Review Article

JHSMR Journal of Health Science and Medical Research

The Evolution of Lupus Nephritis Treatment; from Conventional to Targeted and Biologics Therapy

Warot Piriyasanguanpong, M.D., Siriporn Juthong, M.D., Duangkamol Aiewruengsurat, M.D., Porntip Intapiboon, M.D.

Allergy and Rheumatology Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

Received 25 March 2024 ● Revised 15 May 2024 ● Accepted 16 May 2024 ● Published online 3 December 2024

Abstract

Lupus nephritis (LN) is a common and severe organ manifestation in patients with systemic lupus erythematosus (SLE). LN can present alone or with accompanying extra-renal symptoms. The prevalence and severity vary depending on ethnicity, genetics, and environmental exposure. However, the presence of LN in SLE is a surrogate indicator of disease severity, frequent relapse, increased chronic kidney disease (CKD), and mortality risks. The current conventional standard treatments for LN include corticosteroids, immunosuppressive drugs, and antimalarial drugs. Despite an optimal standard treatment regimen, the outcomes of renal remission, decreased CKD risk, and quality of life are unsatisfactory. In addition, corticosteroid and immunosuppressive drug toxicity are of primary concern. Thus, two dozen promising biological and targeted drugs are being studied in the LN treatment pipeline to improve renal outcomes and mitigate the side effects of conventional therapy. This article aims to review the pathogenesis of LN, summarise the current conventional strategy, and highlight the candidate novel drugs in LN included in Phase II and III clinical trials. These biologics, or targeted therapies, are hoped to facilitate the advancement of the LN treatment paradigm in the era of precision medicine.

Keywords: biologic therapy, lupus nephritis, systemic lupus erythematosus, targeted therapy

Contact: Assoc. Prof. Porntip Intapiboon, M.D.
Allergy and Rheumatology Unit, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla 90110, Thailand.
E-mail: iporntip@medicine.psu.ac.th

J Health Sci Med Res
doi: 10.31584/jhsmr.20241125
www.jhsmr.org

Introduction

Systemic lupus erythematosus and lupus nephritis pathogenesis

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by autoantibody production, contributing to multiple organ inflammation. Its pathogenesis is complex, involving genetic susceptibility, epigenetics, environmental exposure to oestrogen, ultraviolet radiation, smoking, and infection, especially viral pathogens, which contribute to the formation of neoantigens. Moreover, increased cell apoptosis and impaired autoantigen clearance overwhelm autoantigen production[1]. The innate immune response aberrantly initiates the immune activation, wherein these autoantigens are recognised and processed by antigen-presenting cells (APCs) via pattern recognition receptors, such as toll-like receptor (TLR)-3, 7, 8, and 9, retinoic acid-inducible gene-I, melanoma differentiation-associated protein-5, mitochondrial antiviral signalling protein, cyclic GMP-AMP synthase and stimulators of the interferon gene. Processed autoantigens are presented to autoreactive T lymphocytes via the T-cell receptor (TCR) and other costimulatory signals. Subsequently, T lymphocytes and pro-survival signals stimulate the expansion and autoreactive B-lymphocytes differentiation into plasma cells, which produce numerous autoantibodies, such as anti-double-stranded DNA (anti-dsDNA). These autoantibodies combine with autoantigens to form immune complexes, viciously stimulating innate and adaptive immune systems and producing multiple inflammatory cytokines, especially interferon (IFN)-α. Organ damage is caused by excessive immune complex formation, complementing cascade activation, and cytokines production. The kidney is the prototypic organ demonstrating SLE's tissue immune complex deposition.

