant differences in the efficacy between MMF and CYC [19-21]. In a sub-analysis of the Asperva Lupus Management Study (ALMS), the response variation with race and ethnicity was demonstrated, in that Asians and Whites had a similar response to CYC and MMF whereas Black and Hispanics showed the better result with MMF (60.4%) compared to CYC (38.5%) [22]. The retrospective cohort data on children (56% AA, 29% Hispanics) as per treatment protocol was compared which showed which the 5-year renal survival was 91% in MMF group compared to 52% in the CYC group (P<0.01) [23]. The MAINTAIN Nephritis Trial established no significant difference (in terms of renal outcomes and time to disease flare) between MMF (2 gm/day) and AZA (2 mg/kg/day) as maintenance therapy in (mostly) white Europeans [24], and the similar result in Whites was reported in the 10-year follow-up of the MAINTAIN Nephritis Trial [25]. However, the maintenance phase of the ALMS with a much greater proportion of non-Caucasians showed the superiority of MMF over azathioprine for the prevention of renal relapses [26].

**Azathioprine (AZA)**

AZA is another commonly used immunosuppressive regimen in a maintenance therapy of LN. A report on Chinese patients showed treatment with either MMF as both induction and maintenance phase or sequential CYC followed by AZA regimen showed comparable long-term efficacy in the renal preservation and renal outcome [18]. Similarly, in high-risk AA and Hispanics, short-term CYC induction therapy which is followed by either MMF or AZA maintenance showed equal efficacy [27]. Use of AZA in a multi-ethnic cohort study of children proved excellent long-term outcome which further suggested that Non-Caucasians patients may be at increased risk for renal failure when compared to Caucasians [28].

**Calcineurin inhibitors (CNIs)**

CNIs has a primary effect on T-cell expansion and has been used as a potent immunosuppression in the treatment of proliferative LN especially in Asians. Subsequent studies in Chinese patients showed equal efficacy between tacrolimus, IV CYC or MMF [29,30]. The data on long-term use of tacrolimus in Japanese children at a low dose of 0.03-0.075 mg/kg/day along with a tapering dose of steroid with a mean treatment duration for 42 months showed the treatment is beneficial with low cytotoxicity [31]. A small randomized study on Taiwanese children revealed equivocal improvements in renal outcomes treated with cyclosporine A and steroids when compared with oral CYC [32]. A large study in Chinese patients with class III/IV with or without concomitant class V LN under multi-target induction therapy with tacrolimus (4 mg/day), MMF (1 gm/day) and steroid showed higher complete remission rate (45.9 vs. 25.6%, p<0.001) and overall response rate (83.5 vs. 63.0%, p<0.001) when compared with IV CYC and corticosteroids, while the incidence of adverse events did not differ between the two regimens [33]. These patients were further continued to receive maintenance therapy with either multi-target regimen (tacrolimus+ MMF+ steroid) or AZA, resulted in a low renal relapse rate and fewer adverse events in the multi-target group [34]. Data from Asians show that multi-target therapy in patients with pediatric-onset LN can be a promising therapeutic option for introducing and maintaining remission in severe proliferative LN [35,36]. Multi-target therapy in AA and Caucasians with tacrolimus and MMF in MMF-resistant cases showed effective outcome [37,38].

**Rituximab (RTX)**

RTX is a specific monoclonal antibody against human B-cellCD20 receptor which has emerged as a salvage therapy mostly confined to those patients who have resistant or relapsing proliferative
nephritis. There are numerous case series in children demonstrating the usefulness of RTX [39-41]. In a study of childhood-onset LN (mostly Africans) who were treated with RTX 375 mg/m2 once a week for two to four weeks, 93% of patients reportedly achieved improvement in disease activity. However, the safety of RTX remains unanswered [39]. In contrast, the retrospective review in children with most of them being AA and Hispanics failed to show any improvement in renal survival when treated with RTX compared to MMF [23]. Adverse events like infection reactions, anaphylaxis, hematologic toxicity, infections, hypogammaglobulinemia, and progressive multifocal leukoencephalopathy may be seen with RTX treatment. Long-term observational data and large RCTs with the use of RTX in multiethnic groups are warranted in order to identify the response variation and verify its long-term safety profile.

**Adjunctive Therapy**

Antimalarial drug such as hydroxychloroquine (HCQ) as an adjunctive therapy has been recommended in the American College of Rheumatology (ACR), Kidney Disease Improving Global Outcomes (KDIGO) and European League against Rheumatism (EULAR) guidelines for long-term management of lupus nephritis in all patients, unless there is a contraindication because it reduces incidence of renal flares, renal injury, accrual or organ damage, thrombosis and increases long-term survival [42-44]. The result from LUMINA study, a multiethnic cohort of AA, Hispanics and Caucasians demonstrated the reduced occurrence of renal damage and lower renal activity with the use of HCQ [45]. Recently, a large study of SLE patients (93% Caucasians) showed an inverse relationship between the time of exposure to antimalarial drug and risk of infection [46]. The usefulness of HCQ has been studied in lupus patients of all ethnicities [47]. Medicines to control blood pressure using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are not only for hypertension but also plays a crucial role in reducing proteinuria, use of anticoagulants and lipid-lowering drugs which are the mainstay of adjunctive therapy. In addition, calcium and vitamin D supplements are also beneficial. Infection is the commonest cause of death in childhood SLE, therefore children on immunosuppression should be closely monitored.

**Conclusion**

Treatment in LN with advances in immunosuppressive regimens has provided better control of disease activity, good disease response and considerable improvement in overall patient survival rates. However, there are still variations of therapy responses between different races. LN is less common in Caucasians SLE patients with less severity and better outcome compared to AA, Hispanics, and Asians. Thus, Caucasians might get more benefit from relatively low-dose regimens. However, large-scale studies and RCTs in children comparing treatment strategies according to ethnicities are warranted in order to provide safe and adequate treatment. Therefore, the role of ethnic variation in response to treatment and eventual prognosis in children require much attention and research in the future.

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**References**


