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Perspective

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Erythropoiesis-Stimulating Agents — Time for a Reevaluation

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Epoetin alfa was approved in 1989 by the Food and Drug Administration (FDA) for the treatment of anemia associated with chronic kidney disease "to elevate or maintain the red blood cell level . . . and to decrease the need for transfusions." Although epoetin alfa and darbepoetin alfa, a related erythropoiesis-stimulating agent (ESA) approved in 2001, have been widely accepted for this indication, optimal hemoglobin targets have never been established. A number of small studies conducted in the late 1980s supported the concept that higher hemoglobin concentrations are beneficial; the use of ESAs for anemia in patients with chronic kidney disease was purported to improve patients' quality of life, cognitive function, energy, and well-being and to ameliorate left ventricular hypertrophy. Subsequently, randomized trials have endeavored to show that using ESAs to raise hemoglobin concentrations to higher targets improves clinical outcomes. Unfortunately and unexpectedly, all results have suggested the opposite.

The Normal Hematocrit Study provided one of the first suggestions that the use of ESAs to raise hemoglobin concentrations into the normal range could cause harm.[1] The trial tested the hypothesis that normalization, as compared with partial correction, of the hematocrit value would improve cardiovascular outcomes. Some 1233 patients with clinical evidence of congestive heart failure or ischemic heart disease who were undergoing dialysis and receiving maintenance epoetin alfa therapy were enrolled and randomly assigned either to receive increasing doses of epoetin alfa to reach and maintain a "normal" hematocrit value of 42±3% or to continue epoetin alfa therapy to maintain a hematocrit value of 30±3%. The trial was halted after an interim analysis because of an unfavorable trend: after a median follow-up time of 14 months, 33% of patients in the normal-hematocrit group had died or had a nonfatal myocardial infarction, as compared with 27% of those in the low-hematocrit group (risk ratio, 1.3; 95% confidence interval [CI], 0.9 to 1.9). The evidence of harm might have been more persuasive had the trial not been stopped early. Nevertheless, the interim findings were cause for concern and were incorporated into warnings in ESA labels.

Results of the Correction of Hemoglobin and Outcomes in

Renal Insufficiency (CHOIR) trial (ClinicalTrials.gov number, NCT00211120) raised a similar concern regarding patients with anemia and chronic kidney disease,[2] although its study population differed somewhat from that in the Normal Hematocrit Study — patients were not undergoing dialysis and had not previously received ESA therapy, and a history of overt cardiovascular disease was not required for inclusion. Investigators randomly assigned 1432 patients to receive epoetin alfa treatment sufficient to achieve and maintain a hemoglobin target of either 13.5 or 11.3 g per deciliter. The CHOIR trial was also terminated after an interim analysis, with a median follow-up period of 16 months, when a composite end-point event (death, myocardial infarction, hospitalization for congestive heart failure, or stroke) had occurred in 17.5% of patients in the high-hemoglobin group and in 13.5% of patients in the low-hemoglobin group (hazard ratio, 1.34; 95% CI, 1.03 to 1.74; P=0.03). The difference between the groups was driven by differences in the numbers of deaths and hospitalizations for congestive heart failure.

Interpretation of these findings is not straightforward. The most obvious explanation is that higher hemoglobin concentrations increase cardiovascular risk, but several observations run counter to this premise. In both randomized trials, and within each of their treatment groups, higher hemoglobin values were associated with fewer cardiovascular events. Similar associations have been found in the trials that supported the approval of darbepoetin alfa,[3] as well as in observational studies of patients with chronic kidney disease. These associations might be confounded, however, because patients in whom higher hemoglobin concentrations are achieved may be healthier and therefore more responsive to ESAs.