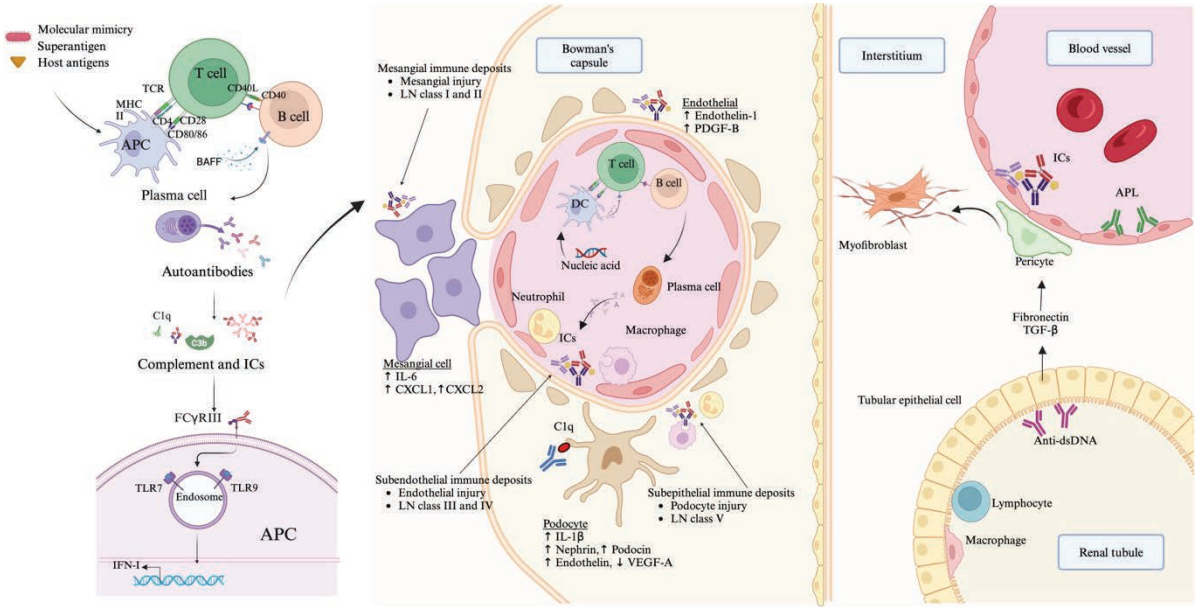
Lupus nephritis (LN) is the most common organ involvement in SLE; severe cases may contribute to permanent kidney damage. Various immune activation processes explain the complexity of LN pathogenesis. In addition, renal microstructures, such as the glomerulus, renal tubules and vessels, are all affected. Glomeruli, which contain networks of capillaries and function as blood filters, are mainly affected by immune complexes and inflammation. Hence, the LN classification is based on glomerular pathology. Inflammation begins when the glomerulus traps immune complexes, which are eliminated by the mesangial cells. At this stage, the production of inflammatory cytokines, for example, interleukin (IL) -6, C-X-C motif chemokine ligand-1, and monocyte chemoattractant protein-1, results in inflammatory cell recruitment and glomerular tissue injury. This pattern corresponds to LN's minimal mesangial (class I) and mesangial (class II). In the following stage, the immune complexes are deposited in the subendothelial layer, damaging capillary vessels. This stage is characterised as focal (class III) or diffuse (class IV) proliferative LN. Additionally, in membranous (class V) LN, IL-1β production increases and immune complexes accumulate in the subepithelial layer of the glomerulus, leading to podocyte inflammation and impairment of their foot process function at maintaining substances in the blood, such as albumin. Finally, transforming growth factor-β, a profibrotic cytokine, facilitated pericyte to myofibroblast differentiation and remodelling, contributing to glomerular fibrosis. This stage characterises advanced sclerosis (class VI) LN. The pathogenesis of SLE and LN are summarised in Figure 1.

Evolution of lupus nephritis treatment

Glucocorticoids (GCs) have been the cornerstone of LN treatment, with dramatic survival improvements from 17% in the pre-GCs era to 55%[2]. However, frequent relapses and GCs toxicity have been major concerns. Hence, the evolution of alternative treatment strategies was studied and first reported in 1985. A randomised controlled trial (RCT) of an intravenous cyclophosphamide (IVCY) and GCs combination regimen demonstrated better renal outcomes than GCs alone for clinically significant LN[3]. A

modified low-dose IVCY (Euro-Lupus regimen) induction regimen was introduced in 2002, as an alternative regimen to mitigate cyclophosphamide (CYC) side effects, along with mycophenolate mofetil (MMF), with similar efficacy and fewer side effects[4,5]. In addition, a novel multitargeted therapy, including MMF and calcineurin inhibitors (CNIs), was found to be effective for LN induction efficacy[6,7]. The evolution of LN treatment is shown in Table 1.

The current LN standard of care (SoC) depends on the LN classification; as defined by the 2018 revision of the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) Classification of LN, and long-term renal outcomes are predicted using the modified National Institutes of Health (NIH)[15,16]. Immunosuppressive drugs are typically unnecessary for LN classes I and II. In contrast, the treatment of proliferative LN (classes III, IV, III/IV, and IV/V) starts with intravenous methylprednisolone (IVMP), followed by a lower GCs dose combined with either CYC or MMF for the induction phase. However, early consideration of add-on belimumab or voclosporin is required if there is an inadequate response to SoC by 3–6 months. Patients that achieve partial or complete remission enter the maintenance phase, which involves continuing the combination of low-dose GCs and AZA, or MMF, for at least three years[17]. For membranous LN (class V), treatment will be indicated if there is proteinuria of more than 1 g/day or abnormal renal function. Additionally, the management plan should advance to the end-stage renal care plan in LN class VI. Current LN management recommendations, including the 2019 European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA), 2023 EULAR



APC=antigen presenting cells, APL=antiphospholipid antibodies, BAFF=B-cell-activating factor, CXCL=C-X-C motif chemokine ligand, DC=dendritic cells, ICs=immune complexs, IFN=interferons, IL=interleukins, LN= upus nephritis, MHC=major histocompatibility complex, PDGF=platelet-derived growth factor, TCR=T-cell receptor, TGF=transforming growth factor, TLR=toll-like receptors, VEGF=vascular endothelial growth factor

