REVIEW

Proliferative nephritis in childhood-onset systemic lupus erythematosus: current therapeutic approaches and future perspectives [version 1; referees: 1 approved, 1 approved with reservations]

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Abstract

Renal involvement occurs in 50-75% of children with childhood-onset systemic lupus erythematosus (cSLE). Proliferative lupus nephritis (LN) represents the most common pattern of renal involvement in cSLE. Despite aggressive treatment, progression to end stage renal disease can occur in up to 5-10% of children. Over the last 2 decades, tremendous advancements have been made in the treatment of pediatric LN. Special considerations in children need to address the impact of disease and therapy on both physical and psychological growth and development. This review will focus on pivotal clinical trials in the treatment of proliferative LN, with a focus on pediatric data when available.

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Introduction
Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune disease characterized by multi-organ system involvement, widespread inflammation and the presence of autoantibodies. Childhood-onset SLE (cSLE), defined as SLE with age of onset prior to 18 years of age, occurs in 15–20% of cases. Despite the similarities between cSLE and adult-onset disease, children have a higher frequency of major organ involvement and are more likely to suffer from damage accrual throughout their lifespan. Renal involvement is no exception and occurs in 50–75% of children with cSLE, with the majority demonstrating evidence of renal involvement within the first 2 years of diagnosis.

The severity of lupus nephritis (LN) varies from mild subclinical disease to diffuse proliferative nephritis. In 1974, the World Health Organization (WHO) introduced a histologic classification criterion for lupus glomerular disease that was revised in 2004 by the International Society of Nephrology/Renal Pathology Society (ISN/RPS). Evaluation of renal biopsy using these criteria is critical in determining the acute management and long-term prognosis of patients affected with LN. Briefly, Class I and II represent mild mesangial disease and typically do not require intensive treatment. In contrast, Class III and IV represent a more progressive proliferative glomerular involvement that requires aggressive induction and maintenance therapy in an attempt to prevent long-term morbidity and mortality. Membranous LN (Class V) is less common and traditionally thought to be less severe.

Proliferative LN (Class III and IV) represents the most common pattern of renal involvement in cSLE. Despite aggressive treatment, progression to ESRD can occur in up to 5–10% of children. Risk factors for progression include delay to treatment, African American race, Hispanic ethnicity, elevated serum creatinine, hypertension, nephrotic range proteinuria, anemia, and biopsy findings (including degree of proliferation and chronic tubulointerstitial changes). In a recent survival analysis conducted by Mok et al., the life expectancy in patients with SLE with renal disease and renal damage was reduced by 15.1 and 23.7 years respectively, as compared to the general population. These findings further underscore the importance of appropriate classification and prompt treatment of LN.

Over the last two decades, tremendous advancements have been made in the treatment of pediatric LN. The majority of data has been extrapolated from clinical trials in adult-onset SLE. Data in children is primarily based on few prospective studies, retrospective investigations, cross-sectional analysis and anecdotal evidence. This review will focus on pivotal clinical trials in the treatment of proliferative LN, with a focus on pediatric data when available.

General treatment considerations
Treatment of cSLE is targeted toward optimizing efficacy while minimizing drug duration and toxicity. Special considerations in children need to address the impact of disease and therapy on both physical and psychological growth and development. The risk of lupus flare and disease relapse is simultaneously a significant concern in adolescents struggling with understanding the concept of a chronic disease and limited insight regarding consequences of poor adherence to therapy. Similar to adults with LN, treatment is often dictated by histological classification seen, with proliferative forms of LN requiring more aggressive management to prevent progression to ESRD.

Corticosteroids
With the introduction of corticosteroids as the mainstay of pharmacological therapy for SLE, patient outcomes have improved dramatically. Treatment regimens vary significantly between physicians and include corticosteroid administration via primarily an oral route, primarily intravenous methylprednisolone pulses or a mixed approach. Recent evidence suggests that high-dose intravenous methylprednisolone pulses have the potential to eliminate the type I interferon signature (a predominant cytokine in the pathogenesis of SLE) by reducing the number of plasmacytoid dendritic cells. These findings were not seen with administration of lower-dose oral corticosteroids.

