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Insights into future management of lupus nephritis

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Lupus nephritis (LN) is a common and serious manifestation of systemic lupus erythematosus and is a major cause of mortality and morbidity. The current standard-of-care treatment for LN include conventional immunosuppressive treatments such as mycophenolate mofetil, cyclophosphamide, or azathioprine, combined with glucocorticoids. However, this treatment approach has several unmet needs, such as achieving only modest remission rates, potential toxicities, and prolonged cumulative steroid exposure, resulting in suboptimal patient outcomes. The LN treatment landscape is evolving rapidly to meet these unmet needs, with belimumab and voclosporin being the first drugs approved specifically for treatment of LN in 2020 and 2021, respectively. Here, we review the likely roles in LN therapy for several targeted therapies, including select therapies under investigation, and interventions in early development such as therapies targeting B cells (obinutuzumab, atacicept, ianalumab, and CD19 chimeric antigen T-cell therapy), inflammatory cytokines (secukinumab and anifrolumab), and the immunoproteasome (zetomipzomib); we also review treatment strategies designed to minimize steroid exposure. Treatments in development have demonstrated encouraging short- and long-term efficacy and steroid-sparing potential, potentially paving the way for improved treatment regimens and patient outcomes in LN.

KEYWORDS

lupus nephritis, glucocorticoids, steroids, immunoproteasome, targeted therapy

1 Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a relapsing and remitting course (1). Lupus nephritis (LN) is a common and serious manifestation of SLE, occurring in ≤50% of patients (2–4), and remains a major cause of mortality and morbidity for patients with SLE (5, 6). Approximately 10%–30% of patients with LN will progress to end-stage kidney disease (ESKD) (7–11). Death directly attributable to kidney disease will occur in 5%–25% of patients within 5 years (8). Active LN is correlated with worse health-related quality-of-life compared with inactive LN or SLE without kidney involvement, as well as higher direct healthcare costs and indirect healthcare costs due to loss of productivity (12–15).

2 Management of LN

Guidelines recommend that patients with SLE and kidney involvement (glomerular hematuria and/or cellular casts, proteinuria >0.5 g/day, spot urine protein-creatine ratio [UPCR] >500 mg/g, or unexplained decrease in estimated glomerular filtration rate

[eGFR]) should have a kidney biopsy performed (16, 17). More recent data, which will be reviewed in this publication, suggest that a broader indication for kidney biopsy should be recommended, such as the presence of glomerular hematuria accompanied by any degree of proteinuria (18–20). The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification represents the gold standard for assessment of kidney biopsies in LN, affirming the diagnosis of LN and guiding treatment decisions (16, 17, 21). The 2018 update to the ISN/RPS classification include an increased emphasis on the National Institutes of Health activity index and chronicity index (22, 23).

Complete clinical remission is the main treatment goal in LN due to its strong association with outcomes such as kidney survival at 10 years: 94% for patients with complete remission, 45% for patients with partial remission, and 19% for patients without remission (7). There is a lack of consensus on definitions of complete and partial clinical remission following treatment, although the criteria usually involve clinical markers of proteinuria and serum creatinine (24). Clinical guidelines have defined complete clinical remission as a reduction in proteinuria to <0.5–0.7 g/day within 6–12 months of starting or escalating therapy; partial clinical remission is defined as ≥50% reduction in proteinuria or UPCR to <3 in the same time period (16, 17).

The terms *induction* and *maintenance*, which have traditionally been used to characterize the treatment of LN, fail to capture evolution in the understanding of LN management; the terms *initial* and *subsequent* have been proposed instead (25). Because there is no consensus on the best terminology, we used *initial or induction* and *subsequent or maintenance* to describe LN treatment in this publication.

Based on the recent Kidney Disease: Improving Global Outcomes (KDIGO) 2021 glomerular diseases guidelines and the European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) 2019 guidelines, treatment for class III or IV LN includes an initial or induction treatment of glucocorticoids, combined with either mycophenolate mofetil (MMF) or cyclophosphamide (CYC) followed by maintenance or subsequent therapy with either MMF or azathioprine (AZA) combined with glucocorticoids (8, 16, 17). Glucocorticoids improve mortality rates in patients with LN and have been the mainstay of LN treatment since the 1960s (26). Landmark trials in the 1970s and 1980s reported that the addition of CYC to glucocorticoids resulted in better preservation of long-term kidney function compared with glucocorticoids alone (27, 28); subsequent data showed that patients receiving either MMF or CYC had similar response rates if they were also receiving glucocorticoids (29), indicating that either MMF or CYC were reasonable options for initial or induction treatment (16, 17).

In recent years, belimumab (2020) and voclosporin (2021) became the first two drugs to be approved specifically for the treatment of LN; these approvals could potentially have significant implications for the current standard of care (SoC) in LN (30, 31). There is increasing support for early use of belimumab and voclosporin in combination with standard therapy, as proposed in the KDIGO 2024 guidelines for the management of LN and the 2023 update of the EULAR SLE recommendations (32, 33).

The optimal treatment duration for LN is not clearly defined; early withdrawal of treatment leads to relapses, whereas prolonged treatment exposure increases the risk of toxicity. The KDIGO 2024 guidelines recommend that the combined duration of initial or induction therapy and subsequent or maintenance therapy for proliferative LN should be ≥36 months (33), whereas the EULAR/ERA-EDTA 2019 guidelines recommend that immunosuppression treatment should continue for at least 3–5 years after achieving complete clinical remission; duration should be individualized according to the timing and magnitude of response, duration of flare-free maintenance, extrarenal SLE activity, and patient preferences (17). In the updated EULAR 2023 recommendations, the duration of treatment was revised to ≥3 years following renal response (32).

