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Recent advances in Immunotherapies for Lupus Nephritis

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Abstract

Childhood-onset systemic lupus erythematosus (SLE) is characterized by increased rates of kidney involvement, termed lupus nephritis. Despite the significant morbidity and mortality associated with this disease, lupus nephritis trials have been plagued by repeated failures to meet clinical endpoints. However, improvements in trial design and the development of targeted approaches have begun to yield promising results, including two new FDA-approved lupus nephritis treatments since 2020. These include belimumab, a monoclonal antibody targeting the B cell survival cytokine BAFF (B cell activating factor), and voclosporin, a cyclosporin analog with improved pharmacokinetic characteristics. In this review, we will summarize the data supporting regulatory approval for these agents in lupus nephritis and highlight ongoing clinical trials targeting the diverse immunologic drivers of renal inflammation in SLE. While pediatric patients remain underrepresented in lupus clinical trials, given the increased severity of childhood-onset SLE and need for long-term protection from kidney damage, we anticipate the need for off-label use of these targeted therapies in the pediatric population. Future studies are needed to define optimal patient selection, drug combinations, and treatment duration in pediatric lupus nephritis.

Keywords

Lupus nephritis; Systemic Lupus Erythematosus; Proliferative lupus nephritis; Immunosuppression; Induction Therapy

Introduction:

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that can affect virtually every organ system in the body. Although most frequently developing in adulthood, childhood-onset SLE accounts for 10-20% of all lupus cases [1]. Pediatric lupus is frequently more severe than adult disease, highlighting the need for effective therapies to control autoimmune inflammation in the pediatric population. Of the many clinical manifestations of SLE, the development of lupus nephritis is associated with a worse

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prognosis, including the risk of long-term kidney damage and progression to kidney failure. Unfortunately, approximately 35-40% of children with SLE develop lupus nephritis, most often within the first 2 years after diagnosis [2-5]. Compared with adult patients, data describing the long-term prognosis of childhood-onset lupus nephritis is sparse. In the era prior to use of cytotoxic immunosuppression, clinical outcomes in lupus nephritis were poor. However, more recent data report 92% and 86% five- and ten-year kidney survival in pediatric lupus nephritis [6]. Despite these improved renal outcomes, children with SLE and lupus nephritis endure significantly higher morbidity and mortality compared to healthy children. For these reasons, the development of safe and effective treatments for lupus nephritis able to both treat renal inflammation and prevent the accrual of kidney damage is of critical importance.

In this review, we aim to first review the current standard-of-care for initial therapy of pediatric proliferative lupus nephritis. Next, we will summarize the clinical trial data that supported regulatory approval of two new agents for the treatment of adult lupus nephritis, belimumab and voclosporin. Finally, we will highlight new targeted approaches for lupus nephritis, including reported data from an early-stage clinical trial of obinutuzumab in lupus nephritis and new studies registered on ClinicalTrials.gov. Unfortunately, enrollment eligibility for lupus nephritis clinical trials is generally limited to patients greater than 18 years of age. Thus, the generalizability of published data to pediatric patients remains uncertain. However, given the potential for worse renal outcomes for childhood-onset lupus nephritis, developing clinical experience with these novel therapies is an important goal for the pediatric nephrology community.

Lupus nephritis pathogenesis and classification

A detailed overview of the pathogenesis of lupus nephritis is beyond the scope of this manuscript. However, we refer the reader to several reviews on the immunologic mechanisms driving renal inflammation in SLE [7, 8]. To assist with interpretation of clinical trial data, we will briefly review the histopathological classification of lupus nephritis. The initial classification system published by International Society of Nephrology/Renal Pathology Society (ISN/RPS) in 2003 was most recently updated in 2018 and divides lupus nephritis into six classes (Table 1) [9, 10]. Most studies cited in this review, including those that supported the approval of belimumab and voclosporin, used the original 2003 classification in their inclusion criteria. Class III and IV lupus nephritis are predominant in children with lupus nephritis, accounting up to 75% of cases of renal involvement, with 29% classifying as class III and 49% as class IV disease in one study [11]. Because of worse renal outcomes in patients with proliferative disease [12], the majority of clinical trials in lupus nephritis focus on patients with Class III and Class IV disease, with variable inclusion of Class V (membranous) lupus nephritis. For example, the obinutuzumab trials enrolled Class III/IV nephritis with or without concurrent Class V disease, while the belimumab and voclosporin (AURA-LV and AURORA 1) trials also allowed isolated Class V disease. Included in the 2018 ISN/RPS revision of the classification system was the addition of the activity and chronicity indices based on the National Institute of Health index, aimed at better prognosticating progression of renal disease. It is important to note that available recommendations based on evidence are intended to guide treatment for patients with high

activity index and low chronicity scores, who should not be managed with the same targeted immunotherapies as patients with low activity index and high chronicity scores.

Initial therapy for lupus nephritis: the current standard-of-care.