Despite the ubiquitous use of corticosteroids in the treatment of cSLE, prolonged usage results in a significant contribution to patient morbidity. Side effects are numerous and include Cushing syndrome, growth suppression, osteoporosis, behavioral disturbances, cardiovascular effects, ophthalmologic toxicity and myopathy. Among all of these, perhaps the most common and most distressing side effect in adolescents with cSLE is the presence of Cushing syndrome, associated with obesity, acne and hirsuitism. These toxicities may be limited by consolidating daily administration to a single dose given in the morning. Alternate day dosing and intravenous pulse therapy have also been shown to minimize adverse effects.

In order to prevent toxicity in growing children, it has become standard practice to initiate treatment with oral or intravenous corticosteroids at the onset of LN, usually in combination with an additional steroid sparing agent. As will be demonstrated in several of the clinical trials listed below, monotherapy with oral or intravenous corticosteroids for proliferative LN is typically inferior to combination therapy with an additional immunosuppressant.

Cyclophosphamide
Cyclophosphamide (CYC), an alkylating agent, is a nitrogen mustard derivative that functions by binding to guanine in DNA, destroying the purine ring and preventing cell replication. The first controlled trial reporting short-term efficacy of CYC in adults with LN was published in 1971. Since that time, a series of randomized controlled trials (RCT) sponsored by the National Institutes of Health (NIH) have investigated various treatment regimens including CYC and corticosteroids in the management of adults with proliferative LN. In the initial landmark study in 1986, Austin et al. demonstrated efficacy and preservation of renal function in patients receiving intravenous CYC (every 3 months) plus low dose steroids as compared to high-dose steroids alone. Subsequently, a RCT by Boumpas et al. defined what is now referred to as the “high-dose” regimen of CYC in the management of LN. In this study, patients received monthly CYC (0.5–1.0 g/m²) for 6 months followed by quarterly pulse CYC for an additional 2 years and demonstrated superior preservation of renal function as compared to high-dose corticosteroids alone. This study was fundamental in demonstrating the need for long-term maintenance therapy to prevent disease flare in patients with LN. An additional NIH trial in 1996 further confirmed the benefits of
intravenous pulse CYC plus corticosteroids in the treatment of proliferative LN, suggesting benefit of combination therapy over either medication alone\(^1\).

Data from these early NIH trials supported the role of CYC in the management of proliferative LN, however high rates of short-term and long-term side effects including infection and premature ovarian failure limited adoption. As a result, investigators in the Euro-Lupus Nephritis Trial established what is now known as the “low-dose” regimen of CYC, consisting of a fixed dose of 500mg every 2 weeks for a total of six doses\(^2\). There were no significant differences in treatment outcomes, renal remission or disease flare in patient receiving low-dose CYC as compared to the conventional high-dose regimen established in the NIH trials. This study, while important in providing an alternative option for CYC dosing in a specified population of patients with LN, has been criticized for having patients with milder forms of renal disease and limited number of higher risk African American patients. It has been suggested that patients of African American descent generally have a less favorable response to CYC as compared to other ethnic groups; thus treatment with high dose CYC or an alternative immunosuppressant (as discussed below) is generally recommended\(^3,4\).

Several smaller prospective and retrospective studies have supported the use of these CYC regimens in the treatment of pediatric patients with proliferative LN. In a prospective study in children with proliferative LN, Lehman et al. demonstrated a reduction in proteinuria, improved renal function, and a reduction in corticosteroid dose in children receiving high-dose CYC with an extended course of therapy\(^5,6\). Similarly, a retrospective study by Baskin et al. demonstrated efficacy of low-dose CYC in the induction therapy of 20 children with proliferative LN\(^6\). In a larger retrospective study of 108 Thai children with severe proliferative LN, a positive renal response was noted after induction therapy with CYC, however long-term results appeared less promising\(^7\). A randomized trial comparing low-dose versus high-dose intravenous CYC in children with proliferative LN is currently underway (clinicaltrials.gov: NCT01861561).

The lack of evidence-based recommendations specific to cSLE led the Childhood Arthritis and Rheumatology Research Alliance (CARRA) to develop consensus treatment plans (CTP) to determine the optimal therapeutic strategy for induction therapy in children with proliferative LN. Based on this CTP, physicians were given an option of choosing monthly doses of intravenous CYC (0.5–1g/m\(^2\)) for a total of six doses to be used in conjunction with one of three options for oral/intravenous corticosteroids\(^8\). The expert panel recommended adjusting the CYC dose for renal insufficiency and for a low white blood cell nadir, which occurs 7–10 days after the infusion of CYC\(^9\).