2.1 Unmet needs in current management of LN

A systematic review of over 18,000 patients found that the 5-year risk of ESKD in patients with LN in 1970 to 1979 was 16%; subsequently, the risk declined gradually until the mid-1990s, when it plateaued at 11%, then increased in the late 2000s (34). This fluctuation highlights the limitations of conventional therapies and the need for new therapies to improve patient outcomes. Repeat biopsy studies have demonstrated that conventional therapies are ineffective at preventing accrual of kidney damage despite good clinical response (35, 36). Remission rates for LN are modest, with <60% of patients achieving complete clinical remission after 2 years (37–39); among those who have achieved clinical remission, kidney flares still occur in 27% to 66% (7, 40, 41). It is worth noting that recent retrospective studies conducted in Europe have reported complete response rates of up to 72% at 18 months (42, 43), highlighting the heterogeneity of treatment response across populations.

Additionally, standard immunosuppressive treatments are linked to significant toxicities, including myelosuppression and infections (44). The use of glucocorticoids has greatly improved survival in patients with LN; however, long-term use is associated with safety concerns, including infections, elevated risk of cardiovascular disease, metabolic side effects (45), and accrual of damage from SLE, which are major causes of morbidity and mortality in SLE (5, 46–49). Hence, treatment strategies that aim to minimize glucocorticoid exposure while maintaining treatment efficacy have substantial clinical value (45).

The LN therapeutic landscape is evolving rapidly, and investigations of novel therapies are ongoing to address the unmet needs of current treatment strategies. Here, we provide an overview of approved targeted therapies that have the potential to address these unmet needs, select treatments that are being investigated in late-stage clinical trials, and promising new treatments in early developmental stages that offer the possibility

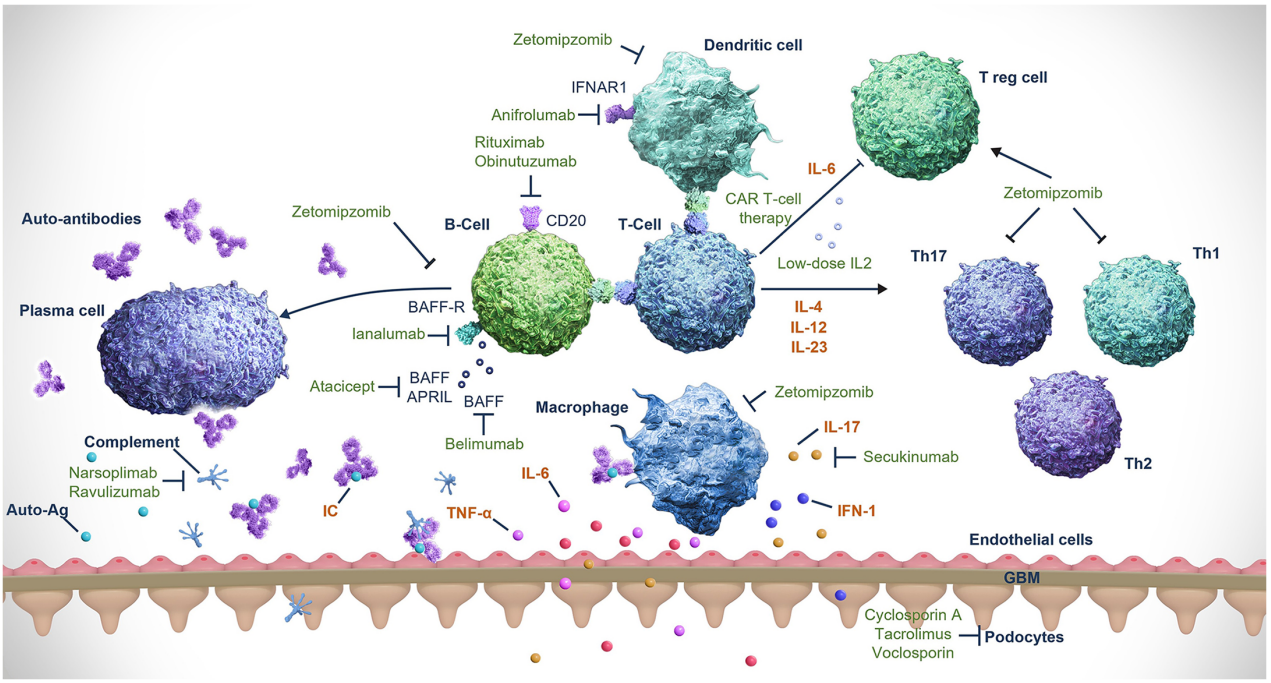

FIGURE 1
Mechanisms of action of treatments for LN. Ag, antigen; APRIL, a proliferation-inducing ligand (also known as ANP32B); ANP32B, acidic nuclear phosphoprotein 32 family member B; BAFF, B-cell activating factor (also known as TNFSF13B); BAFFR, B-cell activating factor receptor (also known as TNFRSF13C); CAR, chimeric antigen receptor; GBM, glomerular basement membrane; IFN, interferon; IFNAR1, interferon alfa and beta receptor subunit 1; IL, interleukin; LN, lupus nephritis; Th, T helper; TNF, tumor necrosis factor; TNFRSF13C, TNF receptor superfamily member 13C; TNFSF13B, TNF superfamily member 13B; T-reg cell, regulatory T-cell. Reprinted from Obrișcă B, et al. (50). Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).

of glucocorticoid-free regimens. The mechanisms of action of these therapies are illustrated in Figure 1, and data from key clinical trials are detailed in Table 1.

2.2 Novel approved targeted therapies

2.2.1 Belimumab

B cells play a significant role in the pathogenesis of SLE, acting directly via autoantibody production and indirectly via antigen-presenting activity to promote T-cell activation and production of inflammatory cytokines (64, 65). Belimumab is a fully human monoclonal antibody (mAb) that inhibits the soluble form of B-cell activating factor [BAFF; also known as TNFSF13B (TNF superfamily member 13b)], thereby inhibiting B-cell survival and reducing the differentiation of B cells into immunoglobulin-producing plasma cells (65, 66).

