

Role of Roxadustat for ESA-Resistant Renal Anemia? —Read with Caution

Akizawa *et al.*¹ recently reported a phase-3, double-blind, randomized controlled trial to investigate the efficacy and safety of roxadustat, in comparison to darbepoetin alfa (DA), for renal anemia in Japanese patients on hemodialysis. In this paper, the changes in doses of roxadustat and DA in patients with high or low high-sensitivity C-reactive protein (hs-CRP) were described as a subgroup analysis, likely *post hoc*. Because the maintenance dose increased from baseline in the DA group but decreased in the roxadustat group in patients with high hs-CRP, the authors mentioned roxadustat may be more effective than erythropoiesis-stimulating agents (ESAs) in patients with inflammation, with a substantial volume of text and figures, and provided a plausible explanation with recent similar subgroup analyses.^{2,3}

However, there are significant concerns in the interpretation of this subgroup analysis. First, this study did not aim to compare the efficacy of study drugs in patients with inflammation, and the too-small number of patients with high hs-CRP in the treatment arms (roxadustat, 14 patients out of a total of 150; DA, 22 patients out of a total of 151) will not allow further statistical analysis including an adjustment for patient backgrounds in the subgroup analysis. Second, the changes in hs-CRP during the study were not considered, although the dose required for the study drugs would have been reduced in those whose inflammation resolved earlier. Third, in patients with high hs-CRP, the hemoglobin levels during the evaluation period in the DA group look slightly higher than in the roxadustat group. Finally, the mean hemoglobin level and the rate of increase in hemoglobin level at 4 weeks were higher in the roxadustat group than in the DA group, suggesting that the initial dose setting of roxadustat had a better power to raise the hemoglobin level than DA. The increase in hemoglobin levels at 4 weeks in the roxadustat group will consequently result in a dose reduction later in the study. In the same period, hemoglobin levels decreased in the DA group, which later necessitated an increase in the dose of DA. Therefore, the authors' assumption that roxadustat would be more effective than DA for renal anemia with inflammation, a cause of erythropoiesis-stimulating agent (ESA)-resistant renal anemia, sounds weak, because that premise disregards the effect of the initial dose setting and the rise of hemoglobin levels in the early phase of roxadustat treatment.

The authors should explain the possibility that the predetermined initial dose setting of roxadustat, when switching from DA, may contribute to the increase in hemoglobin levels in the early phase, and that those levels would eventually cause the later dose reduction of roxadustat in patients with high hs-CRP. The changes in hs-CRP during the study should also be discussed. Generally, it would be better to state clearly in the paper whether the subgroup analysis was prespecified in the protocol or if it was *post hoc*.

The Pharmaceuticals and Medical Devices Agency (PMDA) approved roxadustat in 2019 as a treatment for renal anemia in patients undergoing dialysis. Subgroup analyses of randomized controlled trials should be interpreted with caution. As always, transparent and scientifically fair discussions, based on the results of well-designed studies, are desired. We would like to ask for the continual efforts by the editorial boards to deliver the information that readers and patients really need.

DISCLOSURE

All authors have nothing to disclose.

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REFERENCES

1. Akizawa T, Iwasaki M, Yamaguchi Y, Majikawa Y, Reusch M: Phase 3, randomized, double-blind, active-comparator (darbepoetin alfa) study of oral roxadustat in CKD patients with anemia on hemodialysis in Japan. *J Am Soc Nephrol* 31: 1628–1639, 2020
2. Chen N, Hao C, Liu BC, Lin H, Wang C, Xing C, et al: Roxadustat treatment for anemia in patients undergoing long-term dialysis. *N Engl J Med* 381: 1011–1022, 2019
3. Provenzano R, Besarab A, Wright S, Dua S, Zeig S, Nguyen P, et al: Roxadustat (FG-4592) versus epoetin alfa for anemia in patients receiving maintenance hemodialysis: A phase 2, randomized, 6- to 19-week, open-label, active-comparator, dose-ranging, safety and exploratory efficacy study. *Am J Kidney Dis* 67: 912–924, 2016

See related Letters to the Editor, "Authors' Reply," on pages 2–4.

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