Kidney Medicine

Novel Therapeutics for Management of Lupus Nephritis: What Is Next?

Sayali B. Thakare, Paolo Nikolai So, Sonia Rodriguez, Mohamed Hassanein, Edgar Lerma, and Nasim Wiegley, on behalf of the GlomCon Editorial Team

Lupus nephritis is a severe, organ-threatening manifestation of systemic lupus erythematosus. The current standard of care in the treatment of lupus nephritis is limited to broad-spectrum immunosuppressants, which have significant concerns of short- and long-term toxicity. With traditional approaches, kidney survival and patient outcomes have remained suboptimal. Robust research in the therapeutics of lupus nephritis has resulted in development of many novel drugs targeting specific inflammatory response pathways. Some newer agents have shown a definitive signal of benefit when added to standard of care. With the advent of precision medicine in nephrology, lupus nephritis treatment may undergo a shift toward incorporating approaches using these newer drugs and individualizing care of our patients. This review highlights major advances in management of lupus nephritis over the last 25 years and explores the ongoing trials of emerging therapies in lupus nephritis.

Complete author and article information provided before references.

Correspondence to S. B. ThakareS.B. Thakare (thakare.sayali@gmail.com)

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Lupus nephritis (LN) develops in 40%-60% of patients with systemic lupus erythematosus (SLE). The kidney domain of SLICC/ACR (Systemic Lupus International Collaborative Clinics/American College of Rheumatology) Damage Index is associated with early mortality in SLE.[1] Hence, preventing kidney damage in SLE has long-term prognostic implications. Currently used standard of care, corticosteroids in combination with immunosuppressants, has dramatically improved patient survival in LN (from 17% at 5 years in untreated patients to 80% in those treated with standard of care),[2] though not without the burden of drug toxicities. Yet, 10%-30% of patients with LN progress to kidney failure within 15 years.[3] This article provides an overview of emerging therapies for LN and major randomized controlled trials (RCTs) involved in drug development.

NOVEL THERAPEUTIC TARGETS FOR LUPUS NEPHRITIS

The diversity of immune response[4] in SLE and LN provides many attractive biologic targets (Fig 1). Plasmacytoid dendritic cells are activated by signals from other immune cells reacting to self-antigens. Interferon-alfa released from activated plasmacytoid dendritic cells serves as an amplifier to major axes of immune activation. Plasmacytoid dendritic cells stimulate the production of other antigen-presenting cells. They upregulate major histocompatibility complex II and co-stimulatory molecules leading to the activation of T cells. CD4 helper T cells, thus activated, produce a repertoire of cytokines promoting autoreactive B-cell differentiation to plasma cells. Plasma cells further drive higher auto-antibody expression and immune complex formation in SLE and LN.

Delving into candidate drugs targeting these pathways is arduous. A comprehensive study of clinical trials in LN registered with ClinicalTrials.gov lists as many as 126 RCTs initiated between 1998 and 2020, including those for 27 types of biological agents.[5] Among these, anti-inflammatory agents act acutely by limiting immunologic damage, making them useful as induction agents. Therapies that target autoimmunity work toward attenuating disease activity and thus prevent accruing damage from repeated flares.

Despite tremendous progress in unraveling the pathobiology of LN, only a handful of drugs have shown meaningful benefits with acceptable side-effect profiles in phase 2 and 3 clinical trials (Table 1). Some of these agents have received approval for use by regulatory agencies (Fig 1). Belimumab, an anti-BAFF monoclonal antibody (mAb), was the first biological agent approved for SLE in 2011. After a series of focused trials in patients with kidney involvement,[24] belimumab was subsequently approved for LN in December 2020. Voclosporin, a novel oral calcineurin inhibitor, was approved for LN in January 2021 based on results from the AURORA trials.[25,26] The most recent addition to the armamentarium of SLE is anifrolumab, an anti-interferon-α mAb. Anifrolumab was approved for moderate to severe SLE in August 2021, making it the only new drug for SLE in over a decade. Anifrolumab is currently undergoing a phase 3 trial in LN (Table 2).[27] Noting previously concluded trials helps gain perspective about the impact of a given drug action on the pathogenic pathways in LN. Table 1 outlines an updated list of concluded RCTs that either failed to meet the primary endpoint, showed unacceptable drug toxicity, or were terminated prematurely.

