FDA Advisory Regarding Erythropoiesis-Stimulating Agents

[Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)]

The following alert was published by the FDA on November 11, 2006.

FDA is issuing this alert to advise you of a newly published clinical study showing that patients treated with an erythropoiesis-stimulating agent (ESA) and dosed to a target hemoglobin concentration of 13.5 g/dL are at a significantly increased risk for serious and life threatening cardiovascular complications, as compared to use of the ESA to target a hemoglobin concentration of 11.3 g/dL. The "Correction of Hemoglobin and Outcomes in Renal Insufficiency" (CHOIR) study, published November 16, 2006 in the *New England Journal of Medicine*, reports the adverse cardiovascular complications as a composite of the occurrence of one of the following events: death, myocardial infarction, hospitalization for congestive heart failure, or stroke.

The CHOIR study findings underscore the importance of following the currently approved prescribing information for Procrit, Epogen, and Aranesp, including the dosing recommendation that the target hemoglobin not exceed 12 g/dL.

This information reflects FDA's current analysis of data available to FDA concerning these drugs. FDA intends to update this sheet when additional information or analyses become available.

To report any serious adverse events associated with the use of these drugs, please contact the FDA MedWatch program using the contact information at the bottom of this sheet.

CONSIDERATIONS

Physicians and other health care professionals should consider the following when using erythropoiesis-stimulating agents:

For all patients:

- Adhere to dosing to maintain the recommended target hemoglobin range of 10 to 12 g/dL.
- Measure hemoglobin twice a week for two to six weeks after any dosage adjustment to ensure that hemoglobin has stabilized in response to the dose change.
- Decrease the dose of the ESA if the hemoglobin increase exceeds 1g/dL in any two-week period.

For chronic renal failure (CRF) patients: Measure hemoglobin twice a week after initiating treatment until hemoglobin has stabilized

For cancer patients and zidovudine-treated HIV patients: Measure hemoglobin once a week after initiating treatment until hemoglobin has stabilized

For patients with a history of cardiovascular disease or hypertension: Closely monitor and control blood pressure

INFORMATION FOR THE PATIENT

Physicians and other health care professionals should discuss the following with their patients:

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"Normal" May Not Be Optimal

The November *New England Journal of Medicine* publication of the results of the CHOIR and CREATE studies is yet another reminder of the potential hazards associated with correcting hemoglobin concentrations to the "normal" range in patients with chronic kidney disease (CKD). These studies have confirmed earlier suggestions in the literature that achieving a normal hematocrit or hemoglobin may at worst actually increase the risk for morbidity and potentially life-threatening cardiovascular complications or at best, not confer any clinical benefit to the patient treated to a normal hemoglobin value. Findings such as these seem counterintuitive to what would be the most desirable patient endpoint for the treatment of anemia associated with CKD, yet the accumulating literature seems to confirm that for reasons that are not understood, patient survival is diminished with sustained hemoglobin concentrations that are within the usual normal range.

In many respects, anemia management of dialysis patients has been a success story. CMS annually conducts an analysis of anemia-related outcomes within a randomly selected population of in-center hemodialysis patients. The most recent report from this analysis reveals that the mean ± SD hemoglobin value for all patients was 12.0 ± 1.2 g/dL. Eighty-three percent of all patients within the sample had achieved a mean hemoglobin concentration ≥11 g/dL, with 52% of patients having a mean hemoglobin value ≥12 g/dL and 17% having a mean hemoglobin value ≥13 g/dL. Current clinical practice guidelines from the National Kidney Foundation (NKF) recommend a target hemoglobin of ≥11 g/dL. No upper limit of the target hemoglobin range is specified; however the guideline states that there is insufficient evidence to recommend routinely maintaining hemoglobin concentrations ≥ 13.0 g/dL in patients receiving erythropoiesis-stimulating agents (ESAs). Of note is that prior to the 2006 revision of this clinical practice guideline, the NKF recommendation specified a target hemoglobin concentration range of 11-12 g/dL. The results of the CHOIR and CREATE studies have led some clinicians to call for a return to a target hemoglobin concentration of 11-12 g/dL in an attempt to avoid the adverse outcomes apparently associated with higher sustained hemoglobin values.