Another possibility, and one of long-standing concern to us at the FDA, is that the risk of cardiovascular events is related to the rapidity of the increase in hemoglobin concentration, as well as to oscillations in hemoglobin levels and overshoots of the target concentration; aggressive dosing can cause all these effects. Such instability in hemoglobin concentrations could exacerbate the cardiovascular risk through hemodynamic or rheologic mechanisms. The original label for epoetin alfa included a warning regarding the risk of exacerbation of hypertension with hematocrit increases exceeding 4 percentage points (corresponding to increases in the hemoglobin concentration of approximately 1.3 g per deciliter) within a 2-week period. During a review of the marketing application for darbepoetin alfa, an association was found between rates of increase in the hemoglobin level exceeding 1 g per deciliter per 2-week period and the risk of cardiovascular and thromboembolic events.[3] This observation provided the basis for a warning on the label for darbepoetin alfa (and eventually a stronger warning on the label for epoetin alfa) regarding excessive rates of increase in hemoglobin concentrations. Subsequently, the FDA found a similar relationship between such excessive rates of increase and the risk of adverse cardiovascular events in analyses of data from the Normal Hematocrit Study and the CHOIR trial.[4]

A third possibility is that the adverse cardiovascular events are not related to hemoglobin concentrations at all but are instead due to some off-target effect of ESAs — for example, trophic effects on vascular endothelial or smooth-muscle cells, or conditions precipitated by higher exposure to ESAs (e.g., iron deficiency). We have already found one such effect — the ability of ESAs to enhance tumor progression and shorten survival in patients with some types of cancer.

In 2004, before completion of the CHOIR trial, Amgen approached the FDA during the planning of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) (ClinicalTrials.gov number, NCT00093015).[5] TREAT was originally planned as a multinational, randomized, placebo-controlled, double-blind trial to determine whether treatment of anemia with darbepoetin alfa would reduce the risk of death and major cardiovascular events in patients with type 2 diabetes mellitus and chronic kidney disease. Patients with moderate anemia were to be randomly assigned to receive darbepoetin alfa or placebo. The dose of darbepoetin alfa was to be adjusted as needed to achieve and maintain a hemoglobin concentration of approximately 13 g per deciliter. Patients in the placebo group were to receive mock dose adjustments, with rescue therapy to be implemented if the hemoglobin concentration fell below 9.0 g per deciliter.

The FDA expressed concerns to the company that the 13-g-per-deciliter hemoglobin target was

excessive, higher than that recommended in ESA labeling, and not supported by safety data. Moreover, the risk of cardiovascular events is considerable in the population of patients who were to be enrolled. The FDA allowed the trial to proceed only after working with Amgen to develop conservative dosing and monitoring schemes to limit overshoots of the hemoglobin target, oscillations in the concentration, and rapid rates of increase and only after ensuring that there would be oversight by an independent data and safety monitoring committee. The dosing strategy was conservative. For every range of hemoglobin values, there were three possible dose adjustments that were based on the recent rate of change in hemoglobin level. Adjustments were made on the basis of the concentration determined on the day of each visit, rather than a previous visit. An interactive voice-recognition system was used to communicate computer-determined doses of darbepoetin alfa to investigators to improve adherence to the protocol and reduce errors.[5] The dosing and monitoring schemes in TREAT did not resemble directions on the approved label for darbepoetin alfa or those used in current practice; rather, they were designed specifically to ensure gradual increases in hemoglobin level and to avoid overshoots and oscillations.

Despite these measures, the TREAT investigators documented adverse consequences of using an ESA to raise hemoglobin levels. The trial enrolled 4038 patients; 2012 received darbepoetin alfa, and 2026 received placebo. The median hemoglobin concentrations achieved were 12.5 g per deciliter in the darbepoetin alfa group and 10.6 g per deciliter in the placebo group. With a median follow-up time of 29 months, there was no evidence of benefit and a trend toward overall harm with darbepoetin alfa. Death or a nonfatal cardiovascular event occurred in 31.4% of patients receiving darbepoetin alfa and 29.7% of patients receiving placebo. Although the finding was not significant (hazard ratio for darbepoetin alfa vs. placebo, 1.05; 95% CI, 0.94 to 1.17), there was a significant and substantial increase in the incidence of fatal or nonfatal stroke in the darbepoetin alfa group as compared with the placebo group (5.0% of patients vs. 2.6%; hazard ratio, 1.92; 95% CI, 1.38 to 2.68; P<0.001). There was also a significantly higher rate of thromboembolic events in the darbepoetin alfa group.

The trials raise major concerns regarding the use of ESAs to increase hemoglobin concentrations in patients with chronic kidney disease above a level intended solely to avert the need for erythrocyte transfusions.