Remarkably, not all drugs demonstrating efficacy in SLE display replicable results in LN. The role of local immune pathways, such as the intrarenal inflammatory cycle, interstitial lymphocytic aggregates, or germinal centers within the kidneys, may be implicated.[4] Therapeutic categories of drugs evaluated in trials for patients with LN, such as B-cell therapies and co-stimulatory blockade agents, are described.

B-CELL DIRECTED THERAPIES

B cells have a central role in the pathogenesis of LN and are the most investigated axis for drug therapy.

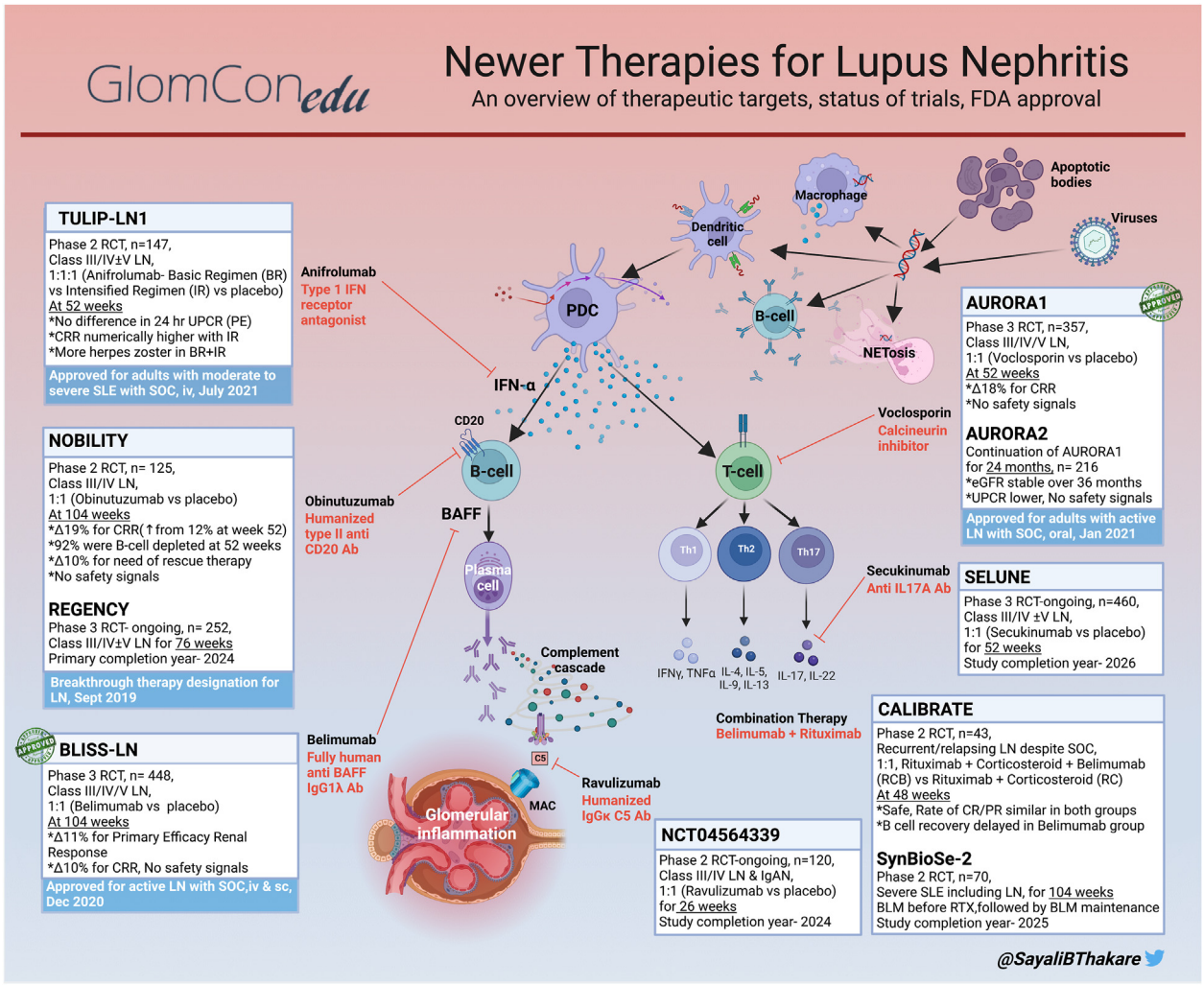

Figure 1. Newer therapies for lupus nephritis. Abbreviations: BAFF, B-cell activating factor; BLM, Belimumab; CR, complete remission; CRR, complete renal response; eGFR, estimated glomerular filtration rate; IFN, interferon; iv, intravenous; LN, lupus nephritis; MAC, membrane attack complex; NET, neutrophil extracellular traps; PDC, plasmacytoid dendritic cell; PE, primary endpoint; PR, partial remission; RCT, randomized controlled trial; RTX, rituximab; sc, subcutaneous; SOC, standard of care; UPCR, urinary protein-creatinine ratio; vs, versus.
*All drugs were assessed as add-on to standard of care.

Approaches include B-cell depletion (ie, rituximab, obinutuzumab, ofatumumab, and ocrelizumab), anti-B-cell activation (ie, belimumab, obexelimab, atacicept, blisibimod, and ianalumab), co-stimulatory blockade (ie, iscalimab, abatacept, ruplizumab, and dapirolizumab pegol), and anti-plasma cell therapy (ie, bortezomib, daratumumab, and ixazomib). Rituximab is the most commonly used mAb for LN at present. Its popularity arises from its ability to act as a steroid sparing agent[28] and from its observed efficacy in refractory/relapsing LN.[29,30] The 2012 LUNAR trial[8] failed to demonstrate improvement in clinical outcomes, however post-hoc analysis of the trial[31] showed that variability in peripheral B-cell depletion likely dictated outcomes, and a complete, lasting peripheral depletion was associated with complete response. Other controlled[32] and observational studies[33,34] later did show benefit of rituximab as well compared to the standard of care. Rituximab continues to be used in real world clinical practice with promising newer data[35] supporting its use.

Obinutuzumab, a humanized anti-CD20 mAb (Fig 1), achieves higher and more sustained B-cell depletion than rituximab and received breakthrough therapy designation from the US Food and Drug Administration for LN in 2019 based on the results of the NOBILITY trial.[36] However, BAFF levels increase with B-cell depletion. Therefore, the sequential use of belimumab with rituximab in the SynBioSe-2 trial (Fig 1) is evaluating synergistic inhibition of the repopulation of autoreactive B cells. Long-lived autoreactive plasma cells are found in the circulation and kidney interstitium and play a role in flares,[37] hence the rationale for using plasma cell-

Table 1. Terminated Randomized Controlled Trials in Lupus Nephritis and Clinical Outcomes