The long-term safety of CYC in children is not well defined. Leukopenia and thrombocytopenia are the most common adverse reactions, although with close monitoring they are rarely clinically significant. Additional risks include infection, bladder toxicity (such as hemorrhagic cystitis), syndrome of inappropriate antidiuretic hormone, GI toxicity, alopecia, malignancy and effects on fertility. It has been suggested that gonadal failure is greatest in sexually mature males, increases with age and is dependent on cumulative dose of CYC. Despite the reduced risk in children as compared to adults, it has been estimated that premature ovarian failure can develop in 11% of girls treated with CYC for cSLE\(^10,11\). As a result, strategies to preserve reproductive potential in girls and boys with SLE have been recommended\(^12\).

Azathioprine

Azathioprine (AZA) is a purine analog that inhibits purine and nucleotide interconversion, interfering with DNA synthesis. It has been used longer than any other second-line agent in the treatment of cSLE. It has advantages of reduced cost, dosing frequency and improved safety profile that has led to the study of AZA as a less toxic alternative to CYC in the treatment of SLE. In early studies of proliferative LN, AZA plus corticosteroids appeared to reduce the risk of all-cause mortality compared to steroids alone, but had minimal effects on long-term renal outcomes\(^13\). In a Dutch Lupus Nephritis Study, patients treated with oral AZA (2 mg/kg/day) and corticosteroids as induction therapy for proliferative LN were more likely to have renal relapse and increasing serum creatinine as compared to intravenous CYC in long-term follow up\(^14,15\). Furthermore, repeat renal biopsies in this group demonstrated a progression in the chronicity index in patients treated with AZA compared to CYC\(^16\). As a result of these studies, AZA is generally not recommended for induction therapy in proliferative forms of LN.

In contrast to these reports, investigations into the use of AZA as maintenance therapy have been more promising. As mentioned previously, the early NIH trials demonstrated the need for longer treatment courses in the therapy of proliferative LN to prevent renal relapse and improve long-term outcomes. Initially achieved with quarterly doses of CYC, this approach was later changed to AZA as a more efficacious and safer agent for long-term maintenance of renal remission after induction with intravenous CYC\(^17,18\). As a result of these studies, the American College of Rheumatology (ACR) recommends AZA (2 mg/kg/day) with low dose corticosteroids as a possible treatment option for the maintenance phase of therapy for proliferative LN. AZA may be preferable in women who are in complete remission and desire to become pregnant or in patients with intolerable side effects from alternate immunosuppressive agents.

Mycophenolate mofetil

Mycophenolate mofetil (MMF), an inhibitor of inosine-monophosphate-dehydrogenase, is a selective, non-competitive inhibitor of purine synthesis that primarily affects T- and B-lymphocytes. MMF was introduced during the late 1990s for the treatment of severe forms of LN with demonstration of favorable renal outcomes, reduced toxicity and ease of administration. Several trials have now justified the use of MMF as an alternative therapeutic option in both the induction phase and maintenance phase in the therapy of proliferative LN.

To evaluate the utility of MMF in the induction therapy of LN, several randomized trials have been performed comparing MMF to both oral and intravenous forms of CYC. The initial study was performed in 2000 in a Chinese population of adults with LN. This was the first comparative study to demonstrate equivocal rates of renal
MMF has also been studied as a maintenance therapy for proliferative LN and has demonstrated superior efficacy to quarterly intravenous CYC\textsuperscript{37}. Comparison with AZA has been evaluated with several studies demonstrating either equivocal or superior results of MMF over AZA. In the MAINTAIN Nephritis Trial (an extension of the Euro-Lupus Nephritis trial), patients were randomized to receive MMF (2 g/day) versus AZA (2 mg/kg/day) after induction with low-dose CYC. There was no difference in renal outcomes or time to disease flare in either group\textsuperscript{35}. In the larger, more ethnically diverse ALMS study, MMF (2 g/day) performed superior to AZA (2 mg/kg/day) with significantly fewer treatment failures and improved renal outcomes\textsuperscript{36}. As a result of these investigations, the ACR recommends treatment with MMF (2–3 g/day) as induction therapy in African American and Hispanic patients, and as an option for maintenance therapy after successful induction.