The treatment of Class III/IV proliferative lupus nephritis has historically been conceptually divided into induction and maintenance phases. While this distinction between treatment phases is somewhat arbitrary, the goal of induction therapy is to achieve remission by controlling inflammation and minimizing parenchymal injury, while the aim of maintenance therapy is to sustain remission and prevent progression of chronic kidney disease. Over the last four decades, significant advances have been made in the treatment of proliferative lupus nephritis, leading to improvements in overall prognosis. A major advance in lupus nephritis therapy was the landmark 1986 trial conducted at the National Institutes of Health (NIH) which showed that cytotoxic chemotherapies, in particular cyclophosphamide, was superior to high-dose prednisone alone in preventing kidney failure in patients with active lupus nephritis [13]. While these findings enhanced clinical outcomes for lupus nephritis patients, the numerous immediate and cumulative adverse effects of cyclophosphamide prompted efforts to discover treatments with improved safety profiles.

In 2000, a trial performed in Hong Kong by Chan et al. demonstrated that mycophenolate mofetil (MMF) resulted in comparable induction of remission compared with IV cyclophosphamide [14]. Despite similar clinical outcomes, MMF treatment was more tolerable, with side-effects such as hair loss and amenorrhea being limited to the cyclophosphamide arm. An important caveat to this study was that few enrolled patients exhibited markers of poor prognosis in lupus nephritis, such as elevated creatinine at time of biopsy, presence of glomerular and tubulointerstitial scarring, and male sex [15]. For this reason, a larger multinational randomized controlled trial, the Aspreva Lupus Management Study (ALMS) group trial, was performed [16]. Using an outcome focused on reduction in urine protein/creatinine ratio and improvement in serum creatinine, the investigators found no significant difference between cyclophosphamide and MMF treatment arms. In addition, no differences were observed in rates of adverse events or infections between treatment groups. An advantage of the ALMS trial was the inclusion of a large and racially diverse population, providing important granular data on differences in response across racial and ethnic groups. The investigators reported that within the subset of black and Hispanic patients, more patients responded to MMF compared to IV cyclophosphamide [16], raising important questions regarding the impact of social determinants of health and structural inequalities on these results. Importantly, while the study did not meet its primary endpoint of showing superior efficacy of MMF compared with IV cyclophosphamide, MMF was found to be consistently effective across all racial/ethnic groups indicating that this therapy is a viable option for initial therapy for proliferative lupus nephritis.

A final strategy for initial treatment of lupus nephritis that limits adverse effects of cytotoxic agents, is a low-dose cyclophosphamide regimen. The Euro-Lupus Nephritis Trial compared the efficacy and toxicity of low- and high-dose IV cyclophosphamide [17]. In the standard high-dose group, patients received 6 monthly IV cyclophosphamide doses (500mg/m^2 titrated up to 1500mg/dose) followed by 2 quarterly doses. In the low-dose group, patients

were given 6 fixed-dose 500mg IV cyclophosphamide infusions every 2 weeks before being transitioned to oral azathioprine. Both regimens achieved similar rates of renal remission after initial therapy, with similar rates of relapses but lower rates of adverse infections in the low-dose group. While the Euro-Lupus Nephritis Trial primarily enrolled subjects with European ancestry, its initial findings were supported by the subsequent Abatacept and Cyclophosphamide Combination Efficacy and Safety Study (ACCESS), in which the Euro-Lupus regimen was used as baseline immunosuppression resulting in similar outcomes to historical data in a racially and ethnically diverse cohort [18].

Founded on these data, the current standard of care for initial therapy in proliferative lupus nephritis specify the use of either cyclophosphamide or MMF in conjunction with corticosteroids. Organizations such as European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) and Kidney Disease Improving Global Outcomes (KDIGO) have published recommendations on initial therapy for proliferative lupus nephritis [19, 20]. As noted above, evidence from randomized clinical trials in children with proliferative lupus nephritis is lacking. For this reason, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) used a structured consensus formation process to develop a consensus treatment plan (CTP) for the treatment of childhood-onset lupus nephritis [21]. This approach was adapted from experience in other pediatric diseases, in which clinical trial data is either lacking or challenging to generate because of limited patient population size. Table 2 summarizes the CARRA CTP for initial therapy of newly diagnosed pediatric proliferative lupus nephritis, which recommends the use of either IV Cyclophosphamide every 4 weeks for 6 months or oral MMF twice per day for 6 months, with three separate standardized corticosteroid taper plans. In Europe, the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) initiative generated a similar set of evidence-based recommendations for the diagnosis and management of childhood lupus nephritis, which outlines a standardized regimen of MMF (1200 mg/m^2/day up to 1800 mg/m^2/day for poor response) or intravenous cyclophosphamide (high or low dose per Euro-Lupus Trial) in addition to prednisone (1-2 mg/kg/day, maximum 60 mg/day), as summarized in Table 2 [22]. The ultimate goal of both the CARRA CTP and SHARE recommendations was to reduce clinical practice variability in order to allow future comparison of clinical outcomes across standardized treatment approaches.