Drug	Mechanism of Action	Trial Registration	Phase	Status
Trials with favorable outcomes				
Filgotinib/lanraplenib	Small molecule inhibitor of JAK1/ATP-competitive inhibitor of spleen tyrosine kinase (SYK)	NCT03285711 (Class V LN)	2	Median reduction of 50.7% in proteinuria at 16 wk for figlotinib, no benefit with lanraplenib[6]
Narsoplimab (OMS721)	MASP-2 inhibitor mAb (lectin pathway inhibitor)	NCT02682407	2	69% reduction of proteinuria in 4/5 patients[7]
Trials with unfavorable outcomes				
B-cell therapies				
Rituximab	Anti-CD20 mAb	NCT00282347 (LUNAR)	3	Failed to meet the primary endpoint, no safety signals[8]
Ocrelizumab	Anti-CD20 mAb	NCT00626197 (BELONG)	3	Early termination because of higher incidence of serious infections. Failed to meet primary endpoint[9]
Atacicept	Fusion protein between TACI and Fc portion of IgG	NCT00573157 (APRIL-LN)	2/3	Terminated early owing to severe infective complications and hypogammaglobulinemia[10]
Blisibimod	Binds to BAFF and prevents interaction with BAFF receptors	NCT02514967 (CHABLIS7.5)	3	Terminated because of failure of prior trial CHABLI SC1[11]
Bortezomib	Proteasome inhibitor	NCT01169857	4	Withdrawn because the previous RCT in SLE did not meet primary endpoint and had higher adverse effects[12]
Ixazomib citrate	Proteasome inhibitor	NCT02176486	1	Terminated because of insufficient enrolment, no safety concerns[13]
Co-stimulatory pathways				
Abatacept	Fusion protein binding to CD80/86 resulting in blockade of CD28 co-stimulation	NCT00774852 (ACCESS)	2	Failed to meet the primary endpoint, no safety signals[14]
		NCT00430677	2/3	Failed to meet the primary endpoint, no safety signals[15]
		NCT01714817 (ALLURE)	3	Failed to meet the primary endpoint, no safety signals[16]
BI-655064	Anti-CD40 mAb (co-stimulatory blockade) for maintenance therapy	NCT02770170	2	Effect size 15.2% and 9.1% for 120-180 mg dose at 52 wk[17]
		NCT03385564 (52-wk extension of NCT02770170)	2	Results awaiting publication
Dapirolizumab pegol (CDP7657)	PEGylated anti-CD40 Ab fragment	NCT02804763	2	Failed to meet primary endpoint, well tolerated, smaller risk of thromboembolic events[18]
Ruplizumab (BG9588)	Anti-CD40L mAb (co-stimulation blocker)	NCT00001789	2	Terminated because of thromboembolic events[19]
Cytokine targeted therapies				
AMG-811	Anti-IFN gamma	NCT00818948	2	Favorable safety profile and PK but no clinical impact[20]
BIIB023	Human mAb against TWEAK	NCT01499355 (ATLAS)	2	Prematurely terminated, no clinical efficacy[21]
Sirukumab (CNTO-136)	Human IgG1k IL-6 mAb	NCT01273389	2	Prematurely terminated, neither increased efficacy nor acceptable safety profile, AE: mostly infections[22]
Ustekinumab	Anti-IL-17/23 mAb	NCT03517722 (LOTUS)	3	Terminated in June 2020 because of lack of efficacy in interim analysis[23]

(Continued)

Table 1 (Cont'd). Terminated Randomized Controlled Trials in Lupus Nephritis and Clinical Outcomes

Drug	Mechanism of Action	Trial Registration	Phase	Status
Others				
Abetimus sodium	Tolerogen: reduces production of double-stranded DNA antibodies	NCT00089804 (ASPEN)	3	Terminated because of lack of efficacy
Deucravacitinib (BMS-986165)	Selective tyrosine kinase Tyk-2 inhibitor selectively blocking the IL-17/23 and IFN type I p/w	NCT03943147	2	Terminated because of insufficient enrolment

Abbreviations: AE, adverse effect; PK, pharmacokinetics.

depleting agents in LN. Bortezomib, a proteasome inhibitor, caused significant neurotoxicity in patients with LN, leading to the early termination of the trial[38] (Table 1). Finally, an immuno-proteosome inhibitor (proteasome inducible by interferon-γ), KZR 616, is currently being investigated with encouraging interim results.[39]

CO-STIMULATORY BLOCKADE AGENTS

CD40/CD40L and CD28/CD80/86 are attractive pathways for therapeutic targets in immune-mediated disorders. A trial involving an anti-CD40L antibody, ruplizumab, was halted because of severe thromboembolic events.[19] A polyethylene glycosylated anti-CD40 antibody fragment, dapirolizumab pegol (CDP7657), was tested in LN with an attenuated risk of thromboembolic events; however, the trial did not meet the primary endpoint.[18] Because of potential benefits, nevertheless, a phase 3 RCT is in progress.[40]

Abatacept, a CD28/CD80 pathway blocker, failed to meet the primary endpoint in 3 RCTs.[14-16] Because no safety signals are reported and because abatacept is an agent affecting autoimmunity, it might work better as maintenance therapy. BI 655064[17] and Iscalimab,[41] both humanized anti-CD40 mAbs, are also therapeutic candidates currently under investigation.