Figure 1 Pathogenesis of systemic lupus erythemaosus and lupus nephritis (created with BioRender.com)

Table 1 The evolution of the current treatment of lupus nephritis

Year/authors	Study comparison drugs	Study outcomes
Induction phase		
1986 Austin et al.[3]	GCs with IVCY 0.5–1.0 g/m^2 every 4 weeks 6–9 cycles (NIH regimen) versus GCs alone	NIH regimen: a combination of GCs with IVCY had better long-term renal outcomes than GCs
2002 Houssiau et al.[4]	GCs with IVCY 500 mg every 2 weeks for 6 cycles (Euro-Lupus regimen) versus GCs with IVCY 0.5–1.0 g/m^2 every 4 weeks for 6 cycles and every 12 weeks for 2 cycles	Euro-Lupus regimen: GCs with low dose IVCY demonstrated similar efficacy with the NIH regimen while having fewer side effects for CYC (infection and ovarian failure)
2009 Appel et al.[5]	GCs with MMF up to 3 g/day versus GCs with 0.5–1.0 g/m^2 IVCY every 4 weeks for 24 weeks	ALMS induction trial: Similar response rate between IVCY and MMF (favour MMF in Hispanic ethnicity)
2015 Liu et al.[7]	GCs with Tacrolimus (TAC) 4 mg/day and MMF 1.0 g/day, versus GCs with IVCY 0.5–1.0 g/m^2 every 4 weeks for 24 weeks	TAC with MMF had a significantly higher complete remission rate than IVCY had at 24 weeks
2020 Furie et al.[8]	GCs with Belimumab IV 10 mg/kg at day 1, 15, 29, then q 28 days, then monthly and MMF up to 3 g/day or IVCY 500 mg every 2 weeks for 6 cycles versus GCs with MMF or IVCY alone	BLISS-LN: Belimumab with MMF or IVCY had a better renal response than those who received MMF or IVCY alone at 104 weeks
2021 Rovin et al. [9]	GCs with MMF 2 g/day and voclosporin (VCS) 23.7 mg twice daily versus GCs with MMF 2–3 g/day for 52 weeks	AURORA 1: MMF with VCS had a complete remission rate of more than MMF only had
Maintenance phase		
2004 Contreras et al.[10]	Azathioprine (AZA) 1–3 MKD or MMF 0.5–3 g/day versus IVCY every 3 months after 7 cycles of monthly IVCY induction therapy	AZA or MMF has more efficacy and fewer side effects, including leukopenia, than IVCY every 3 months
2011 Dooley et al.[11]	MMF 2 g per day versus AZA 2 MKD, plus placebo in each group after response to a 6-month induction trial (ALMS induction trial) for 36 months	ALMS maintenance trial: MMF has a significantly higher maintained remission rate than AZA
2017 Zhang et al.[12]	GCs with TAC 2–3 mg/day and MMF 0.50–0.75 g/day after multitargeted induction versus GCs with AZA 2 MKD after IVCY induction	Multitarget maintenance therapy: TAC plus MMF had a similar relapse rate but fewer adverse events and withdrawal rates than AZA had at 18 months of study
2022 Rovin et al.[13]	belimumab IV 10 mg/kg every 4 weeks add-on AZA or MMF versus placebo add-on AZA or MMF up to week 100	BLISS-LN: Belimumab add-on AZA or MMF had a lower risk of LN flare-over and slower declined eGFR up to week 104
2024 Saxena et al.[14]	GCs with VCS and MMF versus GCs with MMF alone up to month 36 (same dose of study drugs in AURORA 1)	AURORA-2: VSC groups revealed a better complete renal response rate with similar safety compared to MMF alone.

AZA=azathioprine, CNI=calcineurin inhibitor, CYC=cyclophosphamide, GCs=glucocorticoids, IVCY=intravenous cyclophosphamide, TAC=tacrolimus, VCS=voclosporin

recommendations for the management of systemic lupus erythematosus, and 2024 Kidney Disease Improving Global Outcomes (KDIGO) are summarised in Table 2[17–19].

To summarise, the current LN treatment schemes depend on the LN classification, involving induction by a combination of GCs and immunosuppressive therapy, followed by immunosuppressive drug maintenance therapy. Minimising GCs and early targeted or biologics drug initiation are the strategies that aim to achieve early remission, prevent kidney damage, retain long-term remission to prevent disease relapse and ameliorate long-term GCs' adverse effects. If there are no contradictions, renal biopsy should be considered for an accurate treatment and tailored regimen.

