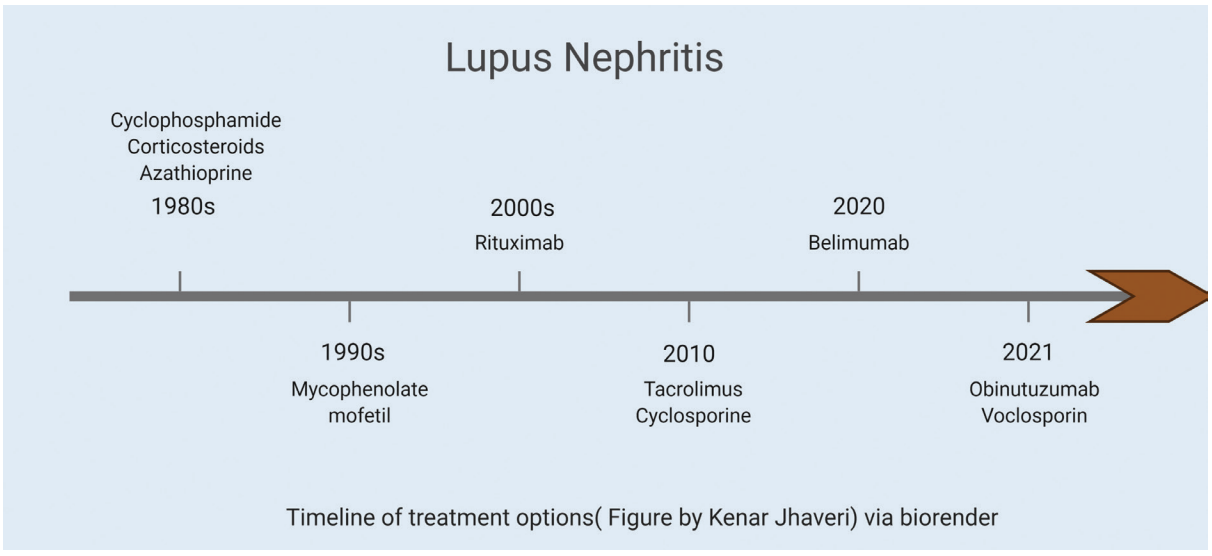
2. Zucker I, et al. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: Uremic pruritus is still a major problem for patients with end-stage renal disease. *J Am Acad Dermatol* 2003; 49:842–846. doi: 10.1016/s0190-9622(03)02478-2
3. Rayner HC, et al. International comparisons of prevalence, awareness, and treatment of pruritus in people on hemodialysis. *Clin J Am Soc Nephrol* 2017; 12:2000–2007. doi: 10.2215/CJN.03280317
4. Martin CE, et al. Have we just scratched the surface? A narrative review of uremic pruritus in 2020. *Can J Kidney Health Dis* 2020; 7:2054358120954024. doi: 10.1177/2054358120954024
5. Simonsen E, et al. Treatment of uremic pruritus: A systematic review. *Am J Kidney Dis* 2017; 70:638–655. doi: 10.1053/j.ajkd.2017.05.018
6. Chou F-F, et al. A study on pruritus after parathyroidectomy for secondary hyperparathyroidism 1. *J Am Coll Surg* 2000; 190:65–70. doi: 10.1016/s1072-7515(99)00212-4
7. Duque MI, et al. Lack of efficacy of tacrolimus ointment 0.1% for treatment of hemodialysis-related pruritus: A randomized, double-blind, vehicle-controlled study. *J Am Acad Dermatol* 2005; 52 (3 Pt 1):519–521. doi: 10.1016/j.jaad.2004.08.050
8. US Food and Drug Administration. FDA Approves Updated Labeling with Boxed Warning and Medication Guide for Two Eczema Drugs, Elidel and Protopic. January 19, 2006. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-approves-updated-labeling-boxed-warning-and-medication-guide-two-eczema-drugs-elidel-and
9. Ishida JH, et al. Gabapentin and pregabalin use and association with adverse outcomes among hemodialysis patients. *J Am Soc Nephrol* 2018; 29:1970–1978. doi: 10.1681/ASN.2018010096
10. Pauli-Magnus C, et al. Naltrexone does not relieve uremic pruritus. Results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; 11:514–519. https://jasn.asnjournals.org/content/11/3/514
11. Legroux-Crespel E, et al. A comparative study on the effects of naltrexone and loratadine on uremic pruritus. *Dermatology* 2004; 208:326–330. doi: 10.1159/000077841
12. Inui S. Nalfurafine hydrochloride to treat pruritus: A review. *Clin Cosmet Investig Dermatol* 2015; 8:249–255. doi: 10.2147/CCID.S55942
13. Sumitomo Dainippon Pharma Co., Ltd. IR News: Toray's Pruritus Treatment REMITCH OD Tablets 2.5 μg to Be Introduced in Japan. May 31, 2017. https://www.ds-pharma.com/ir/news/2017/20170531.html
14. Fishbane S, et al. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med* 2020; 382:222–232. doi: 10.1056/NEJMoa1912770
15. Mathur VS, et al. A multicenter, randomized, double-blind, placebo-controlled trial of nalbuphine ER tablets for uremic pruritus. *Am J Nephrol* 2017; 46:450–458. doi: 10.1159/000484573
16. Endo Pharmaceuticals Inc. NUBAIN (Nalbuphine Hydrochloride). January 2005. https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/018024s040lbl.pdf

