## 2021 and Beyond

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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. ■

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# 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. ■

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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 |