Newly approved treatments for lupus nephritis

Despite improved renal outcomes in proliferative lupus nephritis following standardization of cyclophosphamide and MMF treatment regimens, up to 45% of these patients do not achieve remission within the first 6 months of standard therapy [16]. In addition, protocol kidney biopsies have shown continued histologic activity in a significant portion of patients achieving apparent complete clinical remission [23]. These data emphasize the need to develop additional targeted therapies. In recent years, lupus nephritis clinical trials have showed limited success, including large randomized control trials demonstrating no benefit for drugs targeting diverse immune mechanisms such as co-stimulatory blockade (CTLA4-Ig, Abatacept) [18, 24-26], B cell depletion (anti-CD20, Rituximab [27, 28] and Ocrelizumab [29]), and cytokine blockade (anti-IL-6, Sirukumab) [30]. Fortunately,

researchers and pharmaceutical companies have continued to pursue alternate approaches to treat this challenging disease. This persistence led to two new FDA-approved therapies for proliferative lupus nephritis since 2020: belimumab and voclosporin. We have included a summary of relevant clinical trials of newly-approved and emerging drugs, along with their primary and secondary endpoints and their definitions in Table 3. All included clinical trials use complete renal remission (CRR) as one of their endpoints, as defined by estimated Glomerular Filtration Rate (eGFR) and reduction in proteinuria. While there is variability in the definition of CRR among the trials, remission as defined by normalization in serum creatinine and resolution of proteinuria after immunosuppressive therapy has been shown in previous studies to be a valid predictor for important long-term outcomes such as renal survival and death in the adult lupus nephritis population [31]. In children with class III and IV lupus nephritis, failure to achieve remission at 6 and 12 months after initiation of therapy has been associated with long-term poor renal prognosis (eGFR<60ml/min/1.73m^2 or persistent dialysis) [32].

Belimumab:

Belimumab (Benlysta) is a monoclonal antibody inhibiting the activity of the B cell survival cytokine BAFF (B cell activating factor), also known as BlyS (B-lymphocyte stimulator) [33, 34]. The rationale for targeting this molecule in SLE is supported by several lines of evidence linking elevated serum BAFF to lupus pathogenesis. These include lupus-like disease in BAFF overexpression murine models [35, 36], increased serum BAFF levels in human lupus patients [37], and a genetic risk polymorphism in the *TNFSF13B* gene associated with the development of SLE [38]. These observations spurred the development of BAFF inhibition as a strategy to treat renal and non-renal SLE. In 2011, the FDA approved belimumab for the treatment of extra-renal SLE, based on two large phase III randomized clinical trials, BLISS-52 and BLISS-76. Both studies, involving >1500 total combined patients, demonstrated improved clinical outcomes, as assessed by improvement in SRI (SLE Responder Index), reduced flares, reduced steroid use, and improved serologic activity at 52 and 76 weeks, without increase in rates of serious adverse events [39, 40]. Notably, belimumab was also studied in children with SLE in a phase-2, randomized, double-blinded study examining efficacy, safety, and pharmacokinetics (PLUTO Part A). Children aged 5 to 17 years with active SLE were randomized to receive intravenous belimumab 10 mg/kg every 4 weeks or placebo in combination with standard therapy for 52 weeks. A higher proportion of children in the treatment arm (52.8%) met the primary endpoint of SLE Responder Index (SRI4) response rate compared to with placebo (43.6%) without an increase in adverse events [41].

A notable caveat in both the BLISS and PLUTO trials was that patients with severe active lupus nephritis were excluded. However, a pooled post-hoc analysis of subjects in the BLISS trials with evidence of kidney involvement at enrollment demonstrated more frequent and rapid onset of renal remission, greater reductions in proteinuria, and reduced renal flares in the belimumab arms compared with standard therapy [42]. For this reason, a large multinational, multicenter randomized controlled trial of belimumab in biopsy-confirmed active lupus nephritis was conducted (BLISS-LN). 448 patients were randomized to belimumab 10mg/kg IV q 4 weeks vs. placebo in addition to standard initial

therapy (MMF or cyclophosphamide plus corticosteroids). Primary efficacy renal response was defined as urine protein to creatinine ratio (uPCR) <0.7, eGFR less that 20% below baseline (or >60mL/min/1.73m^2), and no use of rescue therapy. The secondary endpoint of complete renal response was defined as uPCR<0.5 and eGFR <10% of baseline or >90mL/min/1.73m^2. At 104 weeks, a significantly greater proportion of belimumab-treated patients demonstrated primary renal efficacy (43% vs 32%; P=0.03) and complete renal response (30% vs 20%; P=0.02) compared to the placebo group. Although the absolute rate of clinical improvement in this and other BLISS trials was small (~10%), belimumab has an excellent long-term safety profile and is known to reduce disease flares and damage accrual in SLE [43, 44]. Belimumab and potentially other BAFF inhibitors thus have an important role as adjunctive therapy for lupus nephritis. Based on these data, the US FDA approved belimumab for adult patients with active lupus nephritis who are receiving standard therapy in December 2020. Although experience with BAFF blockade in childhood-onset lupus nephritis remains limited, randomized trials of non-renal SLE have demonstrated equivalent efficacy and safety of belimumab in pediatric and adult patients [41, 45]. These pediatric data have facilitated regulatory approval for the treatment of extra-renal lupus from age 5. In summary, while important questions remain regarding appropriate patient selection and duration of treatment, BAFF inhibition is a welcome addition to the repertoire of available therapies to treat proliferative lupus nephritis.