2021 and Beyond—
Lupus Nephritis

By Marco Bonilla and Kenar D. Jhaveri

Figure by Kenar D. Jhaveri using biorender.com

Figure 1. Timeline for lupus nephritis treatment options



Timeline of treatment options(Figure by Kenar Jhaveri) via biorender

Lupus nephritis is a serious end organ manifestation of systemic lupus erythematosus (SLE). Regardless of the remarkable advances in the knowledge and understanding of lupus nephritis pathophysiology, it remains a weighty source of morbidity and mortality, and 10% to 30% of affected patients progress to end-stage kidney disease within 10 years of being diagnosed with SLE (1).

Therapy for lupus nephritis has continued to evolve, from the use of cyclophosphamide, azathioprine, and steroids developed in the 1970s–1980s to the use of mycophenolate, tacrolimus, cyclosporine, and rituximab in the 2000s (Figure 1). Given the significant adverse effects of some of the current agents, novel therapies are in the pipeline. The determination of an ideal management has been extremely challenging. Here, we highlight several potential treatments for lupus nephritis that we may see in 2021 and beyond.

Belimumab

Belimumab is a humanized monoclonal antibody (mAb) against a B cell–activating factor that has been studied in two prospective clinical trials: Efficacy and Safety of Belimumab in Patients With Active Lupus Nephritis (BLISS-LN) (2) and Rituximab and Belimumab for Lupus Nephritis (CALIBRATE) (3) studies.

The BLISS-LN study (2) was a phase 3, multi-center, international, randomized, double-blind, placebo-controlled trial, comparing belimumab (dose of 10 mg/kg of body weight) with matching placebo, in addition to standard therapy. The study showed that patients in the belimumab group had a higher complete kidney response than the placebo group (30% vs. 20%, respectively), and kidney adverse events were lower in the belimumab group compared to placebo. This has led to US Food and Drug Administration (FDA) approval of this agent in use of lupus nephritis. What is interesting is that the primary endpoint of the trial was changed 5 years after the commencement of the trial. The original endpoints categorized responses as complete, partial, or no response, according to the level of proteinuria and estimated glomerular filtration rate (eGFR) from 24 h urine collections, and microscopic examination of urinary sediment, although favoring belimumab, was not significantly different between the belimumab and placebo groups. Limitations of the study include the following: only two induction agents were permitted, the induction agent was not randomly assigned, and low enrollment of patients of Black race. The current trial still leaves us with a few uncertainties but leads the groundwork for ongoing trials using this novel agent. Could belimumab decrease the progression to end-stage kidney disease and subsequent flares in patients with severe lupus nephritis? It is yet to be seen.

The CALIBRATE study (3) was a phase 2, multi-center, randomized, controlled, open-label trial of cyclophosphamide plus rituximab, followed by belimumab, in patients with active lupus nephritis. The study showed at week 48, a complete or partial kidney response in the belimumab group compared to the control group (52% vs. 41%, respectively), and patients in the belimumab group did not have an increased frequency of adverse events. In the final conclusion, the addition of belimumab to a treatment regimen with rituximab and cyclophosphamide was safe in patients with refractory lupus nephritis. This regimen diminished maturation of transitional-to-naive B cells during B cell reconstitution and enhanced the negative selection of autoreactive B cells. Clinical efficacy was not improved with rituximab and cyclophosphamide in combination with belimumab when compared to a therapeutic strategy of B cell depletion alone in patients with lupus nephritis.

Obinutuzumab

Based on their mechanisms of action, CD20 mAbs are grouped into two types. Type I mAbs deplete B cells by inducing complement-dependent cytotoxicity (CDC), such as rituximab, and are referred to as antibody-dependent cell-mediated cytotoxic (ADCC). Alternatively, type II mAbs deplete B cells by initiating a combination of programmed cell death (PCD) and ADCC. Obinutuzumab and tositumomab are examples of type II agents.

