An Update on Treatment and Outcome of Lupus Nephritis in Children

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Abstract

Lupus nephritis (LN) is the most common manifestation of systemic lupus erythematosus (SLE) in children to determine the course and outcome of the disease. Although its prognosis has improved in recent decades, varying degrees of chronic renal impairment, including end-stage renal disease (ESRD), can still develop.

Early and adequate treatment in LN protects the kidneys from developing chronic damage. Treatment should be based on the clinical severity of the disease and renal histology. Although there are still many controversies on the best treatment of pediatric LN, corticosteroids (CS) are still the first-line drugs used for induction therapy. Less severe forms of LN do not require specific therapy, apart from the treatment of underlying SLE itself, but focal or diffuse proliferative glomerulonephritis requires more aggressive therapy with different combinations of other immunosuppressive drugs. Induction protocols in most centers mainly included intravenous cyclophosphamide (CYC) pulse therapies with promising initial results, although more recent studies have been less encouraging. Oral mycophenolate mofetil (MMF) was shown to be at least equally effective as CYC for induction and maintenance therapies and has now become more commonly utilized in pediatric patients. There have also been increasing reports about successful B-lymphocyte depletion therapy with rituximab (RTX) in recent years. Mizonbline, azathioprine, cyclosporine A, and hydroxychloroquine are other therapeutic agents that are used in many centers for induction and maintenance therapies. Plasma exchange and stem cell transplantation can be used in very severe and refractory cases of SLE. New treatment approaches are still under investigation.

Key words: Childhood lupus nephritis, treatment, prognosis

Introduction

Lupus nephritis (LN) is one of the main clinical presentations determining the course and outcome of systemic lupus erythematosus (SLE) in children. It occurs in 40–80% of pediatric patients at presentation and can be even higher during the later stages of the disease. The severity of the disease varies from mild glomerulonephritis to severe manifestations leading to end-stage renal disease (ESRD) [1,2]. After the introduction of immunosuppressive therapies in recent decades, the prognosis of SLE has improved, with a 5-year survival of...
30% in the 1950s increasing to more than 90–95% in the late 1990s [3,4]. However, varying degrees of chronic renal impairment, including ESRD, can still develop. Thus, children with lupus nephritis require early treatment without unnecessary delay to protect the kidneys from developing chronic damage [4,5]. On the other hand, excess and unnecessary treatment with immunosuppressive agents can cause increased side effects, with potentially later malignancies and risks of severe infection [3–5].

Treatment of SLE requires a multidisciplinary and coordinated approach from diagnosis to long-term follow-up. However, there are still many controversies on the best treatment of pediatric lupus nephritis because of the lack of large randomized controlled trials on children, and most therapies are based on studies conducted on adults [4,5]. Treatment of LN should be based on the clinical severity of the disease and renal histology [1,2].

In daily clinical practice, various laboratory parameters, including anti-double-stranded DNA, and complement levels are currently used to assess the disease activity, but recent studies have indicated that the utility of these tests in reflecting disease activity remained controversial [3]. Severity and activity of the disease can be assessed by disease activity indices such as “Systemic Lupus Erythematosus Activity Index (SLEDAI),” “British Isles Lupus Assessment Group (BILAG) Index,” “European Consensus Lupus Activity Measurement (ECLAM),” and “Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index” [3,5,6–8]. However, renal biopsy is still accepted as the gold standard for assessing renal activity and guiding the management of patients [1]. Various current studies are also conducted on new biomarkers in blood and urine such as complement split products, neutrophil gelatinase-associated lipocalin, monocyte chemotactic protein-1, transforming growth factor-beta, and many others, but none of them have been proven to be sensitive, specific and cost-effective yet [5,9,10].

The current and widely used LN classification system was developed in 2003 by the International Society of Nephrology and Renal Pathology Society Working Group (ISN/RPS) and includes six classes of LN [11]. Although the patients may change from one class to another either before or during treatment, the histopathology determines the treatment regimen and prognosis [4]. It is well known that focal or diffuse proliferative glomerulonephritis (GN) (Class III and IV) is a more common type of LN in children with a more severe course requiring more aggressive therapy. Class I and Class II LN are usually thought to be less severe forms and do not require specific therapy apart from the treatment of underlying SLE itself. However, since there is always risk of progression, these patients should be followed up carefully. Pure membranous GN (Class V) is usually considered to be less common and also have better prognosis than proliferative forms of LN, although it has been shown to be refractory to treatment in some recent studies [4,12,13]. Advanced sclerotic LN (Class VI) is characterized by global sclerosis of more than 90% of glomeruli representing ESRD, and immunosuppression is not helpful for these patients [1,2,11].