In the Phase III BLISS-LN trial, 448 patients with LN were randomized to either belimumab or placebo in combination with standard induction therapy. Over 104 weeks, the belimumab group demonstrated a significantly higher renal response rate vs. placebo [43% vs. 32%, respectively; odds ratio (OR), 1.6; 95% CI, 1.0–2.3; $p = 0.03$] and a significantly lower risk of kidney-related events or death [hazard ratio (HR), 0.51; 95% CI, 0.34–0.77; $p = 0.001$]; the safety profile was similar between both groups (51). Based on the positive trial results, both KDIGO 2024 LN guidelines and the updated 2023 EULAR SLE guidelines now state that initial combination treatment with belimumab may be considered alongside standard therapy with MMF or CYC and glucocorticoids (32, 33).

Two additional Phase III clinical trials are ongoing and will evaluate the safety and efficacy of belimumab in LN, including long-term data, across different patient populations (NCT03370263 and NCT05863936) (67, 68). Data from the long-term extension of the extrarenal belimumab studies are reassuring and show no increased risk of side effects with up to 11 years of treatment (69).

2.2.2 Voclosporin

Calcineurin inhibitors (CNIs) such as voclosporin, tacrolimus, and cyclosporine exert immunomodulatory effects on T cells, leading to reduction of lymphocyte proliferation and T-cell–mediated responses, as well as reduction of proteinuria via stabilization of podocytes (70, 71). Due to the unpredictable and complex pharmacokinetics (PK) profile of conventional CNIs (tacrolimus and cyclosporine), therapeutic drug monitoring is required to ensure efficacy and minimize toxicity (72). Voclosporin, a newer CNI and an analog of cyclosporine, has higher potency, a more favorable metabolic profile, and a more consistent PK profile compared with conventional CNIs due to

TABLE 1 Summary of evidence for select novel treatments for LN.

Therapeutic agent	Mechanism of action	Trial	Patient population	Enrollment	Key results
Belimumab	BAFF (also known as TNFSF13B) inhibitor	BLISS-LN; Phase III (51)	Patients with active LN	448	Significantly improved renal response rates (OR: 1.6, 95% CI: 1.0–2.3; $p = 0.03$)
Voclosporin	Calcineurin inhibitor	AURORA 1; Phase III (52)	Patients with active LN	357	Significantly improved complete renal response rates (OR: 2.65; 95% CI: 1.64–4.27; $p < 0.0001$)
Rituximab	CD20-directed monoclonal antibody	LUNAR; Phase III (53)	Patients with active LN	72	Similar renal response rates as placebo ($p = 0.55$)
Obinutuzumab	CD20-directed monoclonal antibody	NOBILITY; Phase II (54)	Patients with active LN	125	Significantly improved complete renal response rates (difference: 19%; 95% CI: 2.7%–35%; $p = 0.026$) and overall renal response rates (difference: 25%; 95% CI: 8.2–42%; $p = 0.005$)
Atacicept	BAFF (also known as TNFSF13B) and APRIL (also known as ANP32B) inhibitor	APRIL-SLE; Phase II/III (55)	Patients with active SLE	246	Post hoc analysis: observed dose-response relationship between atacicept concentrations, reduced Ig levels, and reduced flare rates
Ianalumab	BAFFR (also known as TNFRSF13C) inhibitor	SIRIUS-LN; Phase III	Patients with active LN	≈420	Ongoing; estimated primary completion date: March 2027 (56)
Secukinumab	Anti-IL-17A inhibitor	SELUNE; Phase III	Patients with active LN	275	Ongoing; estimated study completion date: Jan. 2026 (57)
Anifrolumab	Type I IFN receptor inhibitor	TULIP-LN; Phase II (58)	Patients with active LN	147	Similar mean difference from baseline in 24-hour UPCR (GMR: 1.03; 95% CI: 0.62–1.71; $p = 0.905$; GMR <1 favors anifrolumab) and renal response (difference: −0.1%; 95% CI: −16.9% to 16.8%; $p = 0.993$)
Zetomipzomib	Immunoproteasome inhibitor	MISSION trial; Phase II (59)	Patients with active LN	17	64.7% of patients had ≥50% reduction in UPCR from baseline, and 35.3% achieved a complete renal response at week 25
YTB323	Anti-CD19 CAR-T therapy	Open-label Phase I/II	Patients with severe, refractory SLE	≈27	Ongoing; estimated completion date: October 2026 (60)
Low-dose IL-2	Promote T-reg cells	He et al.; Phase II (61)	Patients with active SLE	60; 25 of these had LN	In patients with LN: significantly improved complete remission rates (53.85% in IL-2 group vs. 16.67% in placebo group; $p = 0.036$)
Ravulizumab	Complement inhibitor	SANCTUARY; Phase II	Patients with active LN or IgAN	≈120	Ongoing; estimated primary completion date: April 2024 (62)
Narsoplimab	Complement inhibitor	Open-label Phase II (63)	Patients with LN ($n = 5$) and other nephropathies	≈54	Preliminary data: mean 69% reduction in 24-h urine protein excretion over the treatment period in 4 of 5 patients with LN (63)

ANP32B, acidic nuclear phosphoprotein 32 family member B; APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BAFFR, BAFF receptor; GMR, geometric mean ratio; IgAN, immunoglobulin A nephropathy; IL, interleukin; LN, lupus nephritis; OR, odds ratio; SLE, systemic lupus erythematosus; TNFRSF13C, TNF receptor superfamily member 13C; TNFSF13B, TNF superfamily member 13B; UPCR, urine protein creatinine ratio.

altered binding of the voclosporin-cyclophilin complex to calcineurin and a reduced drug and metabolite load (16, 72); hence, therapeutic drug monitoring is not needed (73). In patients with refractory disease, multitarget therapy (i.e., a combination of CNI and MMF) has shown reasonable efficacy and safety in small-scale observational studies and can be considered an option in this patient population (74–77). However, the initial data on the efficacy of multitarget therapy as initial or induction treatment in LN did not include multiethnic populations and were of low quality, leading to limited generalizability to other populations (16, 17, 71, 78, 79). Newer data evaluating the novel CNI voclosporin support the use of multitarget therapy as initial or induction treatment across multiethnic populations (52, 80–82).