Voclosporin

Calcineurin inhibitors (CNI), particularly tacrolimus and cyclosporin, have been long explored as alternate therapies for the treatment of lupus nephritis. Potential benefits for this class of medications include both inhibition of T cell activation and also direct anti-proteinuric effects via stabilization of the podocyte cytoskeleton [46, 47]. Owing to its more favorable side effect profile and higher potency, tacrolimus is generally preferred over cyclosporin in the treatment of lupus nephritis [48, 49]. A 2015 meta-analysis demonstrated that tacrolimus monotherapy was comparable to MMF and more effective than IV cyclophosphamide at inducing complete remission, while combined MMF and tacrolimus exerted greater clinical benefit than IV cyclophosphamide [50]. However, complex pharmacokinetics requiring frequent drug level monitoring and the potential for both acute and chronic nephrotoxicity have presented challenges in the use of tacrolimus in lupus nephritis [51].

Voclosporin is a cyclosporin analog with an improved pharmacokinetic profile that does not require drug level monitoring [52]. Since the initial discovery of this compound in the mid 1990’s, voclosporin has been studied for multiple conditions, including uveitis [53], plaque psoriasis [54], and kidney transplantation [55]. In each case, promising clinical data was not translated into regulatory approval. This changed after Aurinia Pharmaceuticals acquired the rights to pursue voclosporin as a treatment for autoimmune conditions and designed the phase II (AURA-LV) and phase III (AURORA 1) randomized controlled trials of voclosporin for active lupus nephritis. In AURA-LV, 265 adults with active lupus nephritis were randomized to receive two voclosporin doses (23.7 mg or 39.5 mg BID) or placebo in addition to standard MMF and low dose corticosteroid initial therapy. The primary endpoint was complete renal response (CRR) at 24 weeks, defined as uPCR <0.5 plus eGFR

>60mL/min/1.73m^2 with less than 20% decrease from baseline eGFR. Based on this metric, voclosporin was superior to standard therapy at both 24 weeks (CRR: 32.6% (low-dose) vs 27.3% (high-dose) vs 19.3% (placebo)) and 48 weeks (CRR: 49.4% (low-dose) vs 39.8% (high-dose) vs 23.9% (placebo)). Kaplan-Meier analysis also showed more rapid initial of complete renal response in both voclosporin doses compared with placebo. Unfortunately, these clinical benefits were offset by more serious adverse events, including increased deaths in the low-dose voclosporin group (11.2% (low-dose) vs 2.3% (high-dose) vs 1.1% (placebo)) [56].

Analysis of these data informed the design of a subsequent phase III clinical trial of the lower voclosporin dose (23.7 mg twice per day) in active lupus nephritis (AURORA 1). In this 52-week study, 357 adults with biopsy-confirmed lupus nephritis were randomized to receive voclosporin or placebo in addition to standard MMF and low-dose prednisone initial therapy. The primary endpoint was similar to the phase II AURA-LV study, a composite complete renal response endpoint of uPCR <0.5, eGFR >60mL/min/1.73m^2 (or less than 20% decrease from baseline), no need for rescue medications, and steroid dose of 10mg prednisone per day or less. Complete renal response rates were significantly higher in the voclosporin arm (41% voclosporin vs. 23% placebo; odds ratio 2.65 (95% CI 1.6 – 4.3); p<0.0001), whereas adverse events were reassuringly similar in both groups, including no new onset hypertension, hyperkalemia, or hypomagnesemia [57].

In summary, independent clinical trials showed benefit for a new fixed dose calcineurin inhibitor in active lupus nephritis. In January 2021, the FDA approved voclosporin in combination with background immunosuppression for the treatment of adults with active lupus nephritis. While this new therapeutic option for patients is welcome, important questions remain regarding the use of volcosporin for lupus nephritis. First, although chronic rejection and not direct drug toxicity is likely a major driver of progressive allograft fibrosis in CNI-treated kidney transplant recipients, long-term CNI treatment has been linked with chronic renal fibrosis in non-renal transplant populations [58, 59]. Whether voclosporin treatment carries a similar risk of chronic nephrotoxicity has not been determined, but this concern may be more pertinent to childhood-onset SLE given the need to maintain kidney function for decades. Reassuringly, preliminary data from the AURA2 long-term extension study shows no decline in eGFR following 2 years of volcosporin treatment [60]. Second, it is not yet clear whether the rapid decline in proteinuria in the AURA-LV and AURORA 1 studies is explained by induction of immunologic remission or via podocyte-specific anti-proteinuric effects. If the latter, reduced medication adherence in real world settings may be accompanied by frequent relapse of proteinuric kidney disease. Ultimately, these theoretical concerns are offset by the welcome addition of a new FDA-approved calcineurin inhibitor able to induce remission in patients with proliferative lupus nephritis without requiring frequent drug level monitoring.

New and Emerging Therapies

In addition to the two new FDA-approved therapies, multiple other medications are currently under development for the treatment of lupus nephritis. For the majority of these medications, clinical trials are ongoing and limited data are available to suggest

potential efficacy. For this reason, we will describe recently published data on the use of obinutuzumab in lupus nephritis in detail. The remaining active lupus nephritis clinical trials registered at ClinicalTrials.gov are summarized in Table 4 and Figure 1.