In general, treatment of LN is divided into two phases: induction therapy to control the disease activity by inducing remission or at least impeding disease progression, and maintenance therapy after achieving remission to avoid relapses and control the disease by limiting inflammation and damage [4,5].

**Induction Therapy**

The first part of the therapy in lupus nephritis is to control disease activity with a short course of high-dose immunosuppressive drugs (Table 1). Although a number of standard regimens have been widely accepted as the basis of induction therapy, therapeutic approaches differ vastly between physicians. Each patient requires individual consideration and the therapy should be designed according to the severity of the disease, economic factors, and the clinician’s experience [4].

**Corticosteroids**

Corticosteroids (CS) are still the first-line drugs used for induction therapy in childhood SLE. For patients with mild LN (Class I or II), treatment consists CSs alone for several months and augmentation of immunosuppression is not necessary unless severe extrarenal involvement is present. However, proliferative forms of LN (Class III and IV) require aggressive immunosuppressive therapy [2,5]. This treatment includes high-dose oral CSs (2 mg/kg with a maximum dose
of 60 mg/day) or intravenous pulse methyl prednisolone (PMP) (30 mg/kg, maximum 1 g) given for three consecutive days and followed by high-dose oral prednisolone together with different combinations of other immunosuppressive drugs. In severe cases these pulses may need to be repeated. Because CSs have a lot of serious side effects, like cushingoid feature, hypertension, weight gain, striae, mood and sleep disturbances, hyperglycemia, osteoporosis, and growth retardation, the aim should be to minimize these effects by reducing the dose after the disease became under control [3,5,14].

Patients with membranous LN (Class V) commonly present with nephrotic syndrome, are treated with oral CSs for a few months, and may require a steroid-sparing agent [2,15].

**Cyclophosphamide**

Cyclophosphamide (CYC) has been the most frequently used drug for decades in the induction therapy of LN, which was initially used in oral form (1–3 mg/kg/day) [4,16]. After intravenous (IV) CYC was introduced and was shown to be superior to daily oral CYC, induction protocols in most centers mainly included CYC pulse therapies with promising initial results, although more recent studies have been less encouraging [4,5,17–21]. The most widely used intravenous CYC regimen consists of six monthly IV pulses of CYC at 0.5–1 g/m² with dose reduction in renal failure, and is usually followed by three monthly infusions for 18–24 months [3–5]. Although CYC is effective in the induction of remission, the short- and long-term side effects, including hemorrhagic cystitis, nausea, bone marrow suppression, severe infections, alopecia, amenorrhoea, infertility, and malignancy, cannot be avoided despite protective measures [2,5,20,22].

**Mycophenolate mofetil**

Mycophenolate mofetil (MMF) was introduced for treatment of severe LN during the late 1990s with good responses, the advantage of easier administration and with fewer severe side effects [17,18,21,23,24]. Its major adverse effects are abdominal pain and diarrhea and they can be reduced when the patients are treated initially with low doses, gradually increasing to 0.6–1.2 g/m²/day in two divided doses with

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<thead>
<tr>
<th>Drug</th>
<th>Suggested Dose</th>
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<tbody>
<tr>
<td>Intravenous methyl prednisolone</td>
<td>30mg/kg, maximum 1g for 3 days, then reassessed for further courses</td>
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<tr>
<td>Oral prednisolone</td>
<td>2 mg/kg, maximum 60 mg/day gradually tapering to lower doses</td>
</tr>
<tr>
<td>Oral cyclophosphamide (CYC)</td>
<td>1-3 mg/kg/day</td>
</tr>
<tr>
<td>Intravenous (IV) cyclophosphamide pulse</td>
<td>0.5-1 g/m²/dose monthly pulses for 6 months, Then usually extended to 18-24 months with 3 monthly pulses</td>
</tr>
<tr>
<td>Oral mycophenolate mofetil (MMF)</td>
<td>0.6-1.2 g/m²/day, maximum 3 g/day in two divided doses</td>
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<tr>
<td>Rituximab (RTX)</td>
<td>350-750 mg/m²/dose 2 to 12 IV infusions with 1-2-week intervals</td>
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<tr>
<td>Oral cyclosporin A (Cyc A)</td>
<td>3-5 mg/kg/day</td>
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<tr>
<td>Oral mizoribine intermittent pulse therapy</td>
<td>5-10 mg/kg/day, maximum 500 mg, twice weekly for 12-24 months</td>
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<tr>
<td>Oral azathioprine (AZA)</td>
<td>2-2.5 mg/kg/day</td>
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<tr>
<td>Intravenous immunoglobulin (IVIG)</td>
<td>2g/kg maximum of 70g/day every 4-6 weeks</td>
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<td>Plasma Exchange</td>
<td>5 to 10 plasma exchanges</td>
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<td>Stem cell transplantation</td>
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an oral route [2,5]. Although MMF has been gaining more popularity in recent years, its advantage of the induction of remission over IV CYC pulse therapy has not been proven in children yet. Furthermore, its higher cost brings limitations, especially in low-income countries [4,15,17,25]. Most pediatric rheumatologists or nephrologists start induction therapy with 3–6 months of CYC pulse therapy with a transition to MMF after the good response is achieved. In a recent study conducted by the SLE Subcommittee of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) for the induction therapy of newly diagnosed proliferative LN, a consensus has been achieved by the majority of pediatric rheumatologists in North America on using either MMF or IV CYC in combination with one of the three different CS regimens, including oral, IV, or mixed oral and IV steroids [14]. In patients with Class V LN, MMF is also used as a steroid-sparing agent [2].