In the Phase II AURA-LV trial, 265 patients were randomized to receive either low-dose voclosporin, high-dose voclosporin, or placebo as initial LN treatment. All treatments were combined with MMF 2 g/day and low-dose glucocorticoids (80). Significantly higher complete renal remission rates were observed in patients receiving either low-dose or high-dose voclosporin after 48 weeks compared with placebo at 23.9% (with low-dose voclosporin, 49.4%; OR, 3.21; 95% CI, 1.68–6.13; $p < 0.001$; and with high-dose voclosporin, 27.3%; OR, 2.10; 95% CI, 1.09–4.02; $p = 0.026$) (80). The voclosporin groups had higher rates of serious adverse events (low-dose voclosporin, 28.1%; high-dose voclosporin, 25.0%; placebo, 15.9%), and the low-dose voclosporin group had higher rates of death compared with the other two groups (low-dose voclosporin, 11.2%; high-dose voclosporin, 2.3%; placebo, 1.1%) (80). However, this higher rate of death was not observed in the high-dose voclosporin group, nor was it replicated in the Phase III trial; therefore, it is likely attributable to causes beyond the addition of voclosporin to the treatment regimen (80). The authors of the AURA-LV study explained that the uneven distribution of deaths was likely associated with study-site characteristics rather than the doses of voclosporin received (80).

The subsequent Phase III AURORA 1 trial randomized 357 patients to either voclosporin (using the low dose in the AURA-LV trial) or placebo (52). The primary endpoint of complete renal response was defined as a composite endpoint of UPCR ≤0.5 mg/g, eGFR 60 ml/min or no confirmed increase of eGFR >20% from baseline, and no more than 10 mg/day of prednisolone for 3

consecutive days or for ≥7 days during Week 44 through 52 (52). The voclosporin group had significantly improved complete renal response rates compared with placebo at week 52 (41% vs. 23%, respectively; OR, 2.65; 95% CI, 1.64–4.27; $p < 0.0001$) (52). Unlike the AURA-LV trial, the AURORA 1 trial had similar safety profiles in both groups, and the rates of death were not imbalanced (<1% in the voclosporin group vs. 3% in the placebo group) (52). A pooled *post hoc* analysis of the AURA-LV and AURORA 1 studies ($N = 534$) showed that significantly more patients in the pooled voclosporin groups achieved a complete renal response at 1 year compared with those in the control groups (43.7% vs. 23.3%, respectively; OR, 2.76; 95% CI, 1.88–4.05; $p < 0.0001$) (81). Patients who completed the AURORA 1 trial were enrolled into a follow-up AURORA 2 trial, continuing the same blinded randomized treatment for an additional 2 years (83). The mean reductions in UPCR observed in patients treated with voclosporin in AURORA 1 were maintained in AURORA 2, with no increase in UPCR noted at the follow-up visit 4 weeks after study-drug discontinuation (83).

Based on these positive data, both the KDIGO 2024 LN guidelines and the EULAR 2023 SLE guidelines recommend adding voclosporin to MMF and glucocorticoids as an initial or induction treatment option for patients with LN; use of voclosporin has not been evaluated in combination with CYC or in patients with eGFR <45 ml/min/1.73 m^2 (32, 33). However, because CNIs decrease proteinuria through additional nonimmune mechanisms, clinical trials that use a clinical remission criterion based mainly on reduction in proteinuria must be interpreted cautiously (84). As the AURORA studies used a composite endpoint that assessed improvements in UPCR, eGFR, and steroid use (52), the renal efficacy results of voclosporin are considered robust.

2.3 Unapproved SOC treatment

2.3.1 Rituximab

Rituximab is a type I CD20-directed mAb that mediates B-cell lysis by complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and direct cell death (85, 86). Data from studies evaluating the efficacy of rituximab in patients with SLE and LN have been mixed (53, 87, 88). The Phase III LUNAR trial found that the addition of rituximab to standard induction treatment (MMF and glucocorticoids) did not significantly improve renal response rates in patients with Class III or IV LN after 1 year of treatment compared with the placebo group ($p = 0.55$) (53). However, a *post hoc* analysis of the LUNAR trial demonstrated that patients with complete peripheral B-cell depletion had significantly increased odds of having a complete response (unadjusted OR, 5.8; 95% CI, 1.2–2.8; $p = 0.03$), supporting B-cell depletion as a mechanism of action for LN treatment (89). Accordingly, a systematic review and meta-analysis of 31 studies of refractory SLE/LN patients found the global, complete, and partial response rates of rituximab were 70%, 51%, and 27%, respectively; use of rituximab significantly decreased prednisone dose (mean difference, −12.50 mg/day; 95% CI, −6.36 to −18.64; $p < 0.001$) and demonstrated a numerical but statistically nonsignificant decrease in proteinuria (mean difference, −2.52 g/day; 95% CI, 0.22 to −5.27; $p = 0.07$) (90). Multiple uncontrolled studies have shown that rituximab produced favorable outcomes in patients with refractory LN, including improvements in renal response rates, proteinuria, repeat biopsies, serum autoantibody levels, and disease activity scores (91–94). Despite only low-grade evidence for its use in LN, both the EULAR 2023 SLE guidelines and KDIGO 2024 guidelines recommend off-label use of rituximab in refractory LN (32, 33), as approved treatment options for refractory LN remain scarce.