Studies on the use of MMF in childhood onset SLE are limited and primarily based on case series and retrospective reviews. These studies have confirmed the use of MMF as an efficacious option in the treatment of children with LN without any recorded major side effects\textsuperscript{38,39,40}. In a sub-analysis of adolescent patients (12–18 years old) who participated in the ALMS study, results were similar to that of the adults with equivocal renal response rates between MMF and intravenous CYC for induction therapy and comparable efficacy between MMF and AZA for the maintenance phase\textsuperscript{41}. Few studies have demonstrated less promising results with MMF in proliferative LN in children; however patient numbers were small and primarily included children with refractory disease\textsuperscript{44}. Based on these results, the CTP for induction therapy in proliferative LN in cSLE also includes MMF (600 mg/m\textsuperscript{2}/dose twice daily) with corticosteroids as an alternative option to intravenous CYC\textsuperscript{30}.

Although generally better tolerated than CYC, studies have demonstrated increased risk of gastrointestinal (GI) symptoms and diarrhea with MMF. GI toxicity may be improved by increasing dosing frequency to three or four times per day. Other side effects include cytopenias, infection, malignancy and teratogenicity. This latter issue may be of particular concern in adolescent females with high-risk behavior. As a result, the mycophenolate pregnancy registry has been established to assure enhanced patient education regarding contraceptive options and monitoring of pregnancy status. A final concern notable in the pediatric population is concern for patient adherence. Expert consensus has not been achieved to determine if therapeutic drug monitoring of MMF should be utilized, however random levels may be obtained to screen for patient compliance\textsuperscript{35}.

**Rituximab**

Rituximab, a chimeric monoclonal antibody against B-cell CD20 receptor, has recently emerged as an important therapeutic option in patients with resistant or relapsing proliferative nephritis. Its role in the induction therapy of proliferative LN has been evaluated in the Lupus Nephritis Assessment with Rituximab (LUNAR) study\textsuperscript{42}. In this study, patients with proliferative LN were randomized to either rituximab or placebo (with a background of MMF and corticosteroids). There were no significant differences in renal response rates between rituximab and placebo. Despite earlier uncontrolled trials suggesting possible benefit, these results were insufficient to support primary use of rituximab; therefore it is not recommended as a first-line agent in the induction therapy of LN. In contrast, favorable results have been reported in small observational studies and case reports of proliferative LN that is resistant to MMF or CYC\textsuperscript{43,44,45}.

Limited studies in children have demonstrated refractory LN as the primary indication for the use of rituximab (750–1000 mg/m\textsuperscript{2}/dose given 2 weeks apart) in cSLE with significant improvements in disease activity\textsuperscript{46,47,48}. A report by Lehman et al. additionally suggests benefit in combination therapy with rituximab (750 mg/m\textsuperscript{2}/dose, max 1 g/dose) and cyclophosphamide (750 mg/m\textsuperscript{2}/dose) in 12 children with refractory SLE\textsuperscript{49}. These patients were given the combination therapy for two doses given 2 weeks apart at the start of the study, month 6 and month 18. The results suggest improvement in disease activity with reduced need for corticosteroid administration.

In patients who fail CYC or MMF, a switch to rituximab plus corticosteroids is supported by guidelines from the ACR and the European League against Rheumatism (EULAR). Serious adverse events include infusion reactions and anaphylaxis; thus premedication with antihistamines, acetaminophen and/or corticosteroids is typically recommended. Other side effects include hypogammaglobulinemia, infection and progressive multifocal leukoencephalopathy. Reduced levels of immunoglobulins for prolonged periods appear to be more common and significant in children than adults and thus may require immunoglobulin replacement therapy.

**Tacrolimus and Cyclosporine A**

Calcineurin inhibitors, with primary effects on T-cell expansion, have additionally been evaluated for a potential role in the treatment of proliferative LN. Tacrolimus has been compared with CYC and MMF in several short-term studies in the induction therapy of Chinese adults with proliferative LN. In one study, a combination of tacrolimus (4 mg/day), MMF (1 g/day) and corticosteroids were compared with high-dose intravenous CYC and found to result in greater renal response rates; however the regimen was also noted to have an increased number of serious adverse events\textsuperscript{51}. Two smaller studies similarly showed equivocal remission rates in Chinese patients treated with tacrolimus, intravenous CYC or MMF\textsuperscript{52,53}.
A small randomized study demonstrated equivocal renal outcomes in children treated with cyclosporine A and steroids as compared to oral CYC\textsuperscript{34}. This study was limited by the fact that induction therapy with high-dose corticosteroids began prior to randomization. In another study targeted toward the maintenance phase of therapy, cyclosporine A was shown to be as effective as AZA after induction with oral CYC\textsuperscript{35}. This data, although promising, had limited follow up and thus has been insufficient to support the use of tacrolimus or cyclosporine A as initial therapeutic agents in management of proliferative LN. In addition, use has been limited due to concerns for renal toxicity, hypertension and increasing serum creatinine. These medications should be considered in patients who cannot tolerate or have contraindications to the first-line agents described above.