Obinutuzumab

Dysregulated B cell activation is key driver of lupus pathogenesis [34, 61]. For this reason, B cell depletion has long been considered a promising therapeutic strategy in SLE. However, despite promising data from small initial studies, rituximab, a monoclonal depleting antibody targeting the B cell antigen CD20, failed to meet primary efficacy endpoints in two large randomized controlled studies in extra-renal SLE and lupus nephritis, respectively (EXPLORER and LUNAR) [27, 28]. A separate anti-CD20 depleting antibody, ocrelizumab, demonstrated numerically but not statistically significantly improvements in lupus outcomes compared to standard therapy, but higher rates of infectious complications limited further development of this agent [29].

These clinical failures raised important questions regarding the role for B cells in lupus disease. Perhaps patient heterogeneity and challenges in designing appropriate endpoints in lupus clinical trials masked the efficacy of B cell depletion therapies [62]. Alternatively, since disease-defining anti-nuclear antibodies can predate lupus clinical symptoms by years [63], the primary role for B cells may be to initiate an inflammatory cascade in SLE, rather than sustain tissue damage in established disease. Finally, rituximab-resistant $CD20^{neg}$ plasma cells may be an underappreciated driver of lupus pathogenesis [64]. While these factors may have contributed to negative trial results, both animal and human data suggest that the failure to completely eliminate $CD20^{+}$ B cells is a major contributor to the clinical inefficacy of rituximab in SLE. For example, post-hoc analysis of the LUNAR lupus nephritis trial showed that the depth of B cell depletion correlated with improved renal responses [65]. This is relevant since tissue-resident $CD20^{+}$ B cells are known to resist depletion following rituximab treatment in both human lupus patients and in murine lupus models [66].

For these reasons, new “type II” anti-CD20 monoclonal antibodies have been engineered for more potent B cell cytotoxicity. One such agent, obinutuzumab, exhibits greater direct cell killing and antibody-dependent cellular cytotoxicity (ADCC) compared with rituximab, resulting in enhanced B cell ablation in follicular lymphoma, rheumatoid arthritis, and SLE [67-69]. These improved pharmacologic characteristics prompted the design of a phase II trial of Obinutuzumab in active lupus nephritis (NOBILITY). Notably, addition of obinutuzumab to background MMF resulted in increased complete renal response rates at both 52 weeks (35% (obinutuzumab) vs 23% (placebo), p=0.115) and 104 weeks (41% vs 23%, p=0.026) [70]. Treatment was well-tolerated with only modestly increased rates of infusion reactions and no serious adverse events. An ongoing phase III study of obinutuzumab (REGENCY trial) aims to examine the efficacy, safety, and pharmacokinetics of obinutuzumab compared to placebo in combination with standard therapy in class III and IV lupus nephritis. Patients will be randomized to two different Obinutuzumab regimens (1000 mg IV at baseline and weeks 2, 24, 26, 50 and 52 or 1000 mg IV at baseline and weeks 2, 24, 26 and 52) or placebo in addition to MMF and prednisone and followed for

a primary endpoint of complete renal response at week 76 (NCT04221477). Placed in the context of the failed LUNAR trial of rituximab in lupus nephritis, these data suggest that B cell targeting may yet have a role in the treatment of lupus nephritis, provided anti-CD20 agents are selected for their ability to induce deep and durable B cell depletion.

Active lupus nephritis trials

Table 4 summarizes the active lupus nephritis clinical trials registered at ClinicalTrials.gov. As an overall framework, we have divided these approaches into five main groups: 1) disruption of immune cell crosstalk; 2) specific cytokine blockade; 3) plasma cell and/or autoantibody targeted therapies; 4) complement cascade inhibitors; 5) cell signaling inhibitors; and 6) B cell targeted agents. Figure 1 summarizes each of these therapeutic approaches which may prove beneficial for the treatment of lupus nephritis.

Concluding remarks

After decades of minimal advancement, the past few years have heralded major achievements in the ability to treat proliferative lupus nephritis, one of the most severe clinical manifestations of SLE. This is particularly important for pediatric patients who exhibit a higher risk for developing lupus nephritis and have a longer potential to accrue kidney damage. Although the studies described above report promising efficacy and safety in adults, questions remain regarding the use of these new therapeutic agents in children-onset lupus nephritis including the potential for pediatric specific drug toxicity. For example, the use of B cell targeted therapies prior to completion of primary immunization schedule may increase the risk of poor vaccine response. Moreover, while Janus kinase (JAK) signaling inhibition has shown promise in adult-onset extra-renal SLE, blocking growth hormone (GH)-mediated JAK2 phosphorylation might theoretically decrease linear growth in childhood [71]. Alternatively, these new biologic agents may carry pediatric-specific benefits by sparing children from long-term treatment with corticosteroids or cytotoxic agents, which are known to negatively affect growth, development, and fertility. Relying on off-label use and extrapolating dosing guidelines from adult studies subjects children to treatment without clearly understanding the age-specific risk-benefit ratio. For these reasons, efforts must be made to promote inclusion of children and adolescents in drug-development trials for glomerular diseases. The Pediatric Working Group (of the NephCure Kidney International Gateway Initiative) is a group that is spearheading the initiative to facilitate the inclusion of pediatric patients in clinical trials for glomerular diseases through engagement with regulatory authorities in the United States and Europe [72].