Table 2 Treatment of lupus nephritis class III and IV, based on international treatment recommendations for lupus nephritis

	2019 EULAR/ERA-EDTA recommendations[18]	2023 EULAR recommendations[17]	2024 KDIGO recommendations[19]
Induction phase			
Glucocorticoid	Total IVMP 500–2,500 mg, then prednisolone 0.3–0.5 MKD for up to 4 weeks. taper to ≤7.5 mg/day by 3–6 months	IVMP 250–1,000 mg/day for 1–3 days, then prednisolone 0.3–0.5 MKD and taper to 5mg by 12 weeks	IVMP 250–500 mg/day for 1–3 days, then prednisolone 0.35–1 MKD, taper to <2.5 mg/day by week >25
Immunosuppressive drugs	1. IVCY 500 mg q 2 weeks x 6 doses or IVCY 0.5–0.75 g/m^2 q 4 weeks. for 6 months (high risk for kidney failure) 2. MMF 2–3 g/day or MPA at equivalent dose 3. MMF 1–2 g/day or MPA at equivalent dose with CNIs in the case of patients with nephrotic-range proteinuria	1. IVCY 500 mg q 2 weeks. x 6 or IVCY 0.5–0.75 g/m^2 q 4 weeks. x6 (high risk for kidney failure) 2. MPA (MMF 2–3 g/day or MPS: 1.44–2.16 g/day) 3. MPA (MMF 1–2 g/day or MPS 0.72–1.44 g/day) combination with CNIs 4. Belimumab combination with either IVCY or MPA	1. IVCY 500 mg q 2 weeks x6 or IVCY 0.5–1.0 g/m^2 q 4 weeks x6 or oral CYC 1–1.5 MKD for 2–6 months 2. MPA for at least 6 months (MMF 2–3 g/day or MPS 1.44 –2.16 g/day 3. Belimumab + MPA or reduced dose IVCY 3.1 Belimumab IV 10 mg/kg q 2 weeks for 3 doses, then q 4 weeks up to 2.5 years and MPA 3.2 Belimumab IV 10 mg/kg q 2 weeks for 3 doses, then q 4 weeks up to 2.5 years and IVCY 500 mg q 2 weeks. x6 (if high risk for renal failure or repeated renal flares) 4. CNIs + MPA 4.1 VCS 23.7 mg bid and MPA (GFR >45 ml/min/1.73 m^2) 4.2 TAC 4 mg/day (trough level 5.5 ng/ml), and reduced dose MPA (if SCr <3 mg/dl treatment duration of up to 3 years and consider cyclosporin when VCS or TAC are unavailable
Alternative drugs	1. Rituximab (monotherapy or combined with IS) for active, non-responding/refractory disease 2. Belimumab for add-on therapy to facilitate glucocorticoid sparing, control extra-renal lupus activity and decrease extra-renal flare	1. Rituximab 1000 mg on days 1 and day 15	1. Rituximab for patients with persistent disease activity or inadequate response to initial standard-of-care therapy
Other drugs	HCQ ≤5 MKD	HCQ ≤5 MKD	HCQ ≤5 MKD

	2019 EULAR/ERA-EDTA recommendations[18]	2023 EULAR recommendations[17]	2024 KDIGO recommendations[19]
Maintenance phase			
Glucocorticoid	Prednisolone 2.5–5 mg/day	Prednisolone ≤5 mg/day	Prednisolone <5 mg/day
Immunosuppressive drug	1. MMF 1–2 g/day for 3–5 years 2. AZA 2 MKD for 3–5 years	1. MPA: MMF 1–2 g/day or MPS 0.72–1.44 g/day (replace IVCY) 2. AZA 2 MKD (replace IVCY) 3. MPA (MMF 1–2 g/day or MPS 0.72–1.44 g/day) combination with CNIs (remain from induction) 4. Belimumab in combination with MPA (remain from induction) 5. Belimumab in combination with AZA (replace IVCY) Duration of maintenance phase at least 3 years	1. MPA: MMF 1–2 g/d or MPS 0.72–1.44 g/day 2. Continue with the maintenance of triple IS in patients who received triple IS as initial therapy (Belimumab and MPA or Belimumab and AZA) 3. AZA 1.5–2.0 MKD when there is no access to MPA 4. CNIs or mizoribine or leflunomide if MPA or AZA are not tolerated or available
Other drugs	HCQ for long-term treatment	HCQ is recommended for all patients	

AZA=azathioprine, CNIs=calcineurin inhibitors, CYC=cyclophosphamide, GFR=glomerular filtration rate, HCQ=hydroxychloroquine, IVCY=intravenous cyclophosphamide, IVMP=intravenous pulse methylprednisolone, IS=immunosuppressive drugs, MMF=mycophenolate mofetil, MKD=mg per kg per day, MPA=mycophenolic acid, MPS=enteric-coated mycophenolate sodium, TAC=tacrolimus, SCr=serum creatinine, VCS=voclosporin

The current promising LN treatment beyond conventional drugs

Over the past 40 years, both short-term and long-term renal outcomes have been under-expected; up to 30% of cases progress to chronic kidney disease despite the availability of SoC[20]. Moreover, conventional therapies affect aberrant and normal immune cells, resulting in low treatment efficacy and undesirable side effects; such as opportunistic infections or metabolic disturbances. Recently, novel, alternative therapies; including a new generation of CNIs and two biologics, have been approved and recommended as part of the international recommendation for LN treatment[17,19].