OTHER POTENTIAL TARGET THERAPIES IN LN

These include but are not limited to cytokine-directed therapies (ie, ustekinumab, sirukumab, BIIB023, AMG 811, secukinumab, and guselkumab), anti-complement therapies (ie, ravulizumab, APL-2, iptacopan, and narsoplimab) and miscellaneous (ie, kinase inhibitors, Fc receptor antagonists, and immune-proteasome inhibitors). Itolizumab, anti-CD6 mAb, received fast-track designation from the Food and Drug Administration for LN in December 2019. Most of these agents showed efficacy in previous studies in SLE and are now being investigated for LN.[42] Table 2 lists trials that are currently ongoing and are expected to be completed in the near future. As we eagerly await the results of these trials, optimizing the current broad-spectrum therapy assumes prime importance. Steroid reduction, a strategy incorporated into the current guidelines of standard of care,[43] is one way toward making therapy in SLE and LN safer.

CONCLUSIONS

The armamentarium of SLE is rapidly expanding. However, despite the steady engagement of resources from basic sciences and clinical medicine, there is a long way to go. Successful drug development often unfolds over many years. To transform clinical care globally, benefits from scientific discoveries need to be made widely available and affordable, which assumes the next level of the challenge after the success of a clinical trial. Enthusiasm toward emerging therapies is tempered by a realization that current research focuses heavily on induction agents. More studies are warranted for specific situations like membranous LN, childhood-onset LN, maintenance therapy, and antiphospholipid antibody syndrome. Precision medicine, matching a given drug to the most responsive disease phenotype, appears to be the future in LN (eg, anifrolumab in SLE patients with a high interferon signature). Yet like never before, we could be poised to have plenty more in the immediate future.

ARTICLE INFORMATION

GlomCon Editorial Team: A list of the GlomCon Editorial Team can be found at: https://pubs.glomcon.org/editorial-team/.

Authors' Full Names and Academic Degrees: Sayali B. Thakare, MD, DM, Paolo Nikolai So, MD, Sonia Rodriguez, MD, Mohamed Hassanein, MD, Edgar Lerma, MD, and Nasim Wiegley, MD, on behalf of the GlomCon Editorial Team

Authors' Affiliations: Department of Nephrology, Seth GSMC and KEM Hospital, Mumbai, India (SBT); Private Practice, Manila, Philippines (PNS); Division of Nephrology, University Health Network, Toronto, ON, Canada (SR); Division of Nephrology and Hypertension, University of Mississippi Medical Center, Jackson, MI (MH); Section of Nephrology, University of Illinois at Chicago, Chicago, IL (EL); and University of California Davis School of Medicine, Sacramento, CA (NW).

Address for Correspondence: Address to Dr Sayali B. Thakare, 34A, AKD, Third floor, Old Building, KEM Hospital campus, Acharya Dhonde Marg, Parel, Mumbai, Maharashtra, India, 400012. Email: thakare.sayali@gmail.com

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Table 2. Ongoing Randomized Controlled Trials of Newer Agents in Lupus Nephritis (Source: clinicaltrials.gov)