Despite this lack of pediatric-specific data, regulatory approval of belimumab, volcosporin, and potentially obinutuzumab in the future, will provide multiple new treatment options for the pediatric nephrology community. In addition, academic clinicians and pharmaceutical companies are pursuing multiple independent strategies which may yield additional benefits to patients. Given the heterogeneity of human SLE and the lack of pediatric clinical trial data, a major challenge will be to identify which patients are likely to gain the most benefit from each of these novel agents. Future observational studies are needed to provide additional guidance on clinical decision making on optimal timing and duration of therapy

as well as appropriate patient selection for these new agents. Finally, improved biomarkers of disease activity and remission are also needed to inform the duration of therapy and balance effective control of inflammation with long-term drug toxicity.

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Multiple choice questions

1. What is the current standard of care for initial therapy for pediatric proliferative lupus nephritis?
   - **A.** MMF and corticosteroids
   - **B.** Cyclophosphamide and corticosteroids
   - **C.** Tacrolimus and corticosteroids
   - **D.** Corticosteroids only
   - **E.** A and B
2. Which of the following statements is FALSE regarding the Aspreva Lupus Management Study (ALMS) trial?
   - **A.** MMF exhibited consistent efficacy across all racial/ethnic groups.
   - **B.** More Black and Hispanic patients responded to MMF compared to IV cyclophosphamide
   - **C.** Rates of adverse events were higher in the IV cyclophosphamide group
   - **D.** MMF was found to be equally effective as IV cyclophosphamide, but not superior
3. Which of the following molecules does Belimumab target?
   - **A.** B cell activating factor
   - **B.** CD20
   - **C.** IL-6
   - **D.** Type I INF receptor
   - **E.** Complement factor D
4. Which of the following drugs is FDA-approved for the treatment of adult active lupus nephritis in combination with background immunosuppression after being shown to induce higher rates of complete renal remission compared to standard therapy alone?

A. Obinutuzumab

B. Voclosporin

C. Ocrelizumab

D. Rituximab

E. Tacrolimus

5. Which of the following is true regarding Obinutuzumab?

A. It failed to induce complete renal response rates higher than MMF in patients with lupus nephritis in the phase II trial

B. It is an anti-CD20 monoclonal antibody

C. Long term treatment carries risk of chronic renal fibrosis

D. Rituximab has been shown to exhibit greater antibody-dependent cellular cytotoxicity than obinutuzumab

E. It is only effective in the treatment of extra-renal SLE

Answers: 1. E; 2. C; 3. A; 4. B; 5. B

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Summary points

- The current standard of care for initial therapy in pediatric proliferative lupus nephritis specify the use of cyclophosphamide or MMF in conjunction with corticosteroids.
- Belimumab, a monoclonal antibody against BAFF (B cell activating factor), and voclosporin, a cyclosporin analog with improved pharmacokinetic characteristics, are two newly FDA-approved drugs for the treatment of adult lupus nephritis.
- Obinutuzumab is a new drug under development for treatment of lupus nephritis and has been shown in phase II trials to be effective and well-tolerated.
- There are numerous ongoing clinical trials examining the diverse immunologic drivers of renal inflammation and potential drug targets lupus nephritis.