2.4 Select targeted therapies under investigation

2.4.1 Therapies targeting B cells

2.4.1.1 Obinutuzumab

Obinutuzumab is a novel humanized anti-CD20 type II mAb that was developed to increase B-cell depletion peripherally and in lymph nodes, including in key B-cell subsets that are considered resistant to conventional B-cell–targeted agents, particularly memory B-cells and proliferating tissue plasmablasts (95, 96). Compared with rituximab, obinutuzumab induces better ADCC, less CDC, and higher tissue B-cell depletion *in vitro* (86, 95, 97) and was more effective in improving SLE in murine models (98).

The Phase II NOBILITY trial randomized 125 patients with LN to receive either obinutuzumab or placebo in addition to MMF and glucocorticoids (54). After 52 weeks, a higher proportion of patients in the obinutuzumab group achieved the primary endpoint of complete renal response (35% with obinutuzumab vs. 23% with placebo; percentage difference, 12%; 95% CI, −3.4% to 28%; $p = 0.115$). Exploratory analyses at week 104 reported significantly higher complete renal response (41% with obinutuzumab vs. 23% with placebo; percentage difference, 19%; 95% CI, 2.7%–35%; $p = 0.026$) and overall renal response (54% with obinutuzumab vs. 29% with placebo; percentage difference, 25%; 95% CI, 8.2%–42%; $p = 0.005$) (54). In the obinutuzumab group, 98% of patients achieved B-cell depletion (defined as CD19 count ≤5 cells/μl) at week 2 after one infusion of obinutuzumab, and 94% had sustained depletion at week 52 (26 weeks after the last infusion) (54). In contrast, in the LUNAR study, only 12% of the patients had achieved complete B-cell depletion (defined as CD19 count of 0) at week 2 after one infusion of rituximab, and 78% had done so at week 52 (26 weeks after last infusion). The rates of adverse events and serious adverse events were similar between both groups in the NOBILITY trial (54).

While the NOBILITY trial was considered to meet its primary endpoint, results should be interpreted with caution, considering the high prespecified significance level of 0.2. Additional data from two ongoing Phase III studies of obinutuzumab in LN will be needed to provide more evidence to support its use. The global REGENCY study (NCT04221477) will further evaluate the use of obinutuzumab across a wider population (99). Another study (NCT04702256) will assess obinutuzumab as a replacement for oral glucocorticoids during induction treatment of LN (100);

these results may provide further evidence of the potential for glucocorticoid-free management of LN.

2.4.1.2 Atacicept

Atacicept is a fully human recombinant fusion protein that inhibits soluble and membrane-bound BAFF and a proliferation-inducing ligand [APRIL; also known as ANP32B (acidic nuclear phosphoprotein 32 family member B)], resulting in reduced numbers of B-cells and plasma cells and, consequently, serum IgG, IgM, and IgA (101).

The Phase II/III APRIL-LN trial was to evaluate the use of atacicept in addition to MMF in LN, but it was prematurely terminated due to an unexpected decline in serum IgG levels and the occurrence of serious infections in patients receiving atacicept (102). Data from the Phase II JANUS study in IgA nephropathy were encouraging: atacicept demonstrated an acceptable safety profile, improved proteinuria, and stabilized kidney function (103). Subsequently, results of the Phase II/III APRIL-SLE trial, conducted in patients with non-renal SLE, suggested that patients with elevated levels of BAFF and APRIL had a greater response to atacicept, with no increased risk of infections (55). The Phase III COMPASS trial (NCT05609812) was initiated in November 2022 with the aim of evaluating the efficacy of atacicept compared with placebo, in combination with SoC treatment, in patients with LN; however, the trial had been suspended as of July 2023, although not as a result of regulatory or safety concerns (104).

2.4.1.3 Ianalumab

Ianalumab is a mAb that modulates B-cell survival via a dual mechanism: direct lysis of B-cells by ADCC as well as BAFF receptor blockade that interrupts BAFF-mediated signaling for B-cell maturation, proliferation, and survival (105). Studies suggest that elevated BAFF levels correlated with a shortened duration of B-cell depletion and contributed substantially to SLE flares after B-cell repopulation, paving the way for a dual-mechanism treatment involving B-cell depletion and BAFF blockade (106, 107).

In a Phase II trial in patients with primary Sjögren's syndrome, a disease in which B-cells play a central role, ianalumab showed a marked dose-response relationship with reduction in disease activity (108). Other mAbs targeting B-cells, such as rituximab and belimumab, did not show convincing efficacy in Sjögren's syndrome (109, 110); the efficacy demonstrated by ianalumab could be partially attributed to its dual target mechanism, providing an added blockade of BAFF receptors that could counteract the elevated BAFF levels seen after administration of rituximab (108). Investigations into whether the increased B-cell depletion of ianalumab will translate to better clinical outcomes in patients with SLE (NCT05639114; NCT05624749) and LN (NCT05126277) are currently ongoing (56, 111, 112).

2.4.2 Therapies targeting cytokines

2.4.2.1 Secukinumab

The interleukin (IL)-23/IL-17 axis and CD4+ T-helper (Th17) cells that produce IL-17 have recently emerged as mediators in the pathogenesis of SLE and LN (113, 114) through induction of vascular inflammation, leukocyte recruitment, B-cell activation, and autoantibody production (114). Patients with LN typically present with elevated IL-17 levels, which are independently associated with a worse prognosis (115).

Secukinumab is an anti–IL-17A inhibitor that blocks IL-17A cytokine interaction with the IL-17 receptor (116). To date, only case reports have been published on the use of secukinumab in treating refractory LN (117–119). The ongoing global Phase III SELUNE clinical trial (NCT04181762) on secukinumab and the Phase II ORCHID-LN trial (NCT04376827) on guselkumab, an IL-23 inhibitor, will shed light on the role in therapy for inhibitors of the IL-23/IL-17 axis (57, 120).

2.4.2.2 Anifrolumab

Type I interferons (IFNs) are a central factor in the pathophysiology of SLE (121, 122). In patients with LN, high type I IFN gene signatures are associated with active disease, proteinuria, and treatment failure (121, 122). Type I IFN promotes kidney fibrosis, scarring, and loss via formation of immune complexes, recruitment of leukocytes, and direct action on kidney cells (123).