B-lymphocyte depletion therapy

The multiple roles of B-lymphocytes in the pathogenesis of SLE have led to production of several B-cell-targeted therapies for the treatment of LN [3–5]. In recent years, rituximab (RTX) has been successfully used in both adult and pediatric patients, with SLE usually combined with CYC or with other immunosuppressive drugs [26–30]. Podolskaya et al. [26] used RTX therapy in 19 children with SLE for acute life- or organ-threatening symptoms or findings that had not responded to standard treatment. The dose of RTX was 750 mg/m² and was twice intravenously given usually within a 2-week period. A rapid reduction of SLE disease activity and improvement in renal functions were observed within the first month without serious side effects. On the other hand, Willems et al. [27] treated 11 girls with severe SLE with 2 to 12 IV infusions of RTX (350–450 mg/m²) in addition to steroids. However, severe adverse events developed in five patients. The most frequent adverse effects included severe infections and severe hematologic toxicity, and retreatment with repeated doses of RTX was not recommended unless there was evidence of flare of disease activity after return of B-lymphocytes to the peripheral circulation [5,27]. There are also concerns of the development of human anti-chimeric antibodies and JC (a polyoma) virus-induced progressive multifocal leukoencephalopathy as further side effects with RTX [5]. Studies on drug development to identify a fully humanized monoclonal antibody with B-lymphocyte depletion properties and studies on adult SLE patients with a second-generation antibody called ocrelizumab and a humanized anti-CD22 agent called epratuzumab are also ongoing [5].

Cyclosporin A

Cyclosporin A (Cyc A) can also be used in LN, but there are only a few trials involving a small number of patients studying the effects of it on LN [4]. Aragon et al. [31] showed that together with MMF, Cyc A has been an alternative agent in the induction therapy in children with severe LN. There are also studies in children showing its effectiveness as a treatment option in the treatment of refractory cases of LN, but with high relapsing rates after cessation of the therapy [32,33].

Mizoribine

Mizoribine, a novel purine synthesis inhibitor, was developed in Japan [34,35]. It has been successfully used by Japanese physicians with an intermittent oral pulse therapy protocol for the treatment of flares or as induction therapy in severe LN without any serious side effects [36–38].

Azathioprine

Azathioprine (AZA) is the first-line drug used in the maintenance therapy of mild SLE at a dose of 2–2.5 mg/kg/day and is well tolerated. However, there are also some reports showing its successful use in induction therapy protocols [39,40].

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) can be used as regular infusions at every 4–6 weeks at a dose of 2 g/kg up to a maximum of 70 g. Although it is particularly useful in children with severe hematological disease, its usage has been limited because of its availability and there are very few reports of its use in children with SLE [5].

Plasma Exchange

Although controversies exist, plasma exchange can be used in very severe and refractory cases of SLE in which 5 to 10 plasma exchanges seem to be useful in acute severe disease [1,5].

New drugs and stem cell transplantation

Along with ocrelizumab and epratuzumab, cladribine, fludarabine, belimumab, epratuzumab, atacicept, abetimus,
infliximab, tocilizumab, eculizumab, belatacept, abatacept, sirolimus, and rigeromid are new drugs tested for SLE offering some hope for better outcomes for patients with LN in the near future [4]. There are also limited reports about successful stem cell transplantations in adult SLE patients, but reports including pediatric patients are lacking [41,42].

**Maintenance Therapy**

The second part of the therapy is a longer phase during which less intense immunosuppressive drug regimens are used to sustain remission while attempting to minimize their side effects [4] (Table 2). The goal of this therapy is to control disease activity, to minimize disease flares, and to prevent the progression of chronic fibrous lesions while limiting short-term and long-term drug toxicity [1,4]. However, the choice and length of maintenance therapy in severe LN are debatable.