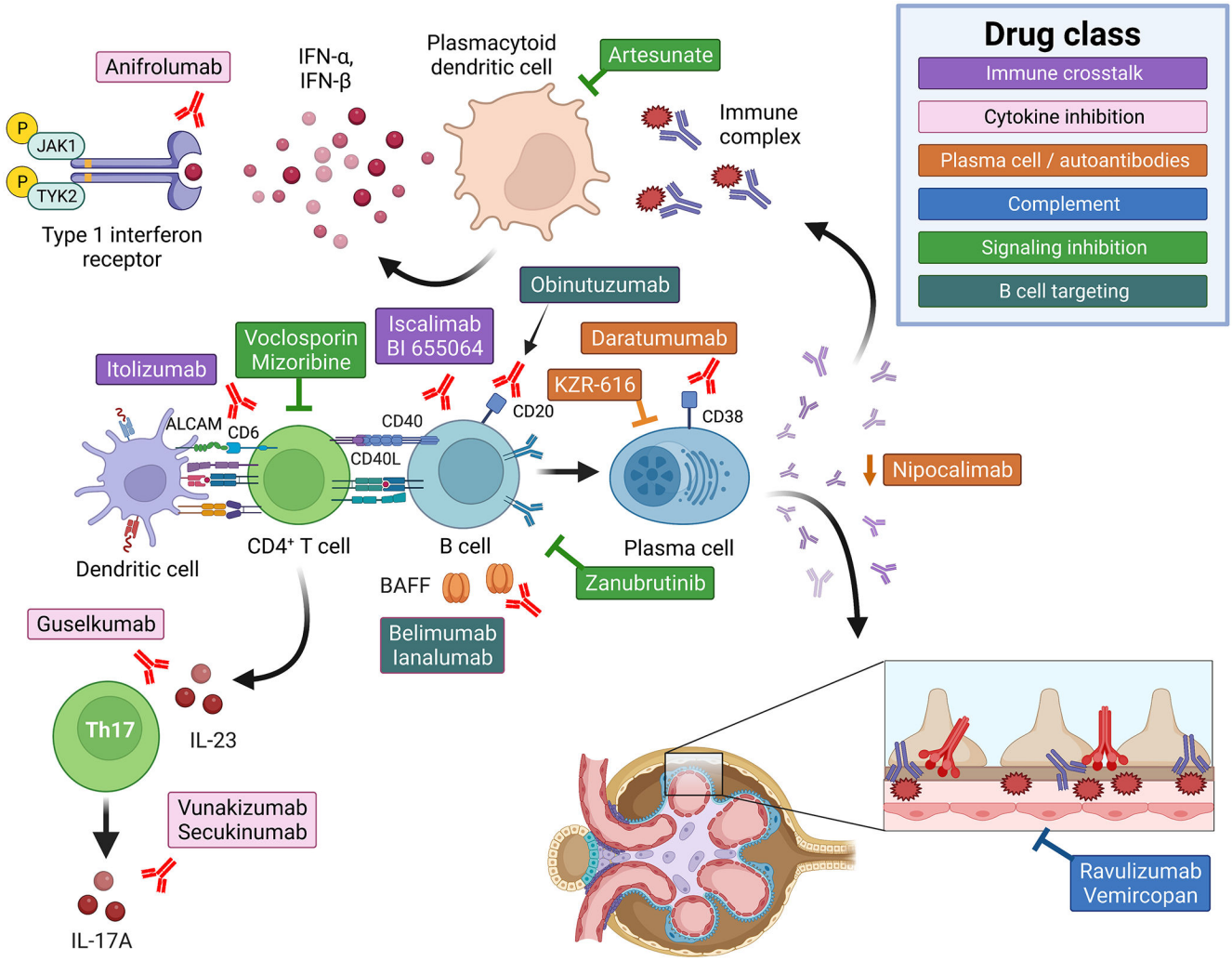

Figure 1: Emerging drug targets for the treatment of lupus nephritis

Diagram depicting the multiple strategies currently being studies for the treatment of lupus nephritis, divided into five groups. **1)** Inhibition of immune cell crosstalk: two separate drugs (Iscalimab and BI 655064) are examining whether blocking CD40:CD40L costimulatory signals prevents autoantibody formation and ameliorates lupus nephritis. Itolizumab targets the T cell activation molecule CD6. **2)** Cytokine inhibition: multiple pro-inflammatory cytokines have been implicated in the pathogenesis of SLE and lupus nephritis. Studies are ongoing examining whether blocking type 1 interferon signals (Anifrolumab), BAFF activity (Lanalumab), or Th17 biology (IL-23: Guselkumab; IL-17A: Vunakizumab and Secukinumab) is an effective treatment strategy in lupus nephritis. **3)** Plasma cell and/or autoantibody targeted therapies: the intra-glomerular deposition of autoantibody:autoantigen immune-complexes (IC) promotes glomerulonephritis. For this reason, independent strategies are being pursued to either deplete plasma cells (Daratumumab and KZR-616) or reduced serum IgG levels via blockade of the neonatal Fc receptor (FcRn; Nipocalimab). **4)** Inhibition of the complement cascade: Given the putative role for complement as a driver of renal inflammation, complement C5 (Ravulizumab) and complement factor D (Vemircopan) inhibitors are being studied in active lupus nephritis. **5)**

Cell signaling inhibitors: Specific targets being pursued include: Bruton's tyrosine kinase, a critical mediator of B cell receptor and Fc receptor signaling (Zanubrutinib); endosomal toll-like receptor signaling pathways (the antimalarial Artesunate); and the anti-metabolite Mizoribine. **6)** B cell targeted therapies: including BAFF inhibitors (belimumab, ianalumab) and anti-CD20 depleting monoclonal Obinutuzumab.

Table 1:

Histopathologic classification of lupus nephritis (developed by International Society of Nephrology/Renal Pathology Society (ISN/RPS). Adapted from [9].

Class I	Minimal mesangial lupus nephritis	• Normal findings by light microscopy • Mesangial immune deposits by immunofluorescence
Class II	Mesangial proliferative lupus nephritis	• Mesangial hypercellularity or mesangial matrix expansion by light microscopy • Mesangial immune deposits by immunofluorescence
Class III	Focal lupus nephritis	• Active or inactive, segmental or global endo or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial deposits, with or without mesangial alterations.
Class IV	Diffuse lupus nephritis	• Active or inactive diffuse, segmental or global endo or extracapillary glomerulonephritis involving ≥50% of glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations
Class V	Lupus membranous nephropathy	• Global or segmental subepithelial immune deposition or their morphologic sequelae detectable by light, immunofluorescence or electron microscopy
Class VI	Advanced sclerosing lupus nephritis	• ≥90% of glomeruli globally sclerosed without residual activity

Table 2:

Consensus treatment plan (CTP) for the initial therapy of childhood-onset proliferative lupus nephritis developed by the Childhood Arthritis and Rheumatology Research Alliance (CARRA; upper panel) and equivalent recommendations generated by the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE; lower panel). Table adapted from [21] and [22].