To identify clinical benefits related to raising the hemoglobin concentration, the three trials evaluated multiple patient-reported outcomes and quality-of-life indexes. Although some individual measures showed improvement, the overall quality-of-life effects were small and inconsistent. The Normal Hematocrit Study showed a significant improvement on the physical-functioning scale of the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) but no significant effects on any of its other seven scales.[1] The CHOIR trial did not show significant improvement on any scale of the SF-36 in the high-hemoglobin group as compared with the low-hemoglobin group.[2] TREAT showed a significant effect on the Functional Assessment of Cancer Therapy–Fatigue instrument but not on quality-of-life assessments based on the SF-36.[5] Thus, none of the quality-of-life findings were corroborated, and it is unclear whether the modest effects found or the measures used (e.g., the fatigue scale for patients with cancer) represent improvements in anemia symptoms that are important to patients. Clearly, the trials did not yield convincing evidence of any consistent quality-of-life benefit that would appear to outweigh the increased risks of nonfatal myocardial infarction, nonfatal stroke, and death.

What the Normal Hematocrit Study, the CHOIR trial, and TREAT do show, however, is that hemoglobin-concentration targets of 14.0, 13.5, and 13.0 g per deciliter — and the ESA regimens used to achieve them — are harmful. It remains to be shown in a controlled trial that assignment to any higher target, as compared with any lower target,

or to ESA dosing regimens necessary to attain these targets prevents cardiovascular events or indeed does not increase their likelihood.

The TREAT results may seem less unfavorable than the others, although the pronounced difference between the two TREAT groups in the rate of stroke is very troublesome. It is tempting to speculate that the conservative dosing algorithm and the monitoring protocol in TREAT may have limited the increase in the risk of cardiovascular events. The true effect of these measures is unknown but could be assessed in randomized trials designed to compare different dosing strategies.

The trials raise major concerns regarding the use of ESAs to increase hemoglobin concentrations in patients with chronic kidney disease above a level intended solely to avert the need for erythrocyte transfusions. The trials do not rule out the possibility, however, that modest increases in the hemoglobin level could be beneficial. Indeed, the alarming rates of serious cardiovascular events in the trials (e.g., more than one death or cardiovascular event per 100 patients per month in both groups in TREAT) suggest that even small reductions in the relative risk could translate into substantial reductions in cardiovascular-related morbidity and mortality.

It is time to establish, through randomized trials, the optimal hemoglobin target, dosing algorithm, and monitoring approach for patients with anemia from chronic kidney disease. Clearly, more conservative hemoglobin targets — well below 12 g per deciliter — should be evaluated. Beyond lowering hemoglobin targets and reducing doses of ESAs, it is also possible that more frequent hemoglobin monitoring and more cautious dosing algorithms — including computer-directed algorithms — might reduce oscillations and overshoots in the hemoglobin concentration and improve outcomes. These approaches should be evaluated as well. The FDA anticipates convening a public advisory committee meeting in 2010 to reevaluate the use of ESAs in the treatment of anemia due to chronic kidney disease.

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1. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998;339:584-90.
2. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085-98.
3. Medical officer clinical review: darbepoetin alfa (Aranesp) for the treatment of anemia associated with chronic renal failure. Rockville, MD: Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, 2001. (Accessed December 29, 2009, at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm086019.pdf.)
4. FDA briefing information for the joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Committee. Rockville, MD: Food and Drug Administration, 2007. (Accessed December 29, 2009, at http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4315b1-01-FDA.pdf.)
5. Pfeffer MA, Burdmann EA, Chen C-Y, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361:2019-32.

Accelerating the Use of Electronic Health Records in Physician Practices

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North Shore Hospital System on Long Island in New York recently announced that it will pay an incentive of up to $40,000 to each physician in its network who adopts its electronic health record (EHR) — paying 50% of the cost to physicians who install an EHR that communicates with the hospital and 85% of the cost if the physician also shares de-identified data on the quality of care.[1] This payment would apparently come on top of the $44,000 incentive that the American Recovery and Reinvestment Act of 2009 (ARRA) has authorized Medicare to pay each eligible health care professional who uses certified EHRs in a meaningful manner. "Meaning-