Obinutuzumab, a type II anti-CD20 mAb that has been shown to be superior to rituximab (type I) in depleting B cells, was tested in the NOBILITY study (4). This was a phase 2, randomized, double-blind, placebo-controlled, multi-center study. The trial included patients with active class III/IV lupus nephritis who received obinutuzumab vs. placebo, combined with mycophenolate mofetil and steroids. The primary endpoint was complete kidney response at 52 weeks. The study showed that obinutuzumab had higher complete kidney response vs. placebo; serious adverse events and serious infections were not increased in the obinutuzumab group. The novel agent was not associated with increases in rates of serious adverse events or serious infections. Forthcoming data through week 104 will permit further assessment of the longer-term safety and efficacy of obinutuzumab in proliferative lupus nephritis. We again await the fully published results of yet another potential treatment for lupus nephritis. However, we should note that obinutuzumab was not compared directly to rituximab.

Voclosporin

The efficacy and safety of this novel calcineurin inhibitor were tested by the Aurinia Urinary Protein Reduction Active-Lupus with Voclosporin (AURA-LV) study. This was a phase 2, multi-center, randomized, placebo-controlled trial. This study showed a higher complete remission rate

Continued on page 12 >

2021 and Beyond

Continued from page 11

in the low-dose group, as well as the high-dose group, when compared to placebo at 48 weeks but a higher frequency of adverse events in the voclosporin group, with a higher mortality rate in the low-dose group when compared to the placebo group (5). In the abstract format presented at the European League Against Rheumatism (EULAR) meetings in 2020, the efficacy seen in Aurinia Renal Response in Active Lupus with Voclosporin (AURORA) was again demonstrated, as voclosporin improved the kidney response by 18.3% at 1 year (40.8% vs. 22.5%) (6). Voclosporin is now FDA-approved as of late January 2021 for use for lupus nephritis (7). At the time of this writing, the peer-reviewed publication of the AURORA trial had not yet been published.

Although the above three drugs may show promise this year, several clinical trials are either completed or recruiting for trials in lupus nephritis with other novel agents. **Pentoxifylline** is an oral phosphodiesterase inhibitor introduced 45 years ago for treatment of vascular insufficiency. It has also recently been found to reduce proteinuria in patients with diabetic nephropathy. The mechanism of this intriguing finding is not certain but may, in part, involve inhibition of the production of tumor necrosis factor (TNF)-α, an inflammatory cytokine known to be present in urine and kidneys of patients with lupus nephritis. Currently, a multicenter, double-blind, placebo-controlled, randomized trial of pentoxifylline or placebo, in addition to standard of care for treatment of proteinuria in patients with lupus nephritis, is ongoing (8).

Borrowing from the onconephrology world, **zanubrutinib** (a Bruton's tyrosine kinase inhibitor) is being studied in lupus nephritis as well. Currently, there is a phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of zanubrutinib in patients with active proliferative lupus nephritis (9). Finally, **guselkumab** is a mAb that binds to human interleukin (IL)-23 with high affinity and blocks binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. It is used in treatment of psoriatic arthritis, generalized pustular psoriasis, and erythrodermic psoriasis. There is an ongoing study (10) that will evaluate the safety and efficacy of guselkumab added to standard of care compared to placebo added to standard of care.

So as we enter 2021, the field of lupus nephritis is exploding with potential novel therapies on the horizon. ■

Marco Bonilla, MD, is a nephrology fellow at Northwell Health, Great Neck, NY. Kenar D. Jhaveri, MD, FASN, is a professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, and is editor-in-chief of ASN Kidney News.

The authors report no conflict of interest related to the article.