Drug	Mechanism of Action	Trial Registration	Phase	Participants (n)	Timeline
B-cell therapies					
Daratumumab	Anti-CD38 mAb	NCT04868838	2	12	2021-2024
Ianalumab (VAY736)	Anti B-cell activating factor (BAFF) receptor mAb	NCT05126277	3	420	2022-2031
Obinutuzumab	Anti-CD20 mAb	NCT04221477	3	252	2020-2028
Co-stimulatory blockade					
Iscalimab (CFZ533)	Anti-CD40 mAb	NCT03610516	2	75	2018-2023
Cytokine targeted therapies					
Guselkumab	IL-23 p19 subunit inhibitor	NCT04376827 (ORCHID-LN)	2	60	2020-2025
Secukinumab	Anti-IL17A mAb	NCT04181762 (SELUNE)	3	460	2020-2026
Complement therapies					
APL-2 (Pegcetacoplan)	Binds and inhibits cleavage of C3 into C3a & C3b	NCT03453619 DISCOVERY	2	21	2018-2022
Iptacopan (LNP023)	Small molecule Factor B inhibitor	NCT05268289	2	240	2022-2028
Ravulizumab	Anti-C5 IgG k mAb	NCT04564339	2	120	2020-2024
Others					
Anifrolumab	Anti-IFN-α	NCT05138133	3	360	2022-2025
Itolizumab	Anti-CD6 mAb	NCT04128579 (EQUALISE)	1b	55	2019-2023
KZR-616	Selective inhibitor of LMP7 & LMP2 (immune-proteosome)	NCT03393013 (MISSION)	1b/2	39 (LN-2)	2018-2022
Nipocalimab	Fc receptor antagonist (increases degradation of IgG)	NCT04883619	2	80	2022-2026
Sirolimus	mTOR inhibitor	NCT04892212 (Single center)	2	20	2021-2023
Zanubrutinib	Bruton tyrosine kinase small molecule inhibitor	NCT04643470	2	200	2020-2023
Belimumab + rituximab	Combination therapy	NCT03747159 (SynBioSe-2)	2	70	2018-2025

Abbreviation: mAb, monoclonal antibody.

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REFERENCES

1. Danila MI, Pons-Estel GJ, Zhang J, Vilá LM, Reveille JD, Alarcón GS. Renal damage is the most important predictor of mortality within the damage index: data from Lumina LXIV, a multiethnic US cohort. *Rheumatology (Oxf Engl)*. 2009;48(5):542-545. doi:10.1093/rheumatology/kep012
2. Parikh SV, Rovin BH. Current and emerging therapies for lupus nephritis. *J Am Soc Nephrol*. 2016;27(10):2929-2939. doi:10.1681/ASN.2016040415
3. Costenbader KH, Desai A, Alarcón GS, et al. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995 to 2006. *Arthritis Rheum*. 2011;63(6):1681-1688. doi:10.1002/art.30293
4. Lech M, Anders HJ. The pathogenesis of lupus nephritis. *J Am Soc Nephrol*. 2013;24(9):1357-1366. doi:10.1681/ASN.2013010026
5. Gao Y, Wang Y, Li R, Zhou X. Comprehensive analysis of clinical trials registration for lupus nephritis therapy on ClinicalTrials.gov. *Front Med (Lausanne)*. 2021;8:680302. doi:10.3389/fmed.2021.680302
6. Baker M, Chaichian Y, Genovese M, et al. Phase II, randomised, double-blind, multicentre study evaluating the safety and efficacy of filgotinib and lanraplenib in patients with lupus membranous nephropathy. *RMD Open*. 2020;6(3):e001490. doi:10.1136/rmdopen-2020-001490
7. Omeros Corporation. Omeros reports more positive data in OMS721 phase 2 trial in renal diseases. March 30, 2017. Accessed August 1, 2022. https://investor.omeros.com/news-releases/news-release-details/omeros-reports-more-positive-data-oms721-phase-2-trial-renal
8. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study.