**Abatacept**

Abatacept is a fully human, soluble fusion protein composed of the Fc region of IgG\textsubscript{1} and the extracellular domain of CTLA-4. It competitively binds to CD80/86 on antigen presenting cells as an inhibitory signal, preventing T-cell activation. Two recent studies in adults with SLE have reported on the use of abatacept as a potential agent in the management of proliferative LN. In the first study, abatacept was administered in combination with low-dose CYC and corticosteroids\textsuperscript{36}. When compared with placebo, abatacept did not appear to have any added benefit on renal outcomes. In another 12-month RCT, patients were randomized to receive placebo, standard dose abatacept (10mg/kg) or higher dose abatacept (30mg/kg followed by 10mg/kg)\textsuperscript{37}. As a result, patients failed to meet their primary endpoint of reduction in lupus flares and were also noted to have increase adverse events (ie. infection). Despite these disappointing results, abatacept is occasionally considered as an alternative therapy in the management of refractory LN and has anecdotally resulted in positive renal responses in two adolescents in our center with prolonged, refractory disease.

**Belimumab**

Belimumab is a fully humanized monoclonal antibody that binds soluble B-lymphocyte stimulator (BLyS, also known as BAFF), an immunomodulatory cytokine that promotes B-cell survival and differentiation. Two large RCT have demonstrated improved disease activity in adult patients with SLE treated with belimumab as compared to placebo\textsuperscript{38,39}. The outcomes of these trials resulted in belimumab becoming the first new drug approved for lupus in over 50 years. Additional trials are additionally underway to evaluate the safety and efficacy of belimumab in children and to examine potential use in adult patients with active LN (clinicaltrials.gov: NCT01649765 and NCT01639339).

**Emerging therapies**

Despite the major advances that have occurred in the treatment of proliferative LN over recent decades, investigators continue to seek out more effective and less toxic treatment protocols to improve the long-term morbidity and mortality related to this disease. Many trials are currently underway to investigate various combination therapeutic approaches and newer biologic agents that target more specific inflammatory pathways.

One group has piloted the “steroid- avoiding rituxilup” protocol consisting of two doses of rituximab (1 g/dose) and intravenous methylprednisolone (500 mg) followed by maintenance therapy with MMF for the treatment of adults with LN\textsuperscript{40}. Early reports have demonstrated that 72% of patients achieved complete response by a median time of 36 weeks, with 11 patients experiencing flare within a median time of 65 weeks. An open label RCT is expected to further address the efficacy of this protocol to treat LN with avoidance of oral steroids (clinicaltrials.gov: NCT01773616).

Epratuzumab, a monoclonal antibody against CD22 antigen on B-cells is a biologic agent that has shown promising results in open-label, phase I and phase II trials in adults with SLE\textsuperscript{41-43}. Epratuzumab has been reported to be well-tolerated and effective in treating numerous SLE disease manifestations. Patients with moderate, stable renal involvement have been included in these studies, suggesting the potential utility of this agent in the treatment of LN. Phase 3 clinical trials are currently ongoing (clinicaltrials.gov: NCT01261793). Tocilizumab, a humanized monoclonal antibody against interleukin-6 receptor has additionally been evaluated for the use in mild to moderate SLE. In a small, open-label, phase I trial, tocilizumab was found to have promising clinical and serologic responses\textsuperscript{44}.

**Less supported therapies**

Current data do not support the role of plasma exchange or abetimus (an immunomodulatory agent targeted against antibodies to dsDNA) in the treatment of isolated proliferative forms of LN\textsuperscript{45-47}. Placebo controlled trials of abetimus have shown significant reductions in anti-dsDNA antibodies, however time to renal flare or number of renal flares was not significantly better than placebo\textsuperscript{48,47}. Ocrelizumab, a fully humanized anti-CD20 monoclonal antibody was evaluated in two phase III RCTs and found to have similar results to rituximab but was stopped due to the incidence of serious infectious adverse events\textsuperscript{49}. Atacicept, a soluble fully human recombinant anti-APRIL fusion protein, was also tested in phase II trials in adult patients with SLE, however the study was halted prematurely due to two reported deaths in the treatment group\textsuperscript{50}.