Calcineurin inhibitors (CNIs)

The mechanism of action of CNIs involves binding to immunophilins, which are high-affinity specific cytoplasmic receptors; including cyclophilin and FK-binding proteins. This complex competitively inhibits calcineurin activity, thus decreasing the nuclear factor of activated T cells (NFAT), signal transduction and blocking IL-2 production. Finally, T lymphocyte activation and differentiation are inhibited. Furthermore, it directly inhibits synaptopodin degradation in podocytes, thereby ameliorating proteinuria. Currently, two new CNI generations, TAC and VCS, are included in the SoC for the induction phase of LN. TAC inhibits calcineurin function by binding specifically to the immunophilin FKBP-12 (FK506 binding protein), forming a new complex and reducing peptidyl-prolyl isomerase activity. A combination of CNIs and mycophenolic acid (MPA) was illustrated as a benefit and proposed as a "multitargeted therapy" approach as well as being recommended for proliferative LN treatment: a combination of TAC 4 mg/day and MMF 1 g/day revealed a significantly higher complete remission rate (CRR) in the multitarget group than that of 0.5–1 g/m^2 IVCY[7]. Likewise, it also showed a favourable outcome in the maintenance phase: the multitarget group had a relapse rate similar to AZA but fewer adverse events[12]. VCS, a novel, potent calcineurin inhibitor derivative of cyclosporin A, combined with a methyl group addition to the aminoacid-1 residue, exhibits fascinating efficacy. It has minimal side effects and was approved by. the US FDA for active LN treatment in January 2021, based on a Phase III RCT (AURORA-I trial) in 357 patients with LN. The results revealed that a combination of VCS and MMF had a higher CRR than MMF alone had at one year. Additionally, proteinuria improvement persisted over three years of follow-up[9,21].

Belimumab

Belimumab, a humanised monoclonal IgG1 against B-lymphocyte stimulator/B-cell activating factor (BLys/BAFF), was the first United States Food and Drug Administration (US FDA) biologic drug for SLE in 2011 and was approved for LN in 2020. Belimumab interferes with the BAFF and BAFF receptor (BAFF-R) interactions, resulting in B-lymphocyte expansion inhibition and diminished autoantibody production (Figure 2). LN treatment efficacy was reported by an RCT (BLISS-LN trial), where add-on belimumab to SoC significantly improved renal outcomes compared to SoC alone. Additionally, belimumab's side effects were comparable to those of SoC alone[22]. The post hoc analysis of this study supports that belimumab had better benefits in MMF subgroups, proteinuria <3 g/day, and LN class III or IV (not pure class V), irrespective of newly diagnosed or relapse[13,23]. Weekly subcutaneous doses of belimumab have recently shown efficacy similar to the original intravenous route[24].

Rituximab

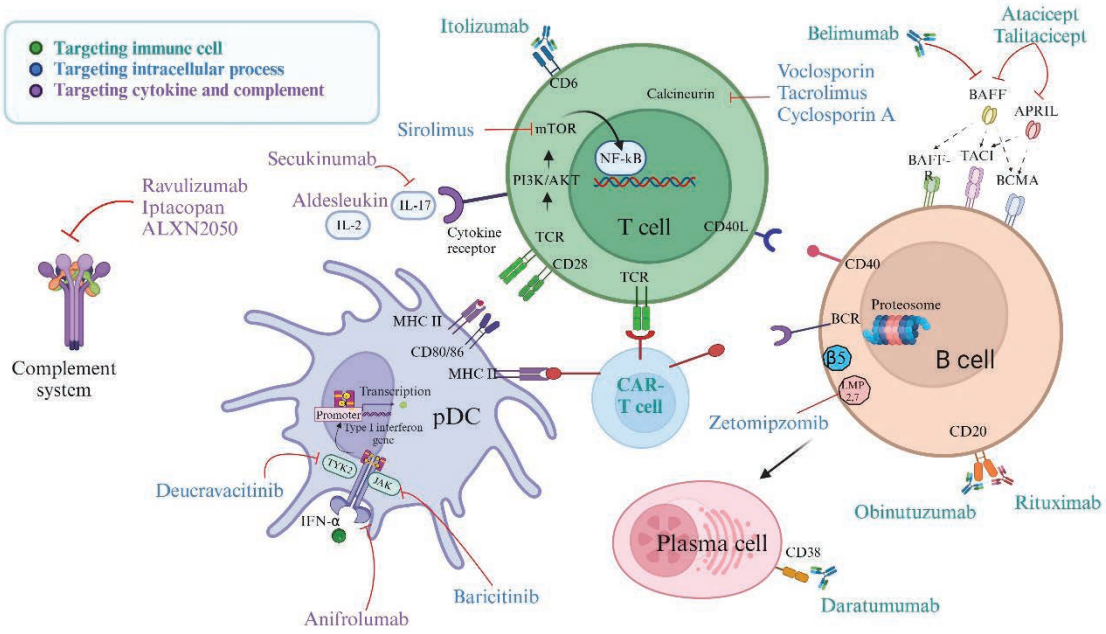
Rituximab is a chimeric monoclonal immunoglobulin G(IgG)-1 to CD20 on B-lymphocyte surfaces. It induces CD20-B-lymphocyte apoptosis via antibody-dependent cellular cytotoxicity (ADCC) and complements direct cytotoxicity (CDC) mechanisms. A Phase III RCT (LUNAR trial) of rituximab in LN did not achieve the primary endpoint