Childhood Arthritis and Rheumatology Research Alliance (CARRA)						
Initial regimen (pick one)						
Cyclophosphamide IV q 4 weeks x 24 weeks 500mg/m^2 body surface area titrated up to 1500mg/dose based on white blood cell (WBC) nadir			Mycophenolate mofetil 600mg/m^2/dose twice per day x 24 weeks (Max 3000mg/d)			
Steroid regimen (pick one)						
	Oral steroid regimen		**IV steroid regimen**		**Mixed regimen**	
	Initial dose	**Taper goal**	**Initial dose**	**Taper goal**	**Initial dose**	**Taper goal**
Weight >30kg	60-80mg/d	20mg/d	Initial pulse then 20mg every 1-4 weeks	10mg monthly	Mixed oral and IV dosing regiment	
Weight <30kg	2 mg/kg/d	0.5mg/kg/d	Initial pulse then 10mg every 1-4 weeks	5mg monthly	Mixed oral and IV dosing regiment	

Single Hub and Access point for paediatric Rheumatology in Europe (SHARE)	
Initial regimen (pick one)	
High-dose IV Cyclophosphamide: 500mg/m^2/dose, if tolerated increase to 750mg/m^2/dose (Max 1000-2000mg/dose), 6 monthly doses OR Low-dose IV Cyclophosphamide: 500mg/pulse (in adults) q 2 weeks x 6 pulses	Mycophenolate mofetil 1200mg/m^2/day x 24 weeks (Max 2000mg/day) When poor response, option to increase to 1800mg/m^2/day (Max 3000mg/day)
Steroid regimen	
High dose prednisone: 1-2mg/kg/day (Max 60mg/day)	

Table 3:

Clinical trials of newly-approved and emerging drug targets and their endpoints

Drug	Trial	Phase	Treatment	Primary Endpoint	Secondary Endpoint
Belimumab	BLISS-LN	III	IV belimumab (10mg/kg) vs placebo + standard therapy	Primary efficacy renal response at 104 weeks: • uPCR≤0.7, • eGFR≤20% below baseline or ≥60ml/min/1.73m^2, • no rescue therapy	CRR at 104 weeks: • uPCR<0.5 • eGFR≤10% below baseline or ≥90ml/min/1.73m^2 • no rescue therapy
Voclosporin	AURA-LV	II	Voclosporin 23.7 mg BID vs. 39.5 mg BID vs. matched placebo + MMF (2 g/d) + rapidly tapered corticosteroids	CRR at 24 weeks: • uPCR≤0.5 • eGFR<20% below baseline or >60ml/min/1.73m^2 • No rescue therapy	CRR at 48 weeks
Voclosporin	AURORA-1	III	Voclosporin 23.7 mg BID vs. placebo + MMF (2g/d) + rapidly tapered low oral corticosteroids	CRR at 52 weeks: • uPCR≤0.5 • eGFR<20% below baseline or >60ml/min/1.73m^2 • no rescue therapy	• Time to uPCR≤0.5, • Partial renal response (PRR) (≥50% reduction from baseline eGFR) • Time to 50% reduction in uPCR • CRR at 24 weeks
Obinutuzumab	NOBILITY	II	IV obinutuzumab 1000mg vs. placebo on day1 and weeks 2, 24, 26 + MMF + corticosteroids	CRR at 52 weeks: • uPCR<0.5 • serum creatinine ≤ULN and <15% below baseline • inactive urinary sediment (<10 RBC/HPF, no RBC casts) • no rescue therapy	PRR at 52 weeks: • ≥50% reduction in uPCR • ≤15% increase in serum creatinine from baseline, • urinary RBC<10/HPF or ≤50% from baseline

Table 4:

Ongoing clinical trials of emerging therapies in lupus nephritis

Drug	Trial Phase	Target	ClinicalTrials.gov Identifier:
Immune cell crosstalk			
Iscalimab	Phase 2	Anti-CD40	NCT03610516
BI 655064	Phase 2	CD40	NCT03385564
Itolizumab	Phase 1	CD6	NCT04128579
Cytokine inhibition			
Anifrolumab	Phase 3	Type I INF receptor	NCT05138133
Anifrolumab	Phase 2	Type I INF receptor	NCT02547922
Vunakizumab	Phase 2	IL-17A	NCT04924296
Secukinumab	Phase 3	IL-17A	NCT04181762
Guselkumab	Phase 2	IL-23	NCT04376827
Plasma cell / antibody targeted			
Daratumumab	Phase 2	Anti-CD38	NCT04868838
Nipocalimab	Phase 2	FcRn	NCT04883619
KZR-616	Phase 1/2	Immunoproteasome	NCT03393013
Complement cascade inhibition			
Ravulizumab	Phase 2	C5 complement	NCT04564339
Vemircopan	Phase 2	Complement factor D	NCT05097989
Cell signaling inhibitors			
Zanubrutinib	Phase 2	BTK	NCT04643470s
Artesunate	Phase 4	Antimalarial	NCT03214731
Mizoribine	Phase 3	Purine antagonist	NCT02256150
B cell targeted			
Ianalumab	Phase 3	BAFF	NCT05126277
Obinutuzumab	Phase 3	Anti-CD20	NCT04221477

Active lupus nephritis trials registered on ClinicalTrials.gov. Excluded are studies resulted/terminated before 2018, non-drug therapies, interventions terminated due to insufficient evidence for efficacy, drugs tested for SLE only (not lupus nephritis), and medications already discussed in body of this review.