**Adjunctive treatment**

In integral component of improving renal outcomes in children with LN is the use of supportive therapies in combination with the immunosuppressive agents discussed above. Hydroxychloroquine (HCQ) has been shown to prevent SLE flares and may reduce the risk of renal damage and clotting events\textsuperscript{50,71}. Dose adjustments may be required in patients with impaired renal function to prevent ophthalmologic toxicity. In addition, anti-hypertensive agents, diuretics, anticoagulants and lipid lowering agents are the mainstay of adjunctive therapy. In patients with proteinuria, anti-hypertensive agents that inhibit the renin-angiotensin system (ie. angiotensin converting enzyme inhibitors and angiotensin receptor blockers) play a crucial role in reducing urinary protein excretion, which has been shown to be an independent risk factor for progression to ESRD. Calcium and vitamin D supplementation is also beneficial in improving bone health in children with SLE and a prolonged corticosteroid burden. Lastly, infection remains the most common cause of mortality in cSLE, thus close monitoring is required for children on immunosuppression.

**Conclusion**

Renal outcomes in pediatric LN have significantly improved with current induction and maintenance protocols. Despite improved
survival rates, long-term outcomes and life expectancy in children with proliferative LN remains unacceptable. Increased efforts toward early diagnosis, targeted therapy with reduced toxicities and special attention to infectious and thrombotic complications are critical in optimizing care for these children. In addition, further investigation into the duration of therapy to prevent disease flares while limiting unnecessary long-term medication toxicity is warranted.

Competing interests
No competing interests were disclosed.

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References


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Open Peer Review

Current Referee Status: ✔️

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Overall this is a thorough review of the current accepted treatments for childhood/pediatric SLE.

Data provided was fair and balanced with a good overview of the current literature. First paragraph of introduction could use supporting references. It would be helpful to clarify which studies included pediatric patients throughout (it is clear in the cytoxan section but notably absent in the azathioprine section). Additionally, the corticosteroid section includes recommendations on dosing schedules but is lacking references. Similarly, the Adjunctive Therapy section could also benefit from additional sources.

There was a recent study (published after this paper was submitted) on maintenance therapy that would be appropriate for inclusion: 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 Aug;42(8):1392-400.

In “Less Supported Therapies” section, it would be useful to know cause of fatalities in study that was concluded early due to deaths.

In conclusion, this is a well-researched review with a good summary of the available data. Additional sources could be added to assist the reader looking to do further research, but the article as it stands will provide a useful resource for those looking to learn more about this topic.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Anne Eberhard
Department of Pediatrics, Cohen's Children's Medical Center of New York, New York, NY, USA
The author has provided a review of proliferative nephritis in childhood SLE, the aim of the review was to concentrate on the pediatric data where available.

Comments:

**Introduction**

1. References are left out from the introduction; the first 4 paragraphs are making statements essentially without any references.

2. In para 3 the study cited, authored by Mok *et al.*, is primarily in adults and that needs to be clarified.

3. Para 4 line 4: add in “based on a few…”

**Corticosteroids**

1. Remove the 2 'primarily's in lines 4 and 5 of para 1.

2. Reference the statement on alternate day dosing and reduced side effects.

3. As the aim of the paper was to outline studies in children, I would expand the studies referenced regarding pediatrics in this section They have been reduced to a paragraph. Refer back to pediatric vs adult outcomes in these studies and if they differ.

**Azathioprine**

1. The authors have failed to mention studies done in children with AZA – some referenced below:

   Immunosuppressive Therapies for the Induction Treatment of Proliferative Lupus Nephritis: A Systematic Review and Network Metaanalysis.
   Simon Yu Tian, Brian M. Feldman, Joseph Beyene, Patrick E. Brown, Elizabeth M. Uleryk and Earl D. Silverman

   J Rheumatol. 2002 Dec;29(12):2635-42.
   Longterm followup of childhood lupus nephritis.

2. Please also reference the ACR article on using AZA as maintenance.

**Rituximab**

1. Mention that children will need to be revaccinated, particularly against pneumococcus.

**Belimumab**

1. Specifically address the efficacy of belimumab in proliferative nephritis in these studies.

**Adjunctive Therapy**

1. First word, first line is In but should be An.

**Conclusion**

1. Regarding the statement in last paragraph (life expectancy in proliferative LN) reference this and compare results between adults and children.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
Competing Interests: No competing interests were disclosed.