(superior response rate with rituximab). However, there were significant improvements in serum complement levels, anti-dsDNA, proteinuria, and a lower GCs dose with a longer follow-up time. Simultaneously, a higher rate of LN worsening requiring CYC was reported in the SoC group[25]. Despite failing to address the primary endpoint of LN treatment efficacy, rituximab remains widely prescribed for SLE, including LN, as B-lymphocytes are universally believed to play a crucial role in SLE pathogenesis. Additionally, the efficacy of rituximab has been confirmed by numerous prospective observational studies as well as systematic reviews[26,27]. Hence, rituximab was included in the current international LN management recommendations for treating resistant cases[17,19].

Novel biologics and targeted therapy in Lupus Nephritis

Translational research improves the understanding of SLE and LN pathogenesis, leading to innovative targeted and biological therapies having aberrant cell selectivity. This advancement improves treatment efficacy and minimises the toxicity of the current conventional treatments. Phase II and III clinical trials of biologic and targeted therapies for LN have been extensively studied based on the knowledge of disease pathogenesis. The complexity of immune pathways has been discovered in LN, allowing for various treatment targets for emerging therapies, including targeting immune cells, intracellular processes, cytokines and complement systems.

The novel potential biologics and targeted therapy in lupus nephritis are summarised in Figure 2.



BAFF-R=B cell-activating factor receptor, BCMA=B-cell maturation antigen, CAR T Cell=Chimeric antigen receptor-modified T-cell, IFN-α=interferon alfa, JAKs=Janus-associated kinases, PI3K=Phosphoinositide 3-kinases, mTOR=mammalian target of rapamycin, NF-κB=nuclear factor kappa B, TACI=transmembrane activator and calcium modulator and cyclophilin ligand interactor, TCR=T-cell receptor, TLR=Toll-like receptor, TYK2= tyrosine-protein kinase 2, Ub=ubiquitin

Figure 2 The Novel potential biologics and targeted therapies mechanism of action in Lupus Nephritis (created with BioRender.com)

Targeting immune cells

Anti-B-lymphocyte and B-lymphocyte Signalling Inhibitors

Obinutuzumab: A glycoengineered, humanised anti-CD20 monoclonal antibody type 2 that differs from rituximab and ocrelizumab by having greater ADCC activity due to a glycoengineered Fc in addition to reduced internalisation, which is attributed to the potent induction of direct cell death and B-lymphocyte depletion. A phase II RCT (NOBILITY trial) of a combination of MMF and obinutuzumab administered every 24 weeks revealed that the obinutuzumab group through week 104 of the study had significantly more remarkable, complete remission achievement than the placebo group had a 19% difference[28]. A phase III RCT on proliferative LN (REGENCY trial) is ongoing.

Atacicept: Atacicept is a soluble, fully human, recombinant fusion protein inhibiting BAFF and proliferation-inducing ligand (APRIL) function. Phase II/III RCT (APRIL-SLE trial) revealed the benefits of a lower flare rate and longer time to first flare in patients with SLE. Unfortunately, the 150 mg arm was prematurely terminated due to the death of two patients[29]. The Phase II/III RCT (APRIL-LN) was also terminated early because of low serum IgG and serious infection[30]. A Phase III RCT (COMPASS trial) using atacicept 150 mg in combination with MMF in patients with active LN was recruited.

Telitacicept: A humanised recombinant TACI-Fc fusion protein inhibiting BAFF and APRIL. A 52-week phase III RCT of telitacicept in patients with SLE demonstrated that telitacicept 160 mg had a significantly higher rate of SLE response by achieving an SLE Responder Index (SRI) of 4[31]. Currently, a phase II RCT of telitacicept in patients with LN (NCT05680480) is ongoing.