Arthritis Rheum. 2012;64(4):1215-1226. doi:10.1002/art.34359
9. Mysler EF, Spindler AJ, Guzman R, et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. *Arthritis Rheum*. 2013;65(9):2368-2379. doi:10.1002/art.38037
10. Ginzler EM, Wax S, Rajeswaran A, et al. Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial. *Arthritis Res Ther*. 2012;14(1):R33. doi:10.1186/ar3738
11. Merrill JT, Shanahan WR, Scheinberg M, Kalunian KC, Wofsy D, Martin RS. Phase III trial results with blisibimod, a selective inhibitor of B-cell activating factor, in subjects with systemic lupus erythematosus (SLE): results from a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2018;77(6):883-889. doi:10.1136/annrheumdis-2018-213032
12. Ishii T, Tanaka Y, Kawakami A, et al. Multicenter double-blind randomized controlled trial to evaluate the effectiveness and safety of bortezomib as a treatment for refractory systemic lupus erythematosus. *Mod Rheumatol*. 2018;28(6):986-992. doi:10.1080/14397595.2018.1432331
13. National Library of Medicine. Safety, tolerability and pharmacokinetics of multiple rising doses of ixazomib in lupus nephritis (LN). Accessed July 12, 2022. https://clinicaltrials.gov/ct2/show/results/NCT02176486
14. ACCESS Trial Group. Treatment of lupus nephritis with abatacept: the abatacept and cyclophosphamide combination efficacy and safety study. *Arthritis Rheumatol*. 2014;66(11):3096-3104. doi:10.1002/art.38790
15. Furie R, Nicholls K, Cheng TT, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. *Arthritis Rheumatol*. 2014;66(2):379-389. doi:10.1002/art.38260
16. Dooley MA, Appel GB, Furie R, et al. A phase III randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of abatacept or placebo on standard of care in patients with active class III or IV lupus nephritis. *Arthritis Rheumatol*. 2018;70:1086-1088.
17. Jayne D, Steffgen J, Romero-Diaz J, et al. POS0687 A randomised dose ranging, placebo-controlled, phase ii study assessing the efficacy and safety of BI 655064, an antagonistic anti-CD40 antibody, in patients with lupus nephritis. *Ann Rheum Dis*. 2021;80(suppl 1):589-590. doi:10.1136/annrheumdis-2021-eular.1401
18. Furie RA, Bruce IN, Dörner T, et al. Phase 2, randomized, placebo-controlled trial of dapirolizumab pegol in patients with moderate-to-severe active systemic lupus erythematosus. *Rheumatol (Oxf Engl)*. 2021;60(11):5397-5407. doi:10.1093/rheumatology/keab381
19. Boumpas DT, Furie R, Manzi S, et al. A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. *Arthritis Rheum*. 2003;48(3):719-727. doi:10.1002/art.10856
20. Boedigheimer MJ, Martin DA, Amoura Z, et al. Safety, pharmacokinetics and pharmacodynamics of AMG 811, an anti-interferon-γ monoclonal antibody, in SLE subjects without or with lupus nephritis. *Lupus Sci Med*. 2017;4(1):e000226. doi:10.1136/lupus-2017-000226
21. Furie R, Malyar A, Navarra S, et al. Evaluation of the efficacy, safety, and tolerability of BIIB023 as an adjunct to standard of care in subjects with lupus nephritis. *Arthritis Rheum*. 2017;68(suppl 10):749.
