ESA Resistance 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.[1] Sakaguchi *et al.*[2] 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 $=200$),[3] 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.[4]

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DISCLOSURES

None.

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Equivalent Doses Matter, Rather Than Types

We read the article by Sakaguchi *et al.*[1] 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 $\alpha/\beta/\kappa$ 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,

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