Anti T-lymphocyte

Itolizumab: A humanised monoclonal antibody against CD6 on the surface of T lymphocytes that inhibits the binding of CD6 to activated leukocyte cell adhesion molecules. Recently, a proof-of-concept Phase Ib study reported an interim result showing a clinically meaningful response in high-proteinuria LN; 83% achieved a complete or partial response, and 67% achieved >50% proteinuria reduction, with no concern for safety signal reported through six months of study. This drug continues to be tested in a Phase II study (EQUALIZE trial) in patients with proliferative LN.

Anti-plasma cell

Daratumumab: Humanised monoclonal IgG1k to CD38 on the plasma cell surface. Recently, a case series of daratumumab monotherapy showed efficacy in six refractory LN[32]. A Phase II RCT of daratumumab (NCT04868838) in LN is still ongoing.

Anti dendritic cell

Daxdilimab, a humanised monoclonal antibody to the immunoglobulin-like transcript- 7 at the plasmacytoid dendritic cell surface, reduces the production of type-1 IFN, tumour necrotic factor-α, and IL-6. A Phase I study reported a favourable outcome of daxdilimab in SLE with mucocutaneous involvement. However, it did not achieve the primary endpoint of the Phase II study. In spite of this, the daxdilimab study will continue in 200 patients with LN (NCT05540665), and this trial is anticipated to be completed in 2026.

Targeting intracellular processes

Anti-intracellular signalling

Baricitinib: Janus kinase (JAK)-1 and JAK-2 inhibitors reduce intracellular signalling transmission after being stimulated by type-1 IFN, IL-2, IL-6, IL-12, and IL-23. Based on the vague efficacy and discordance results in two pivotal Phase III RCTs (SLE-BRAVE-I and II trials), the company announced the discontinuation of the study on lupus[33, 34]. However, a small RCT study included 60

patients with proliferative LN. The study demonstrated that baricitinib 4 mg improved disease activity, proteinuria, C3, and anti-dsDNA more than IVCY did[35].

Deucravacitinib is a tyrosine-protein kinase (TYK)-2 inhibitor with a similar effect to the JAK inhibitor but with more selectivity. Deucravacitinib has demonstrated promising efficacy in a phase II RCT (PAISLEY-SLE trial) in patients with SLE by reaching all primary and secondary endpoints; especially skin and musculoskeletal. The further two-phase III studies are still ongoing. For phase II trials, the RCT of LN (PAISLEY-LN trial) was terminated due to failure in enrolling patients.

Sirolimus: an anti-mammalian target of rapamycin (mTOR), inhibits IL-2 and T lymphocyte intracellular signalling. The ameliorating proteinuric effect of sirolimus was reported in 16 refractory proliferative LN, and a systematic review of 111 patients with SLE found that sirolimus can subside disease activity. Additionally, 95.5% maintained remission in quiescent LN, with acceptable side effects[36, 37]. However, to date, no RCT trials have compared SoC in LN.

Anti-proteosome

Zetomipzomib, a selective anti-proteasome drug, inhibits many pathways involving inflammatory cells and cytokines. In a Phase Ib/II clinical trial (MISSION) in patients with active LN, treatment with zetomipzomib resulted in proteinuria reduction and a steroid-sparing effect[38]. Another trial is PALIZADE, an ongoing phase IIb study on LN with proteinuria >1 g/day, is planned to be completed in 2026.

Targeting cytokines and complements

Cytokine inducibility

Aldesleukin: Deficiency of IL-2, a vital regulatory T-lymphocyte-regulated and hemostatic factor, has been reported in SLE and LN patients. Several case reports and open-label studies using aldesleukin (ILT-101), a recombinant analogue of low-dose IL-2 supplements in refractory LN, have suggested promising outcomes, including increased IL-2 and regulatory T-lymphocyte expansion, proteinuria reduction, and a higher complete remission rate[39, 40]. For this reason, a single-centre Phase II RTC was conducted in 60 patients with refractory SLE, including LN; more than half of the patients with LN in the aldesleukin group achieved CRR and a significant decrease in proteinuria[41]. A larger Phase II multicenter RCT (LUPIL-2) was conducted in patients with moderate-to-severe SLE; however, that study did not focus on patients with LN[42]. The small number of patients and short follow-up time are the limitations of these studies. There have been no ongoing Phase III studies on SLE or LN. Interestingly, a comparative study of human umbilical cord transplantation and low-dose IL-2 for LN (NCT05631717) is currently being conducted.

