Which ESAs You Will Choose for Dialysis Patients?

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In the past two decades, the use of erythropoiesis-stimulating agents (ESAs) revolutionized the management of anemia in dialysis patients (1). ESAs correct effectively renal anemia and reduce largely the risk of blood transfusion. The mechanism of erythropoietin relies primarily on its direct interaction with the erythropoietin receptor on the surface of red blood cells. This interaction will trigger the activation of many signal transduction pathways and result in the proliferation and terminal differentiation of erythroid precursor cells. It will also prevent the apoptosis of red blood cell precursors (2, 3). Epoetin-alpha was the first recombinant human erythropoietin produced, followed by epoetin-beta, darbepoetin-alpha, methoxy polyethylene glycol-epoetin beta (Mirceα®) and several related products (4-8).

Recombinant human erythropoietin is an established and effective treatment for anemia associated with both chronic kidney disease and cancer and has improved the management of anemia over alternatives such as transfusion (9). The efficacy of recombinant human erythropoietin is not only evaluated on the basis of blood level of erythropoietin; more importantly, it is controlled by the duration of erythropoietin blood concentrations maintained (10). Consequently, subcutaneous administration of erythropoietin results in slower absorption than intravenous use of erythropoietin and leads to an apparent extended terminal half-life of erythropoietin. However, barriers to subcutaneous use of erythropoietin include the additional needle stick pain and the possible increased risk of immunogenicity compared with intravenous use of erythropoietin.

The addition of polyethylene glycol (PEGylation) to erythropoietin has been employed to further extend the terminal half-life of erythropoietin. Darbepoetin-alpha (Aranesp®) is just a hyperglycosylated erythropoietin and biochemically distinct from epoetin-alpha (5, 6). It contains five N-linked carbohydrate chains, with two chains more than epoetin-alpha. Owing to its increased sialic acid-containing carbohydrate content, darbepoetin-alpha has an increased molecular weight and greater negative charge. Compared with epoetin-alpha, darbepoetin-alpha has an approximate threefold longer in blood half-life and greater in vivo potency. Therefore, the dosing intervals of darbepoetin-alpha can be extended to once a week or once every two weeks. The feasibility of every-three-week dosing of darbepoetin-alpha has also been demonstrated (11). Darbepoetin-alpha is currently being widely used clinically for treatment of anemia in predialysis and dialysis patients. In fact, some other strategies such as the activation of the erythropoietin receptor is still under investigation (12).

The properties of longer half-life and greater in vivo potency of darbepoetin-alpha allow patients to be treated with longer dosing intervals compared with patients using epoetin-alpha. The relative potency between epoetin-alpha and darbepoetin alpha is not a fixed relationship but is dependent on several factors (13, 14). Because 200 U of epoetin-alpha contains the same peptide mass as 1 µg of darbepoetin-alpha, a fixed dose conversion ratio of 1 µg darbepoetin-alpha to 200 units epoetin-alpha is commonly recommended for dialysis patients in the package insert,
either by conversion from epoetin-alpha or as de novo treatment. The dosage of darbepoetin-alpha should be titrated individually according to each patient’s hemoglobin response (9, 15).

However, the dose conversion ratio does not necessarily predict an appropriate dose conversion between these two drugs across the entire spectrum of dose ranges. Results of previous relevant clinical studies indicate greater relative potency differences between epoetin-alpha and darbepoetin-alpha for higher dosage of epoetin-alpha and longer dosing intervals (13-17).

In this issue, Yu and colleagues explored specifically the efficacy and dose conversion ratio for Taiwanese hemodialysis patients (18). They conducted a retrospective chart review in all 117 regular hemodialysis patients who had switched from epoetin-alpha to darbepoetin-alpha in 2006. Another 20 patients were excluded owing to hospitalization during the study period (14 patients), death (2 patients) and loss in follow-up (4 patients). They found that the dose conversion ratio of darbepoetin-alpha to epoetin-alpha was 1:178 at 6 months and 1:183 at 12 months. Moreover, they also found that the conversion ratio for epoetin-alpha to darbepoetin-alpha was non-linear. The dose conversion ratio for patients with baseline epoetin ≤ 5000 units/week was 1:165 while that for baseline epoetin > 5000 units/week was 1:189, implying that darbepoetin-alpha had better efficacy for patients with baseline dosage of epoetin-alpha > 5000 units/week.

