Erythropoietin Stimulating Agents and Epoetin Alfa Revisited: What's Really Relevant?

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It has been more than 20 yr since the introduction of recombinant human erythropoietin (rHuEpO) to treat the anemia of chronic kidney disease (CKD; initially in dialysis-dependent patients but subsequently in patients with CKD-associated anemia before dialysis) (1). It heralded a very important era in the treatment and care of the patient with CKD. The first commercially available form of rHuEpO was epoetin alfa, but there are now many erythropoietin-stimulating agent (ESA) products, all of which are fundamentally very effective in correcting CKD-induced anemia and maintaining hemoglobin (Hb) levels. In this issue are three articles specifically related to epoetin alfa; two concern the pharmacokinetics and pharmacodynamics of epoetin alfa and their relevance to dosing intervals, and the third addresses patient responsiveness to epoetin alfa.

The quandary for the clinician, however, remains a broader one; it concerns the provision of individualized treatment for the patients with CKD-induced anemia. This clinical dilemma has been made even more difficult by the fact that the Clinical Practice Guidelines, which have historically helped to guide care, have been characterized by incomplete and/or inadequate evidence (2). More recently, the complexity has been further amplified by the need for conservatism after meta-analysis publications indicating that using ESA to target higher levels (>13 g/dl) (3) compared with control ranges (9.5 to 11.5 g/dl) is likely to produce net harm (increased mortality and major vascular events) rather than benefit. Despite the fact that criticism of the meta-analysis data occurred (4), because of the heterogeneity in the patient demographic data (ranges of stages of CKD and associated comorbidities) and the uncertainty surrounding the effect of preexisting comorbidities, acute inflammation, and other factors on the ability to achieve Hb targets, the concern raised by the meta-analyses and the FDA response to it and the accumulated evidence all have contributed to the very real current practical clinical problem of trying to achieve and maintain patient control within very narrow Hb target ranges (generally 11.0 to 12.0 g/dl) (5).

The pharmaceutical industry (which has also supported the three articles in this issue) has been full of activity in the past 2 decades, progressively developing a number of variations on the original rHuEpO molecule and, therefore, now the clinician is also practicing in an environment where the industry players are very competitive given the enormous market and profit potential and especially considering the ever-expanding numbers of patients with CKD and end-stage kidney disease. The different physical and pharmacokinetic profiles of the various ESA have been justifications at various times along the way for different dosing regimens, modes of administration, and administration intervals. Indeed, now, dosing intervals as infrequent as once every 4 wk are possible—very different from the original recommendations for epoetin alfa, which was usually administered three times per week.

Darbepoetin alfa, which is a highly glycosylated ESA and has a three-fold longer serum half-life (approximately 25 h) than epoetin alfa (6), or epoetin beta (approximately 8 h) and continuous erythropoietin receptor activator (CERA; a pegylated ESA), has a very prolonged serum half-life (approximately 130 h) (7). On the surface, it is therefore not surprising that numerous studies have suggested that both darbepoetin alfa and CERA could be given at less frequent dosing intervals up to 4 wk both for maintenance and for correction of anemia in populations of patients with CKD as well as those with end-stage kidney disease. Even though the serum half-life for epoetin alfa is relatively short and the open-label, nonblinded nature of the study is a limitation, it should also now perhaps come as no surprise that epoetin alfa can be initiated and administered at longer intervals for correction of anemia in pre-dialysis patients without loss of effect as demonstrated by Spinowitz *et al.* (8) in this issue of the journal and similar to that shown previously for maintenance (9). The response to erythropoietin is best measured by reticulocyte counts, increasing Hb or hematocrit levels, and the life span of erythrocytes—events that are occurring well after the immediate time relevance of the serum half-life of the drug. Thus, the accompanying article by McGowan *et al.* (10) confirms some minor differences in *pharmokinetics* across intervals of epoetin alfa dosing between 1 and 4 wk compared with traditional three times per week but importantly a consistent *pharmacodynamic response*, which was similar over the complete range of dosing intervals.