Anti-cytokine

Anti-interferon type I: Anifrolumab, a humanised monoclonal IgGk1 inhibiting type I IFN receptor (IFNAR1); thus, decreasing interferon gene signature (IGS) expression, inflammatory cytokines, and antibody production. The US FDA approved this drug in 2022 as an add-on therapy in patients with SLE of moderate disease activity, especially musculoskeletal symptoms[17]. Unfortunately, in the 1-year results of a phase II RCT in LN (TULIP-LN trial), neither the intensified regimen (900 mg for the first three doses followed by 300 mg every four weeks), nor the basic regimen (300 mg every four weeks) met the primary endpoint (improve proteinuria). However, greater CRR and sustained GC reduction were observed in the intensified group[43]. The 2-year extension study recently demonstrated attained CRR and simultaneously achieved sustained GC tapering in the intensified group[44]. This finding was explained by a pharmacokinetic analysis study that showed a 50% lower serum anifrolumab concentration in the renal group than in the non-renal group due to proteinuria. Although anti-interferon therapy demonstrated favourable efficacy in LN, intensified regimens showed an

optimistic signal for LN treatment. Determining the optimal dose using pharmacodynamic and pharmacokinetic studies may increase the drug's efficacy. An IRIS phase III RCT (NCT05138133) is underway to evaluate the efficacy and safety of anifrolumab as an adjunct therapy to MMF and GCs in patients with active LN class III or IV.

Anti-IL-17A: secukinumab is a monoclonal antibody against IL-17A. The ongoing Phase III RCT (SELUNE trial) resulted in 400 proliferative LN, with add-on secukinumab 300 mg monthly with SoC compared to SoC alone and will be released in 2024.

Complement inhibitors:

Complement originates from an interaction between autoantibodies and self-antigens, causing multi-organ damage in patients with SLE. The complement inhibitors are ongoingly studied as adjunctive therapy to SoC; including ravulizumab, a monoclonal antibody targeting C5 (NCT04564339), iptacopan, an oral factor B inhibitor (NCT05268289), and ALXN2050, an oral factor D inhibitor (NCT05097989).

Chimeric antigen receptor-modified T-cell (CAR T-cell)

A CAR T-cell is a modified T-lymphocyte via inserting a gene that expresses TCR to CD19 on the B-lymphocyte surface. When CAR T-cells pair with CD19, using a pre-treatment lymphodepletion protocol, autoreactive B-lymphocytes are eliminated, and immune cells are reset. The favourable outcomes of CAR T-cell therapy in refractory SLE with LN have been demonstrated in case reports as well as case series by decreasing proteinuria, disease activity, and anti-dsDNA levels[45,46]. Although, CAR T-cell therapy seems to be an emerging strategy that has reported favourable outcomes for SLE and LN, owing to the complexity of SLE pathogenesis; especially autoreactive B-lymphocyte repopulation, a well-designed, larger study population and longer follow-up duration are needed.

Novel distinctive strategies in lupus nephritis treatment

Combine targeted therapy: SLE pathogenesis is complicated, so using a single treatment regimen might not be enough to ameliorate all autoreactive cells. Additionally, paradoxical side effects might occur; for example, BAFF levels will increase after using anti-CD20 therapy; such as rituximab. Thus, the idea of complementary mechanism-targeted therapy has been proven by a phase II proof-of-concept study in refractory SLE, including LN, that combined a single course of rituximab with continued monthly belimumab for two years of study. The results revealed a favourable clinical and serological response, concordant with a more significant CD20-B-lymphocyte depletion and longer repopulation in the responder group[47]. A phase II RCT (CALIBRATE trial), using rituximab and IVCY, followed by belimumab, was performed to illustrate the efficacy of this treatment strategy in refractory LN. However, the results showed no significant differences between the groups[48]. Furthermore, an exploratory analysis of a phase II RCT (the BEAT-LUPUS trial) demonstrated that serum IgA2 and anti-dsDNA were biomarkers associated with active LN and predicted treatment responses. In addition, a significantly longer duration of B-lymphocyte repopulation was observed in the add-on belimumab group[49].

Precision and personalised medicine: Patients with SLE have different immunophenotypes and unpredictable outcomes with conventional therapy. Translational research using immunophenotypic studies for treatment guidance has provided better outcomes. For instance, a previous study reported a biomarker for predicting disease flare-ups using IGS[50]. In addition, high IGS is correlated with disease activity, especially in the musculoskeletal and mucocutaneous domains, which is concordant with the

better efficacy of anifrolumab treatment[51]. In contrast, some SLE patients have a B-lymphocyte-dominant immunophenotype; therefore, disease flares can be predicted using BLyS/BAFF levels. A meta-analysis, which included the BLISS-52 and BLISS-76 trials, illustrated that belimumab had better efficacy in patients with high BAFF levels, IFN-type I mRNA, and BAFF mRNA expression[52].

Conclusion

LN arises from many factors; including genetics, the environment, and aberrant immune responses. Individual patients manifest variable kidney pathologies and responsiveness to treatments. Through the evolution of LN treatment, renal outcomes have dramatically improved over the past half-century. However, the current conventional approaches have suboptimal outcomes, and toxicity is a significant concern. Hence, novel targeted therapies might provide hope for a better renal outcome and improved quality of life.

Conflict of interest

The authors declare no conflicts of interest.

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