Anifrolumab is a mAb that binds to the type I IFN receptor with high specificity and affinity, inhibiting type I IFN signaling (124). In the Phase III TULIP-2 trial, anifrolumab demonstrated a significant reduction in disease activity scores in patients with nonrenal SLE compared with placebo at week 52 (125), although patients with severe LN were excluded from the study. This finding led to the Phase II TULIP-LN trial, in which 147 patients with LN were randomized to receive either a basic regimen of anifrolumab, an intensified regimen of anifrolumab, or placebo; all three regimens were combined with MMF and glucocorticoids (58). The primary endpoint, which was the change in baseline 24-h UPCR at week 52 for combined anifrolumab vs. placebo groups, was not met [geometric mean ratio (GMR), 1.03; 95% CI, 0.62–1.71; $p = 0.905$; GMR <1 would have favored anifrolumab] (58). The complete renal response rates were also not statistically different between the combined anifrolumab groups and the placebo group (difference, −0.1%; 95% CI, −16.9% to 16.8%; $p = 0.993$), although a numerical improvement was noted in the intensified regimen group vs. the placebo group (difference, 14.3%; 95% CI, −5.8% to 34.5%; $p = 0.162$) (58). The lack of benefit observed in the study was partially attributed to the suboptimal exposure obtained with the basic regimen of anifrolumab, resulting in the anifrolumab exposure being approximately half that normally achieved in nonrenal SLE (58). The authors of the TULIP-LN trial suggested that suboptimal exposure with the basic regimen was likely due to increased clearance associated with proteinuria in LN. Only the intensified regimen of anifrolumab achieved serum exposure and pharmacodynamic neutralization levels similar to those in nonrenal SLE. The efficacy and safety of anifrolumab in LN will be further investigated in the Phase III IRIS trial (NCT05138133) (126).

2.4.3 Therapies targeting the immunoproteasome

2.4.3.1 Zetomipzomib

Proteasomes contribute to the degradation of intracellular proteins, providing dynamic control of key cell signaling components and the maintenance of overall cellular homeostasis (127). Proteasomes are expressed ubiquitously throughout the body, while immunoproteasomes, which are derived from constitutive proteasomes, are expressed primarily in immune cells (127, 128). Immunoproteasomes regulate multiple immune effector cell functions, including class I antigen presentation, cytokine expression, and plasma cell proliferation, migration, and adhesion (128, 129). Expression of immunoproteasomes is induced in nonimmune cells by inflammatory and autoimmune conditions (128); this process occurs in LN, and increased immunoproteasome expression has been seen in murine models of LN and in kidney cells of patients with LN (130). Selective inhibition of the immunoproteasome results in broad immunomodulatory activity across both the innate and adaptive immune systems without leading to the apoptosis or immunosuppression seen with dual proteasome inhibitors (129, 131, 132). In murine models, selective immunoproteasome inhibition blocked differentiation of inflammatory Th1 and Th17 cells, promoted differentiation of regulatory T cells (Tregs), and inhibited the release of proinflammatory cytokines, such as IFN-α, from dendritic cells (129, 131, 132). Hence, the immunoproteasome has emerged as an attractive therapeutic target in various inflammatory conditions, including LN.

Zetomipzomib is a first-in-class selective immunoproteasome inhibitor (133). In mouse models of LN, treatment with zetomipzomib ameliorated disease progression, resulting in resolution of proteinuria and marked decreases in the incidence of glomerular nephritis, glomerular sclerosis, and tubular changes (133). In these animal models, zetomipzomib did not affect normal immune-response mechanisms (133). In the Phase II part of the MISSION Phase 1b/II trial ($n = 17$), which evaluated the efficacy and safety of zetomipzomib in patients with LN, 64.7% of patients had ≥50% reduction in UPCR from baseline, and 35.3% had achieved a complete renal response at week 25; renal responses were sustained or improved until the end of study at week 37, 12 weeks after end of treatment (59). A reduction in daily steroid dose to 10 mg/day was achieved in 82.4% of patients at week 25, and doses of other background immunosuppressive therapies remained stable throughout the study (59). Further evaluation of zetomipzomib in active LN is ongoing in the Phase IIb PALIZADE trial (NCT05781750) (134).

2.5 Potential interventions in early development

2.5.1 Chimeric antigen T-cell (CAR-T) therapy

Based on clinical experience with B-cell therapy, a complete and sustained B-cell depletion may lead to better response in patients with SLE or LN. CAR-T therapy may induce more robust B-cell depletion, especially in tissues that are easier for engineered cells to access (135).

Case reports have suggested the potential efficacy of anti-CD19 CAR-T therapy in SLE and LN: in one case, a 20-year-old woman with severe refractory SLE and LN was prescribed anti-CD19 CAR-T and low-dose glucocorticoids and stopped all other therapy for LN (136). The patient demonstrated substantial improvements in serological markers and disease activity scores, and her proteinuria decreased from over 2000mg/g to <250 mg/ g (136). A subsequent case series similarly demonstrated the efficacy of anti-CD19 CAR-T therapy in refractory LN (137, 138). Larger clinical trials evaluating the long-term efficacy and safety of anti-CD19 CAR-T therapy are warranted (137). An open-label Phase I/II study to assess the safety, efficacy, and cellular kinetics of YTB323, an anti-CD19 CAR-T therapy, in refractory SLE and LN is ongoing (NCT05798117) (60).