In contrast to the randomized, controlled trials that composed the meta-analyses and in which the Hb levels were targeted to >13.0 g/dl, the large CKD observational population

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studies show that in the breakdown of patients who *achieved* Hb levels of >11.0 g/dl, there was a relationship between lower ESA dosage and achievement of these levels and furthermore that achieved levels >11.0 g/dl were associated with relative benefit (11). The increasing recognition that there may be an association between suboptimal ESA responsiveness (and/or epoetin *resistance*) and poor outcomes may be an indication that *responsiveness* is a measure of underlying comorbidities. Ironically, the data in the third article in this issue come from the original Normal Hematocrit Cardiac Trial (12), which raised concerns about targeting of higher hematocrit levels being associated with adverse outcomes and formed the highest weighting of the data relevant to the meta-analysis mentioned (3). The article by Kilpatrick *et al.* (13) also reminds us that the achieved Hb level in a patient on an ESA will represent a combination of the ESA dosage and the responsiveness of the patient to erythropoietin, which can be enormously variable. It also helps to explain why despite the worse outcome for the higher targeted Hb in the original study (12), there was a positive association between outcome and achieved Hb. Although this study has acknowledged limitations, it does similarly suggest that lower erythropoietin responsiveness (measured as the ratio of weekly hematocrit change per epoetin alfa dosage increase [1000 IU/wk]) is an independent and powerful predictor of mortality. It is postulate generating, and, for future clinical trials, it may therefore be necessary to evaluate fixed dosages of ESA and measure responsiveness to the ESA as well as the historically measured achieved Hb level. That an ESA such as epoetin alfa can be given at intervals as infrequently as every 4 wk may in itself be just another measure of *responsiveness*. The mechanisms of *responsiveness* and *nonresponsiveness* or *resistance* remains curiously undetermined, and more randomized, clinical trials will need to be performed.

From a practical point, all of the various ESA products are similarly efficacious. In the care of the individual patient with CKD and anemia, the clinician might need to consider being not so concerned with the differences between ESAs in terms of pharmacokinetics, physical properties, and molecular structures. Rather, the clinician may do well to examine his or her current treatment protocols, with a view to ensuring that the protocols, practices, or processes currently in place are neither contributing to the nonidentification of the nonresponsive or the resistant (14) patient nor contributing to frequent or unwarranted ESA dosage changes. Awareness of factors such as acute inflammation (15), adequacy of iron status, and other comorbidities in an individual patient and correcting these (where possible) before resorting to ESA dosage adjustments (especially upward) are important. Although the precise clinical relevance of Hb variability (16) (Hb fluctuations or Hb cycling) is unknown, it has as one of its associations frequent ESA dosage changes (17). The intensity of cycling is also associated with a range of other factors, including acute inflammation (18) and comorbidity (19), which are in turn associated with nonresponsiveness (15).

The partnership with the pharmaceutical industry in developing, trialling, and administering ESA (*e.g.*, epoetin alfa) in clinical practice has been an important one for patients with CKD. The challenge is to refine our care in such a way that we now use these agents better than we have previously and with the aim of further improving outcomes for patients.

Disclosures

Rowan G. Walker has served on local medical advisory boards for Janssen-Cilag, Amgen, and Roche.

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See related articles, "Pharmacokinetic and Pharmacodynamic Profiles of Extended Dosing of Epoetin Alfa in Anemic Patients Who Have Chronic Kidney Disease and Are Not on Dialysis," on pages 1006–1014, "A Randomized Study of Extended Dosing Regimens for Initiation of Epoetin Alfa Treatment for Anemia of Chronic Kidney Disease," on pages 1015–1021, and "Greater Epoetin alfa Responsiveness Is Associated with Improved Survival in Hemodialysis Patients," on pages 1077–1083.