Maintenance therapy in severe LN should continue at least 2–3 years and possibly indefinitely in many cases [5]. Low-dose daily or alternate-day treatment with corticosteroids for several years is usually needed [1,5,21]. Azathioprine is the other drug that has been widely used in the maintenance therapy of childhood SLE. However, in recent years, MMF has been found to be more effective than AZA in maintenance therapy, with better patient and event-free survival in adult and pediatric patients [5,25,21].

Oral hydroxychloroquine at a dose of 4–6 mg/kg/day (up to 10 mg/kg/day) is useful in children with marked skin disease, lethargy, arthritis, and hyperlipidemia, improving cardiovascular outcomes and reducing the incidence of atherosclerosis. Patients receiving hydroxychloroquine prior to development of LN were shown to have less severe courses with better survival rates [1,5]. However, annual ophthalmological examinations of these patients should not be neglected to check color vision.

### Supportive Therapy

Supportive therapy is also an important approach for the improvement of SLE outcomes. As children with LN have become more likely to survive to adulthood than ever before, late complications such as the development of premature atherosclerosis, neurocognitive impairment, and osteoporosis were increased [1]. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) are used in most children for hypertension and/or proteinuria, resulting in the delay of kidney deterioration and cardiovascular disease [4,5]. Anticoagulants may be beneficial in treating nephrotic syndrome patients who have positive anticardiolipin antibodies, antiphospholipids or previous cloths [5]. Monitoring of normal growth and pubertal development, calcium and vitamin D supplementations in osteoporosis are also necessary [4]. Infectious complications should be promptly detected and treated. Finally, renal replacement therapies including renal transplantation can be used together with supportive treatment in patients who progressed to ESRD [4].

### Prognosis

The natural history of SLE showed that few patients with severe LN survived more than 2 years [5]. In recent decades, the survival rates in childhood SLE have increased with the introduction of new drugs and therapeutic regimes for the management of the disease itself and its secondary complications, like infections. Many studies from different countries show that 3-year survival rates are between 88–91%, while 5-year survival rates are between 76% and 84% [43–46]. Some current studies also suggest 5-year survival rates exceeding 90% in many countries [3,15,47]. Despite this improvement in mortality rates, there are still a significant number of patients that have developed ESRD due to LN even in most developed countries [48–49]. Five-year renal survival was reported to be between

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**Table 2. Maintenance therapy in childhood lupus nephritis.**

<table>
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<th>Drug</th>
<th>Suggested Dose</th>
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<tr>
<td>Oral prednisolone</td>
<td>10-15 mg/day or alternate days (where possible)</td>
</tr>
<tr>
<td>Oral azathioprine (AZA)</td>
<td>2-2.5 mg/kg/day</td>
</tr>
<tr>
<td>Oral mycophenolate mofetil (MMF)</td>
<td>0.6-1.2 g/m2/day, maximum 3 g/day in two divided doses</td>
</tr>
<tr>
<td>Oral hydroxychloroquine</td>
<td>4-6 mg/kg/day (up to 10 mg/kg/day)</td>
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75–82.4% in Malaysia, Korea and Egypt [45,47,50]. In a study from the USA, 5-year kidney survival was 77% among 73 patients with proliferative LN [48]. We also found the renal survival rates at 5, 10, and 14 years as 78.9% in a study conducted on 46 patients with diffuse proliferative LN (Class IV) [16].

Different studies report different effects of racial, ethnic and regional variations on the prognosis of LN [4,5]. However, the presence of proliferative LN, and continuously active nonremitting or relapsing disease are the primary risk factors for death or poor outcomes in LN. Gibson et al. [48] found that remission, whether complete or partial, and early response to therapy were associated with improved kidney survival, while nephritis relapse and treatment resistance are strong predictors of progression to ESRD.

Despite preventive measures, disease flares frequently occur in LN. Urinalysis, proteinuria and kidney functions are fundamental tools for monitoring these patients and a repeat biopsy can be needed on an individual basis to determine the management protocol of the patient [4]. Non-adherence to therapy, especially in an adolescent age group, also results in relapse of symptoms and sometimes causes an acute presentation with renal failure after initial successful treatment. In this situation, IV agents can be considered to ensure adherence and disease control [5].

**Conclusion**

Although the prognosis of LN has improved in recent decades, varying degrees of chronic renal impairment, including ESRD, can still develop. Thus, children with lupus nephritis require early and adequate treatment to protect the kidneys from developing chronic damage. However, determining the optimal balance between potential benefits and adverse side effects of the drugs is always a difficult process in the management of pediatric lupus nephritis and there is still no consensus on the best treatment model. Each patient requires individual consideration and the therapy should be designed according to the severity of the disease, economic factors, and the clinician’s experience. Investigations on new drugs and treatment approaches are offering some hope for better outcomes for patients with LN in the near future.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**


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