2.5.2 Low-dose Il-2

IL-2 is produced by activated T-cells and dendritic cells and is crucial for maintenance of T-cell–mediated self-tolerance (139). Decreased serum IL-2 levels in healthy mice led to a strong reduction in the number of CD4+ T-regs, progression of nephritis, and mortality (140). Lupus-prone mouse models and blood samples from patients with SLE revealed impaired IL-2 production (140, 141). Low-dose IL-2 treatment in patients with SLE selectively corrected T-reg defects and expanded the T-reg population (141), resulting in marked reductions in disease activity (142). In a randomized clinical trial evaluating the use of low-dose IL-2 compared with placebo, combined with standard treatment, complete remission was achieved in 7 of 13 patients (53.85%) with LN in the IL-2 group and 2 of 12 (16.67%) in the placebo group (61). Larger randomized controlled trials are warranted to further evaluate the efficacy of the IL-2 regimen across multiple patient cohorts (61).

2.5.3 Complement-targeting therapies

Dysregulated complement activation and complement deficiencies are associated with impaired processing of immune complexes and clearance of cellular debris (143). This process can contribute to kidney damage and LN flares and may result in development of SLE and LN (143).

Narsoplimab is a mAb that blocks mannan-binding lectin (MBL) associated serine protease 2 (MASP2), an effector enzyme that activates the lectin pathway of the complement system (144). Ravulizumab is a terminal complement inhibitor that binds to complement protein C5 with high affinity, inhibiting its cleavage to C5a and C5b and preventing the formation of the membrane attack complex (145). Phase II clinical trials on these two therapeutics in the treatment of LN (NCT02682407, NCT04564339) are ongoing (62, 146).

2.6 Future directions in the treatment of LN

2.6.1 Early diagnosis and treatment

In patients with SLE, guidelines recommend thresholds of proteinuria ≥0.5 g/day or UPCR ≥0.5 g/day as indication for a kidney biopsy (16, 17). However, proteinuria should not be the sole consideration for kidney involvement in SLE because many patients with low-grade proteinuria still present with early LN in their kidney

biopsies (19, 20). A retrospective analysis of 222 patients with SLE and glomerular hematuria found that 85% of patients with proteinuria <0.5 g/day and 76% of patients with proteinuria <0.25 g/day had class III or IV LN (20); another retrospective analysis reported that 40 of 52 (76%) and 9 of 10 (90%) patients with proteinuria <1 g/day and <0.5 g/day, respectively, had LN detected in their biopsies (19). Studies in silent LN have shown that a substantial proportion of patients with proliferative LN have no urine abnormalities (147, 148). These data suggest that other parameters, such as glomerular hematuria, should be taken into account when deciding whether to perform a kidney biopsy. A broader indication for kidney biopsies, such as the presence of glomerular hematuria accompanied by any degree of proteinuria, could allow for earlier diagnosis and treatment of LN, which could potentially decrease the need for steroids with the current treatment regimens.

2.6.2 Decrease of glucocorticoid exposure and consideration of glucocorticoid-free regimens

We propose that the main treatment goal for LN is to achieve long-term complete clinical remission without the need for glucocorticoids in order to minimize the adverse effects from prolonged and/or cumulative exposure to glucocorticoids (45). Several glucocorticoid-free treatment protocols have been evaluated to date; one example is the Rituxilup protocol, which comprises two doses of rituximab and methylprednisolone followed by maintenance with MMF and without the use of oral glucocorticoids (149). In a prospective single-center cohort study, 45 of 50 patients (90%) achieved a renal response to treatment with the Rituxilup protocol after a median follow-up duration of 37 weeks (149).

Novel targeted therapies may facilitate a reduced dose and a faster taper of oral glucocorticoids in the management of LN. Recent clinical trials on novel therapies, such as zetomipzomib, have used glucocorticoid reduction as an outcome measure (59), while other clinical trials, such as the BLISS-LN and the AURORA 1 trials, have incorporated glucocorticoid target doses as part of the primary endpoint or treatment failure protocol (51, 52). Additionally, LN clinical trials are increasingly using accelerated glucocorticoid-tapering regimens in their treatment protocols, such as the AURORA 1 trial (which tapered to 2.5 mg/day at week 16) and the NOBILITY trial (which tapered to 7.5 mg/day by week 12) (52, 54). An ongoing Phase III study (OBILUP; NCT04702256) will evaluate the use of obinutuzumab with MMF as induction treatment; oral glucocorticoids will not be used except in cases of extrarenal involvement (100). Future clinical trials evaluating novel therapies should consider assessing their glucocorticoid-sparing effect in light of increasing recognition for the reduction of glucocorticoid exposure as an important outcome in LN management. Validated measures of glucocorticoid toxicity, such as the Glucocorticoid Toxicity Index, can possibly be incorporated as an endpoint in future clinical trials to objectively measure the impact of LN treatments on glucocorticoid-induced toxicity (150).

2.6.3 Combination therapies

Based on the latest clinical trial data and global guideline recommendations, a proposed treatment algorithm for patients with LN is outlined in Figure 2. We propose that the approved LN therapies (belimumab and voclosporin) should be used early within the treatment paradigm for LN. A more aggressive approach to initial or induction therapy, using combinations of either MMF/CYC plus belimumab or MMF plus voclosporin, is recommended to better preserve kidney function and allow for earlier tapering of oral glucocorticoids: belimumab may help reduce the risk of relapses, and voclosporin can lead to faster proteinuria reduction (52, 80, 151). Based on data from the BLISS-LN trial, belimumab can be used with either MMF or CYC; voclosporin should be used with MMF only because of a current lack of data on the use of voclosporin with CYC or AZA (51, 52). Additional studies of belimumab and voclosporin are needed to confirm their use in other combination regimens.

After completion of the initial or induction phase (which typically lasts approximately 3–6 months), subsequent or maintenance treatment options include either MMF plus belimumab or plus voclosporin, or AZA with belimumab; these combination regimens are based on data from the BLISS-LN and AURORA studies (51, 52, 82). We propose that the dose of prednisone should be tapered to a maximum of 5 mg/day and tapered to zero if possible.

