ESAs May Be a Potential Confounder for Mortality among Different ESA Types

Today, it is well known that patients with CKD with erythropoiesis-stimulating agent (ESA)–resistant renal anemia have a poorer prognosis than those without ESA-resistant renal anemia. Sakaguchi et al. reported that patients treated with long-acting ESA showed higher mortality rates than those with short-acting ESA after adjusting patient characteristics. This raises a critical question whether widely used long-acting ESA per se has some adverse effects on the prognosis of patients with CKD.

In their study, patients were divided into the first to the third tertile according to ESA doses, and all-cause mortality in the same tertile was compared between long-acting and short-acting ESA. As ESA doses increased up to the third tertile, the adjusted hazard ratio for all-cause mortality in long-acting ESA users became significantly worse than that in short-acting ESA users. However, we are concerned about the appropriateness of this approach because it is difficult to interpret the results obtained from ESAs with different pharmacodynamics. Although the authors calculated the ESA resistance index from ESA doses, hemoglobin level, and body weight, a conversion ratio such as epoetin alfa/beta (EPO) to darbepoetin alfa (DA) should be taken into consideration. It has been reported that 1 µg of DA is equivalent to 200 U of EPO (EPO/DA ratio = 200), whereas in their study, the EPO/DA ratio was 163, 167, and 136 in the first, second, and third tertile, respectively. This suggested that long-acting ESA users were more resistant to ESA than short-acting ESA users by origin, and this difference may bias the study conclusion. Detailed information regarding patient characteristics for the first to the third tertiles of long-acting and short-acting ESA users may help better understanding.

As review team members in the Pharmaceuticals and Medical Devices Agency, the authority for new drug approval in Japan, we consider the study as a preliminary analysis at this moment, and more careful interpretation and further well-designed, randomized, controlled trials are necessary to draw a solid conclusion. Of note, no significant difference for mortality was observed in a recent meta-analysis of randomized, controlled trials comparing DA and EPO.

DISCLOSURES
None.

REFERENCES


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Equivalent Doses Matter, Rather Than Types

We read the article by Sakaguchi et al. with much interest, it raised important issues in clinical practice. However, we
would like to point out a specific issue in the management of anemia in Japan that might be misleading to readers elsewhere. The maximum dose allowed by the package insert differs considerably across the four types of erythropoiesis-stimulating agents (ESAs) available in Japan. The maximum allowed dose of epoetin α/β/κ is 9000 IU/wk, whereas those of darbepoetin and epoetin β pegol are 180 μg/wk and 250 μg/2 wk, respectively. In Sakaguchi et al.’s study, the dosing of each ESA seems to follow these regulations; the ESA doses in the highest tertile were 7618±2071 IU/wk, 56.1±26.3 μg/wk, 181.6±65.4 μg/mo, and 7841±2144 IU/wk, for epoetin α/β, darbepoetin α, epoetin β pegol, and epoetin κ, respectively, as shown in their Supplemental Table 4. Conversion ratios from epoetin to ESAs with longer t1/2 have been debated because the ratios can vary according to the patient’s condition or even the time course of ESA therapy. For example, the conversion ratio from epoetin to darbepoetin is reported to be 200–400 IU/μg in many studies.2,3 Even when adopting 200 IU/μg, which is an underestimation of darbepoetin activity, 56.1 μg of darbepoetin would have action equivalent to 11,220 IU of epoetin, which is a modest estimate. Yet, by adopting a higher conversion ratio, the equivalent dose would be much larger. A similar issue is also true for epoetin β pegol. We appreciate the authors’ efforts to eliminate bias, which is inevitable in an observational study, but the fact that differences in mortality by ESA type increased in a dose-dependent manner clearly shows that it was the higher doses of ESA that were associated with worse survival and not ESA type per se. ESA hyporesponsiveness is well known to be associated with worse survival.4 The outcomes for the entire population might have been swayed by the presence of patients requiring higher equivalent doses of long-acting ESAs, which in Japan can be prescribed at higher doses than epoetin. We therefore consider that the title of the article is misleading, and that it was in fact a higher dose of long-acting ESAs that was associated with worse survival. Elucidating the true association between ESA type and mortality is reserved for future prospective studies with between-group adjustments for doses of ESA.

DISCLOSURES

Dr. Hanafusa and Prof. Tsuchiya have received lecture fees from Kyowa Hakko Kirin, Chugai Pharmaceutical, and Kissei Pharmaceutical. Dr. Hanafusa is an academic consultant for the Dialysis Outcomes and Practice Pattern Study program and is receiving fees from Kyowa Hakko Kirin. However, these have no bearing or influence on the content of this article.

REFERENCES


See related Letters to the Editor, “Analysis of Other Confounding Factors Is Mandatory before Considering That Long-Acting Erythropoiesis Stimulating Agents Are Deleterious to Patients on Dialysis,” “ESA Resistance May Be a Potential Confounder for Mortality among Different ESA Types,” and “Authors’ Reply,” on pages 1771–1772, 1772, and 1773–1776, respectively.

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Authors’ Reply

We thank Rostoker et al.1 for their comment on our paper.2 We acknowledge that our database lacks several clinical factors that may relate to the patients’ prognoses, including those pointed out by Rostoker et al. Like any other observational studies, our analysis was also subject to unknown confounders. Although randomization is an ideal method to control for confounding, we took an alternative approach—an instrumental variable (IV) analysis—that can deal with even unmeasured confounders. This sophisticated statistical technique enabled us to confirm that patients treated with long-acting erythropoiesis-stimulating agents (ESA) had worse prognoses. Notably, the IV of our study, namely, the facility-level preference for the long-acting ESA, was strongly predictive of the type of ESA prescribed for individual patients (F-statistic in the first stage of the two-stage least squares regression: 35,549 [>10]). As discussed in our paper,2 it was unlikely that the facility-level preference for the long-acting ESA had a direct effect on the outcome, but it had an indirect effect only through the choice of ESA, especially under the medical insurance system for dialysis therapy in Japan. Therefore, although our study was observational, we think the influence of confounders on the observed association was minimal.

We deeply appreciate the comments by Tanaka et al.3 and Hanafusa et al.4 We agree that patients taking long-acting ESA could have higher ESA resistance given that they received relatively high doses of ESA compared with those

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