In fact, two studies conducted on Taiwanese peritoneal dialysis patients found that the dose conversion ratio was 197:1 and 273:1, respectively (19, 20). As in our patients, the most possible reason for higher conversion ratio in peritoneal dialysis patients is poor compliance to subcutaneous epoetin-alpha. Many patients with peritoneal dialysis and chronic kidney disease admit that they occasionally forget to receive the subcutaneous epoetin-alpha. In addition to the inadequate dose frequency profile of epoetin-alpha, all factors which may influence the response of ESAs would probably lead to under- or over-estimation of dose conversion ratio. These include the adequacy of dialysis, status of iron store, status of inflammation and nutrition, co-morbidities, route of ESA administration, target and range of hemoglobin level. For example, another study from Hirai and colleague also reported a significantly higher dose conversion ratio of 1:350 at 24 weeks and 1:286 at 52 weeks in Japanese hemodialysis patients (21, 22). The authors attributed the extremely high dose conversion ratio to better dialysis adequacy from ultrapure dialysate and biocompatible high flux.

On the contrary, Yu and colleagues reported a lower dose conversion ratio in Taiwanese hemodialysis patients. They suggested that the lower dose conversion ratio was related to the significantly lower albumin level after patients switched from epoetin-alpha to darbepoetin-alpha treatment (3.77 versus 3.64 and 3.63 mg/dL, P < 0.001). However, many factors which may affect the dose conversion ratio could not be well controlled owing to the retrospective nature of their study, which was its major limitation. In their study, another 13 patients (15 patients to 28 patients) developed lower serum albumin of less than 3.5 g/dL after conversion to darbepoetin-alpha treatment. They also confirmed that lower albumin level tended to necessitate higher dose of darbepoetin and lower dose conversion ratio. Although not mentioned by the authors, another factor that may influence the dose conversion ratio in their study is the slightly increased level of hemoglobin after switching to darbepoetin-alpha treatment. The mean hemoglobin level during epoetin-alpha treatment was 10.4 ± 1.0 g/dL. After the switch to darbepoetin-alpha treatment for 6 and 12 months, the mean hemoglobin level became 10.6 ± 1.0 g/dL and 10.7 ± 1.0 g/dL, respectively. Although the P value of difference did not reach significance (0.0088), this small difference in level of hemoglobin could also reduce the dose conversion ratio in their study.

As we all know, the target level of hemoglobin changes with time in the past decade. This change would reasonably affect the results of studies performed in 2006. In 2000, the target level of hemoglobin was 11-12 g/dL, as stated in the KDOQI Anemia Guideline. While the target level of hemoglobin exceeded 11.0 g/dL, there was also caution against intentionally maintaining hemoglobin level above 13.0 g/dL in the KDOQI 2006 Anemia Guideline (23). Some reports indicate that targeting higher hemoglobin or higher dosages of ESA was associated with poor outcomes (24, 25). Consequently, the current FDA recommendation states a hemoglobin goal of 10 to 12 g/dL for all patients with chronic kidney disease, regardless of dialysis status (26).

Aggressive supplement of intravenous iron will reduce the dosage of ESAs, and also influence the conversion dose ratio (27). Again, in the study of Yu et al., the mean ferritin level increased slightly after conversion. The mean ferritin levels were 476 ± 197 ng/mL before conversion, 489 ± 289 ng/mL after 6 months, and 527 ± 278 ng/mL after 12 months.

Moreover, treating either inflammation or infection or hyperparathyroidism in hemodialysis is effective in reducing the dosage of ESAs with the same target level of hemoglobin. However, the authors failed to provide the data of C-reactive protein and intact PTH (9). Switching dialysis patients from older, more frequently dosed epoetin-alpha to less frequently dosed ESAs, such as Aranesp® or Mircera®.
could reduce time spent by nurses administering anemia drugs in dialysis clinics (28). The valuable time saved could be spent on other important aspects of patient care. In particular, the cost of ESAs has indeed attracted more attention from nephrologists in consideration of the global health care budget.

In conclusion, the recommended dose conversion ratio from epoetin-alpha to darbepoetin-alpha is 200:1. Accordingly, the dosage of ESAs should be further titrated individually. All factors affecting the response of ESAs may reduce the dose conversion ratio after patients switch from epoetin-alpha to darbepoetin-alpha treatment. An important note is to improve the adherence and hemoglobin response to ESAs, regardless of which kind of ESA is chosen for the dialysis patients.

References