

erythropoietic agent was somehow systematically linked to characteristics of the patients treated. Similarities or differences in clinical response may reflect either baseline patient characteristics or the effects of the therapy being studied.

Another major limitation of observational studies is that the researcher typically has no control over the manner in which the intervention under study has been delivered. In this instance, an additional difficulty with using observational studies to assess the equivalence of dosages of epoetin alfa and darbepoetin alfa in chemotherapy-induced anemia in cancer patients is that the response to these drugs may be disease-driven, dosage-driven, or both (depending for example, among other factors, on the individual cancer patient's level of endogenous erythropoietin). A large range of dosages of both epoetin alfa and darbepoetin alfa may show similar effects in any given patient and higher than necessary dosages may not be reflected in greater elevations of hemoglobin. More generally, the populations in the reported studies may show different results due to differences in demographics, health status, types of cancer, and cancer treatments.

Beyond these methodological concerns, the question of what constitutes the best indicator of drug effect remains unsettled. Studies in the literature have used one or more of the following end-points to analyze the effects of erythropoietic drugs:

1. Hemoglobin response—an increase from baseline of >2 g/dL (usually in the absence of transfusion in the preceding 28 days)
2. Hematopoietic response—Hemoglobin increase of >2g/dL from baseline or a hemoglobin >12g/dL
3. Mean change in hemoglobin “the mean increase in hemoglobin from baseline (usually in the absence of transfusion in the preceding 28 days)
4. Transfusions of red blood cells “the number (percent) of patients requiring transfusion measured at various time intervals.

Studies submitted by one of the manufacturers proposed additional measures such as “early hemoglobin response” (the hemoglobin rise from baseline at 4 or 5 weeks) and the “area under the curve” defined by hemoglobin increases from baseline. The FDA has not used these measures as criteria for registration (i.e., market approval) and they do not appear to be regularly used in the peer reviewed literature of erythropoietic drugs and their use either in kidney disease or in

oncology. Therefore, their clinical significance is unclear at this time. They do, however, raise the question of how hemoglobin response patterns affect symptoms that matter most to patients. Both companies are conducting additional clinical studies to address further the potential importance of front-loaded regimens that provide high initial doses of erythropoietic drugs in order to stimulate a more rapid clinical response.

During the process of exchanging and critiquing study methods, Amgen and Ortho-Biotech each raised significant methodological concerns about the study designs used to obtain new data. In addition to the overall concern about the observational methodology and selection of the outcome chosen for purposes of comparison, the following concerns were raised:

- the use of survival curves to analyze clinical data in this context
- the possible effect of patient functional status on erythropoietic response
- the technique for calculating mean values for drug dosages (arithmetic vs geometric means)
- the strategy for deciding how to handle data from patients who received transfusions
- the significance of an early rise in hemoglobin, and/or the significance of measures of hemoglobin response over the entire 12–16 week treatment interval

Each company provided extensive and compelling discussions of these and other issues, highlighting the fact that conclusions regarding the relative potency of these products are inherently limited by the nature and quality of the clinical data that currently exist. Despite the limitations of the available studies, CMS believes that it has sufficient data to establish a reasonable conversion ratio for payment purposes.

Amgen submitted several observational studies, including one community-based study and three medication use evaluations (MUE). While interim results from two of these studies have been published in peer-reviewed journals, final results have not yet been subjected to full peer review. In one study (Vadhan-Raj, 2003), patients were started on darbepoetin at 3 mcg/kg every other week (QOW). The patients received up to 8 doses (16 weeks). The patients had hemoglobin (Hgb) responses comparable to that seen with epoetin 40,000–60,000 IU per week. The protocol allowed a dose increase and 43 percent of participants had their darbepoetin dose increased to 5 mcg/kg/QOW per the protocol.

Virtually all of the Amgen studies produced results that suggested a conversion ratio of 400:1.

Ortho Biotech submitted early unpublished results from a multicenter head-to-head trial of 40,000 IU of epoetin weekly compared to 200 mcg of darbepoetin every other week. The primary end-point is the change in Hgb from baseline at week 5, and initial results show significantly greater increase in Hgb for patients treated with epoetin. Ortho Biotech also submitted data from several retrospective analyses of medical charts and electronic medical records, totaling several thousand patients. None of these studies have yet been peer-reviewed or published. All of the Ortho-sponsored studies provide results suggesting that the appropriate conversion ratio is 260:1 or less.

In the observational studies that directly compare Aranesp and Procrit for the treatment of CIA, and report total dose per patient per episode of both epoetin and darbepoetin, the ratio of mean total doses is 341:1 and the ratio of median total doses is 352:1. However, selection bias may affect the validity of these studies. CMS therefore believes that the above-mentioned ratios may still overestimate, at least modestly, the potency of darbepoetin alfa relative to epoetin alfa. An analysis of Medicare claims data from 2002 and 2003 determined that the ratio of utilization of Procrit to Aranesp in Medicare patients was 330:1 (units:mcg).

As noted above, a conversion ratio between the dosages of these two products is not meant to guide what should be done for individual patients in clinical practice. In addition, by using a conversion ratio CMS is not attempting to establish a lower or upper limit on the amount of either biological a physician can prescribe to a patient. CMS expects that physicians will continue to prescribe these biologicals based on their own clinical judgment of the needs of individual patients.

Based on our own review of the evidence, our consultation with the independent contractor who also reviewed the evidence, and our discussions with Amgen and Ortho Biotech, CMS concludes that an appropriate conversion ratio for the purposes of a payment policy is 330 International Units of epoetin alfa to one microgram of darbepoetin alfa (330:1) for the purpose of treating chemotherapy-induced anemia.

*Chronic Kidney Disease without dialysis:* It is well established that as a patient progresses through the stages of chronic kidney disease (CKD), erythropoietin levels decline and anemia tends to develop. Furthermore,