2.6.4 Treatment of refractory disease

We consider complete renal response as UPCR ≤0.5 mg/ g and eGFR stabilization of within 10%–20% after 6–12 months of initiating therapy. In nonresponders or patients with refractory disease, observational data and guideline recommendations have suggested clinical benefit in switching to an alternative first-line immunosuppressive regimen (i.e., MMF to CYC or vice versa) (16, 152–154). The addition of rituximab to either MMF or CYC has demonstrated efficacy in refractory LN, including meaningful improvements in response rates, proteinuria, and disease activity scores (91–94).

The combination of rituximab, belimumab, and MMF demonstrated good renal response and sustained B-cell depletion in a small Phase II proof-of-concept study; MMF dose was tapered to avoid an excess of immunosuppression (155). In the CALIBRATE trial ($N = 43$), the add-on of belimumab to a combination of CYC and rituximab did not increase the frequency of adverse events among patients with recurrent or refractory LN, but there was no significant difference in complete response rates (156). Similarly, data from several studies have indicated the efficacy of multitarget immunosuppression (i.e., CNI with MMF) in refractory LN (157, 158). Minimal data exist for the use of CNIs with belimumab: in a small, single-center, retrospective analysis of 33 patients with SLE (including 11 patients with renal flares) treated with a combination of belimumab and tacrolimus, a state of low disease activity of lupus was achieved in 64.0% of patients at 52 weeks after initiation compared with 9.1% at initiation; the combination did not appear to increase the risk of infectious complications (159). A recent publication by Baum et al. discussed data from four patients with LN treated with a combination of both voclosporin and belimumab, including one patient treated with triple therapy (MMF plus voclosporin and belimumab) who achieved a

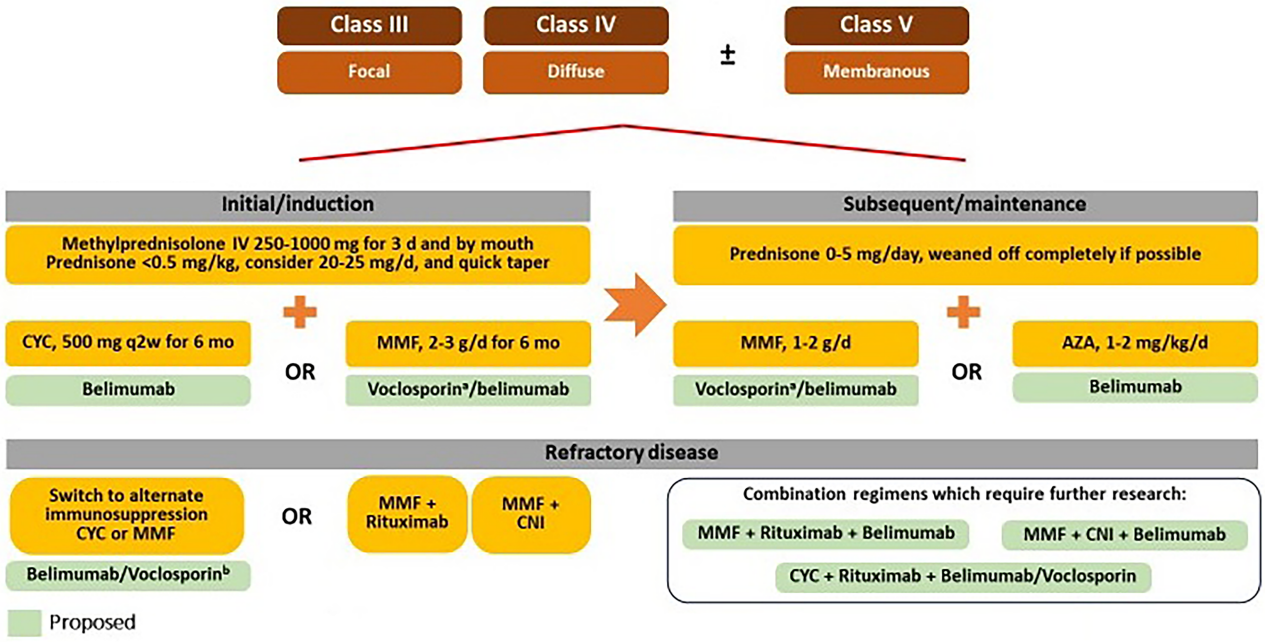

FIGURE 2
Proposed future treatment algorithm for LN. AZA, azathioprine; CNI, calcineurin inhibitor; CYC, cyclophosphamide; ESRD, end-stage renal disease; GFR, glomerular filtration rate; IV, intravenous; MMF, mycophenolate mofetil. [a]Use of voclosporin is not indicated in patients with GFR <45 ml/min. [b]Voclosporin should only be used in combination with MMF.

reduction in proteinuria and glucocorticoid dose after 8–14 months without evidence of toxicity or intolerable side effects (160). Although initial data is promising, further research on combination therapies with belimumab and voclosporin is needed to establish their role in treatment of refractory LN.

2.6.5 Cessation of background immunosuppressive therapy

Newer agents in development for LN offer the exciting potential for achieving remission that would allow background immunosuppressive treatment to be discontinued or paused. The recent CAR-T data suggest that long-term drug-free remissions are possible for patients with LN (136–138). The opportunity to taper off background therapy is attractive to patients because it will simplify their treatment regiments and reduce potential toxicities from these medications.

3 Conclusion

Patients with LN face several unmet needs with current treatments, including unsatisfactory response rates, progression to ESKD, and adverse effects of treatment, especially with long-term use of glucocorticoids. The treatment landscape for LN is rapidly evolving; the development and evaluation of many new therapeutics with novel mechanisms have the potential to address these unmet needs to improve patient outcomes.

Author contributions

AA: Writing – original draft, Writing – review & editing. MD: Writing – original draft, Writing – review & editing. SA: Writing – original draft, Writing – review & editing.

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Conflict of interest

AA: Investigator/Consultant: Abbvie, Amgen, AstraZeneca, Aurinia, BMS, Celgene, Eli Lilly, Idorsia, Janssen, Genentech,

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