References

1. Parikh SV, et al. Update on lupus nephritis: Core curriculum 2020. *Am J Kidney Dis* 2020; 76:265–281. doi: 10.1053/j.ajkd.2019.10.017
2. Furie R, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med* 2020; 383:1117–1128. doi: 0.1056/NEJMoa2001180
3. Atisha-Fregoso Y, et al. Phase II randomized trial of rituximab plus cyclophosphamide followed by belimumab for the treatment of lupus nephritis. *Arthritis Rheumatol* [published online ahead of print August 4, 2020]. doi: 10.1002/art.41466; https://onlinelibrary.wiley.com/doi/10.1002/art.41466
4. Furie R, et al. A phase II randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of obinutuzumab or placebo in combination with mycophenolate mofetil in patients with active class III or IV lupus nephritis (abstract). *Arthritis Rheumatol* 2019; 71 (Suppl 10):939. https://acrabstracts.org/abstract/a-phase-ii-randomized-double-blind-placebo-controlled-study-to-evaluate-the-efficacy-and-safety-of-obinutuzumab-or-placebo-in-combination-with-mycophenolate-mofetil-in-patients-with-active-class-iii/
5. Rovin BH, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int* 2019; 95:219–231. doi: 10.1016/j.kint.2018.08.025
6. Arriens C, et al. AURORA phase 3 study demonstrates voclosporin statistical superiority over standard of care in lupus nephritis. Aurinia. June 5, 2020. https://d1io3yog0oux5.cloudfront.net/_b9287cb2b9b32ac3fbb5d08113841567/auriniapharma/db/246/1327/pdf/EULAR+2020+AURORA_Presentation+Deck+05Jun2020.pdf
7. Aurinia. FDA Approves Aurinia Pharmaceuticals' LUPKYNIS™ (voclosporin) for Adult Patients with Active Lupus Nephritis. January 22, 2021. https://ir.auriniapharma.com/press-releases/detail/210
8. MetroHealth Medical Center. Pentoxifylline in Lupus Nephritis (Pentoxifylline). ClinicalTrials.gov: NCT03859570. https://clinicaltrials.gov/ct2/show/NCT03859570
9. BeiGene. Zanubrutinib in Participants with Active Proliferative Lupus Nephritis. ClinicalTrials.gov: NCT04643470. https://clinicaltrials.gov/ct2/show/NCT04643470
10. Janssen Research & Development, LLC. A Study of Guselkumab in Participants with Active Lupus Nephritis (ORCHID-LN). ClinicalTrials.gov: NCT04376827. https://clinicaltrials.gov/ct2/show/NCT04376827

Novel Anemia Treatment: HIF-PH Inhibitors

By Daniel W. Coyne

For more than 30 years, erythropoiesis-stimulating agents (ESAs) have reigned supreme as the treatment for chronic kidney disease (CKD)–related anemia. Can hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) topple ESAs? HIF-PHIs are oral medications taken three times a week or daily and have been shown in trials to achieve and maintain goal hemoglobin to the same degree as ESAs. HIF-PHIs are small molecules that inhibit the prolyl hydroxylase enzyme that continually marks the HIF for degradation. Each dose transiently increases intracellular HIF2a, a transcription factor, leading to activation of a series of genes, including erythropoietin (EPO) and several iron transport genes. Consequently, endogenous EPO levels increase, and iron absorption and mobilization are enhanced (Table 1).

Phase 3 clinical trials of the HIF-PHI roxadustat show that it can replace ESAs in the dialysis population for anemia management and can reduce intravenous iron requirements. Roxadustat reduced major adverse cardiovascular event (MACE) rates compared to ESA in incident dialysis patients and had similar MACE rates to ESA in prevalent patients receiving dialysis. In CKD trials versus placebo, roxadustat achieved goal hemoglobin and did not significantly increase MACE.

It may not be clear sailing for HIF-PHIs, however. Recent phase 3 randomized clinical trials of vadadustat showed that it could replace ESA in managing anemia but raised serious safety issues. Two international trials in patients with CKD found that vadadustat significantly increased MACE rates compared to the ESA darbepoetin (hazard ratio [HR] 1.17, confidence interval [CI] 1.01–1.36). In those trials, the hemoglobin target was 10–11 g/dL in the United States, and 10–12 g/dL in all non-US sites.

An analysis showed MACE was not increased in the vadadustat arm versus the ESA arm in US patients (HR 1.01, CI 0.83–1.23) but was increased with vadadustat compared to ESA in the non-US patients (HR 1.29, CI 1.03–1.60). In contrast, two vadadustat vs. ESA trials in the dialysis population showed comparable anemia management, and no increase in MACE compared to ESA therapy.

Whether safety differences in trials to date reflect unique actions of particular HIF-PHI agents, differences in trial designs, or other factors remains to be answered. Phase 3 randomized clinical trials with daprodustat, another HIF-PHI, are completed in dialysis patients, and results will be released later in 2021. The daprodustat trial in CKD non-dialysis patients should be completed in April 2021. ■

Daniel W. Coyne, MD, is professor of medicine, Washington University, St. Louis, MO.

The author participated as a site investigator in trials of roxadustat and daprodustat and has been a consultant to the manufacturer of all three HIF-PHIs.

Table 1. Select HIF-PHIs and approval status

HIF-PHI Product	Half-Life	Phase 3 Trials' Status	US Approval Status	Approved for Use in
Roxadustat	14.7–19.4 h	All completed	Submitted for approval; FDA response required 3/20/21	Japan, China
Vadadustat	1.9–3.6 h	All completed	Anticipated FDA new drug submission early 2021	Japan
Daprodustat	0.9–2.3 h	Completed, except CKD-non-dialysis study (tentative closure April 2021)	Anticipated FDA new drug submission 2021	Japan