22. Rovin BH, van Vollenhoven RF, Aranow C, et al. A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of treatment with sirukumab (CNTO 136) in patients with active lupus nephritis. *Arthritis Rheumatol*. 2016;68(9):2174-2183. doi:10.1002/art.39722
23. Johnson & Johnson. Janssen announces discontinuation of phase 3 LOTUS study evaluating ustekinumab in systemic lupus erythematosus. June 26, 2020. Accessed July 16, 2022. https://www.jnj.com/janssen-announces-discontinuation-of-phase-3-lotus-study-evaluating-ustekinumab-in-systemic-lupus-erythematosus
24. Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med*. 2020;383(12):1117-1128. doi:10.1056/NEJMoa2001180
25. Rovin BH, Teng YKO, Ginzler EM, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2021;397(10289):2070-2080. doi:10.1016/S0140-6736(21)00578-X
26. Saxena A, Teng O, Collins C, England N, Leher H. 1202 Voclosporin for lupus nephritis: results of the two-year AURORA 2 continuation study. *Lupus Sci Med*. 2022;9(suppl 3):1202. doi:10.1136/lupus-2022-lupus21century.84
27. National Library of Medicine. Phase 3 study of anifrolumab in adult patients with active proliferative lupus nephritis (IRIS). Accessed June 4, 2022. https://clinicaltrials.gov/ct2/show/NCT05138133
28. Condon MB, Ashby D, Pepper RJ, et al. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. *Ann Rheum Dis*. 2013;72(8):1280-1286.
29. Teng S, Tian Y, Luo N, Zheng Q, Shao M, Li L. Efficacy and safety of an anti-CD20 monoclonal antibody, rituximab, for lupus nephritis: a meta-analysis. *Int J Rheum Dis*. 2022;25(2):101-109.
30. Goswami RP, Sircar G, Sit H, Ghosh A, Ghosh P. Cyclophosphamide versus mycophenolate versus rituximab in lupus nephritis remission induction: a historical head-to-head comparative study. *J Clin Rheumatol*. 2019;25(1):28-35. doi:10.1097/RHU.0000000000000760
31. Gomez Mendez LM, Cascino MD, Garg J, et al. Peripheral blood B cell depletion after rituximab and complete response in lupus nephritis. *Clin J Am Soc Nephrol*. 2018;13(10):1502-1509. doi:10.2215/CJN.01070118
32. Zhang J, Zhao Z, Hu X. Effect of rituximab on serum levels of anti-C1q and antineutrophil cytoplasmic autoantibodies in refractory severe lupus nephritis. *Cell Biochem Biophys*. 2015;72(1):197-201. doi:10.1007/s12013-014-0437-z
33. Moroni G, Raffiotta F, Trezzi B, et al. Rituximab vs mycophenolate and vs cyclophosphamide pulses for induction therapy of active lupus nephritis: a clinical observational study. *Rheumatol (Oxf Engl)*. 2014;53(9):1570-1577. doi:10.1093/rheumatology/ket462
34. Basu B, Roy B, Babu BG. Efficacy and safety of rituximab in comparison with common induction therapies in pediatric active lupus nephritis. *Pediatr Nephrol*. 2017;32(6):1013-1021. doi:10.1007/s00467-017-3583-x
35. Roccatello D, Sciascia S, Naretto C, et al. A prospective study on long-term clinical outcomes of patients with lupus nephritis treated with an intensified B-cell depletion protocol without maintenance therapy. *Kidney Int Rep*. 2021;6(4):1081-1087. doi:10.1016/j.ekir.2021.01.027

