EDITORIALS

Therapy for Anemia in Chronic Kidney Disease — New Interventions and New Questions

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Anemia, including its causes and treatments, in patients with chronic kidney disease (CKD) has been a focus of research for 40 years. Huge strides were made when erythropoietin was discovered and injectable erythropoiesis-stimulating agents (ESAs) were developed, followed by the conduct of randomized, controlled clinical trials that changed clinical practice. Multiple trials in which various ESAs have been compared with placebo or with each other have tested hypotheses about the value of targeting higher hemoglobin levels in patients with CKD. Such investigations showed variable signals for benefit (e.g., a reduced need for transfusions or improved quality of life) but also signals for harm (e.g., increased thrombosis of arteriovenous fistulas, stroke, and cancer-associated mortality).[1-5] Whether the harms identified were due to increases in hemoglobin concentrations, excessive administration of ESAs, or the use of ESAs in subpopulations with high rates of coexisting conditions is unknown. The apparent harms resulted in cautious interpretation of the "ideal" hemoglobin target (10 to 11 mg per deciliter for all patients) and a black-box warning for ESAs. Current recommendations regarding therapy for anemia include iron repletion and the administration of injectable ESAs.[6]

Given the concern about harms with ESAs, the discovery and development of a newer class of agents to treat anemia — hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors — is exciting. These oral agents may increase patient comfort and adherence to treatment, especially among patients receiving subcutaneous ESA injections. Some HIF prolyl hydroxylase inhibitors (e.g., roxadustat) are already approved for use in some countries.[7]

This issue of the *Journal* includes two articles that describe trials in which vadadustat, a HIF prolyl hydroxylase inhibitor molecule, was compared with active therapy with darbepoetin alfa, a commonly used ESA. Each article is based on the results of pooled analyses of two trials; the trials reported by Eckardt et al.[8] involved patients who were undergoing dialysis, and those by Chertow et al.[9] involved patients who were not undergoing dialysis. All four trials had an open-label, noninferiority design.

Noninferiority trials are generally used to show that a predetermined minimum level of efficacy has been achieved with a new agent, as compared with current therapy, and that the new agent provides at least similar benefit. If the new treatment is shown to be noninferior to the current therapy (in this case, an ESA), evidence of additional benefit, lower risk of adverse effects, cost savings, or better adherence or convenience for patients is still needed. The two pooled analyses reported by Eckardt et al. and Chertow et al. were designed to address efficacy (rise in hemoglobin concentration) and safety (major adverse cardiovascular event [MACE]).

The noninferiority design is unfamiliar to many, so readers often struggle with interpretation. Noninferior does not mean equivalent, but rather that one agent is not significantly worse than the other. The noninferiority margins of 1.25 for a first MACE were chosen during the design phase by the investigators in consultation with regulatory agencies and were based on those used in other trials of different drugs in patients with high cardiovascular risk. The degree to which one agent is worse than another is important, since readers need to decide whether the new treatment could be preferable because

of additional benefits (e.g., cost or convenience). When noninferiority is not shown, interpretation is more complex — the new agent could be inferior to or worse than the active control or the results could be inconclusive.[10]

Eckardt et al. showed that, among 3923 patients with anemia and incident or prevalent dialysis-dependent CKD, vadadustat was noninferior to darbepoetin alfa with respect to cardiovascular safety, and the incidence of a first MACE was similar with the two agents (i.e., vadadustat was not determined to be less safe than darbepoetin alfa). Target hemoglobin concentrations were achieved in both trials, in diverse international populations of patients.

Chertow et al. showed that, among 3476 patients with anemia and non–dialysis-dependent CKD, the noninferiority criterion was met with respect to hematologic efficacy but was not met with respect to a first MACE. The pooled analysis included data from one trial in which patients had not received previous ESA treatment and data from another trial in which patients were receiving active ESA therapy. The percentage of patients who had a first MACE was higher in the vadadustat group than in the darbepoetin alfa group, for reasons that are unclear. Both trials enrolled patients from various geographic regions, and both targeted hemoglobin concentrations that were appropriate to each patient's region of origin. The authors highlight differences in target hemoglobin concentrations in the United States as compared with other countries, and the higher incidence of MACE in the vadadustat group than in the darbepoetin alfa group seemed to be driven by findings in the non-U.S. participants. However, the mean achieved hemoglobin concentrations in the two groups were similar, as were mean changes from baseline, and the fact remains that vadadustat did not meet the prespecified noninferiority risk margin for the primary end point.

The discovery of HIF prolyl hydroxylase inhibitors has reinvigorated the field of research involving anemia associated with kidney disease. As with any intervention, understanding what we are trying to achieve, why we are evaluating it, and the trade-off with respect to adverse effects and risks is essential. We now have another treatment option to increase hemoglobin concentrations. Whether that has beneficial effects on outcomes of importance to patients remains unclear. Current treatment targets are underpinned by avoidance of harm when ESAs are used in high-risk populations; whether the same targets apply to HIF prolyl hydroxylase inhibitors is open to debate. The two reports published here may stimulate discussion regarding the appropriateness of a noninferiority trial design to answer questions about comparative drug safety. Furthermore, the attributable risks and benefits of treatments for anemia in non–dialysis-dependent populations remain unclear.

The data are convincing that vadadustat is effective in increasing hemoglobin concentrations in both dialysis-dependent and non–dialysis-dependent populations but are less convincing with respect to safety. The issues raised in these trials should motivate us to answer critical questions regarding goals of therapy, risks, and benefits, with trials specifically designed to do so. To enable us to have informed discussions with our patients, many more questions need to be asked and answered.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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