36. Furie RA, Aroca G, Cascino MD, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2022;81(1):100-107. doi:10.1136/annrheumdis-2021-220920
37. Almaani S, Rovin BH. B-cell therapy in lupus nephritis: an overview. *Nephrol Dial Transplant*. 2019;34(1):22-29. doi:10.1093/ndt/gfy267
38. Alexander T, Sarfert R, Klotsche J, et al. The proteasome inhibitior bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus. *Ann Rheum Dis*. 2015;74(7):1474-1478. doi:10.1136/annrheumdis-2014-206016
39. Furie R, Parikh S, Wang J, et al. POS0695 KZR-616, a selective immunoproteasome inhibitor for the treatment of systemic lupus erythematosus: results from the completed dose escalation phase 1b portion of the mission study. *Ann Rheum Dis*. 2021;80(suppl 1):595-596. doi:10.1136/annrheumdis-2021-eular.2158
40. National Library of Medicine. A study to evaluate the efficacy and safety of dapirolizumab pegol in study participants with moderately to severely active systemic lupus erythematosus (PHOENYCS GO). Accessed July 2, 2022. https://clinicaltrials.gov/ct2/show/NCT04294667
41. National Library of Medicine. Safety, pharmacokinetics and preliminary efficacy study of CFZ533 in patients with lupus nephritis. Accessed July 21, 2022. https://clinicaltrials.gov/ct2/show/NCT03610516
42. Tsang-A-Sjoe MWP, Bultink IEM. New developments in systemic lupus erythematosus. *Rheumatol (Oxf Engl)*. 2021;60(suppl 6):vi21-vi28. doi:10.1093/rheumatology/keab498
43. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4S):S1-S276.