In the management of anemia of CKD patients, "more" does not appear to be "better." Pharmacists working with CKD patients should analyze their patient outcomes and share the results of the CHOIR and CREATE studies with their clinical colleagues. Share the FDA Alert with those who are prescribing ESAs. Let the evidence drive your practice. ●

— Curtis A. Johnson, PharmD

to infect many individuals. Since contraception, in general, is taboo, it is not surprising that protection within marital relations is absent. While protection to prevent the spread of sexually transmitted infections is still uncommon, it is reassuring to see the increasing popularity of contraception such as Norplant implants to control population growth. Many others cling to traditions that use only natural methods as a way of preventing pregnancies.

Adherence to traditions cannot be seen as primitive, only as an attempt to maintain culture in a country that is being pulled in a Western direction as attempts to develop the country imply Western superiority. It is inspiring, however, to see that some cultural rituals are being moved to the clinic setting as individuals recognize the importance of hygiene and value of educated health care professionals. Circumcisions have in the past been done in rural villages and have been followed by large communal celebrations. Today the procedure is carried out in a clinic while many continue to celebrate in the village afterwards. Childbirths are also moving from unsanitary homes to maternity wards staffed by mid-wives, or mid-husbands as was the case at Bomu. In both cases, individuals are in and out of the facility in a timely manner in order to save the patient unnecessary expenses.

As Kenya struggles to make economic progress in an age where global competition is virtually essential to success, it is commendable that the country realizes the important role of health care in national development. Without a population of healthy, well-bodied, well-minded individuals, developing countries lack the human resources essential to progress. Hope stems from the success of projects to extend health care to as many individuals as possible. As long as the government and citizens continue to work with international agencies in a forward direction, projects will continue to find success that will allow for socioeconomic progress. ●

Ashley Fargen is a pre-pharmacy student at UW Madison. She was a participant in the program described in this article.

REFERENCES

1. www.unicef.org/infobycountry/kenya_statistics.html
2. www.un.org/millenniumgoals/

Erythropoiesis-Stimulating Agents (ESAs), *continued from page*

- The goal of treatment with erythropoiesis-stimulating agents (ESA) is to increase the number of red blood cells which can help them in treating their anemia.
- Treatment with an ESA can be harmful if not closely monitored.
- The importance of keeping their appointments for their blood tests
- The need to monitor their blood pressure every day (if appropriate) and call you if there are any changes outside of the range established for the patient.
- To call you if they experience any of the following symptoms:
  - Pain and/or swelling in the legs
  - Worsening in shortness of breath
  - Increases in blood pressures
  - Dizziness or loss of consciousness
  - Extreme tiredness
  - Blood clots in hemodialysis vascular access ports

DATA SUMMARY

Safety concerns related to the use of erythropoiesis-stimulating agents in the treatment of the anemia of chronic renal failure (CRF) is the topic of two clinical studies and an editorial published in The *New England Journal of Medicine* on November 16, 2006. The 1,432 subject CHOIR study demonstrated increases in serious and potentially life threatening cardiovascular events when epoetin alfa (Procrit®) is administered to reach higher target hemoglobin levels than lower target hemoglobin levels. The 603 subject CREATE study showed a trend toward more cardiovascular events in a pattern similar to the CHOIR study, thus supporting the findings of the CHOIR study. The CREATE study examined the use of epoetin beta, a product not approved in the USA.

- The CHOIR study was a randomized, open label design in which anemic chronic kidney disease (CKD) subjects were randomized to be dosed to either a higher average target hemoglobin (13.5 g/dL) or a lower average target hemoglobin (11.3 g/dL). All subjects received Procrit®. The primary endpoint was a time to event analysis for a composite cardiovascular endpoint (all cause mortality, congestive heart failure (CHF) hospitalization, non-fatal MI, or non-fatal stroke).
- Procrit® was administered as 10,000 units SC weekly and titration allowed to a maximum dose of 20,000 units weekly.
- Overall, 715 subjects were randomized to the high target hemoglobin (13.5 g/dL) and 717 randomized to the low target hemoglobin (11.3 g/dL). At the end of the study, the average hemoglobin was 12.6 g/dL for the high group and 11.3 g/dL for the low group.
- The composite cardiovascular endpoint was statistically worse in the higher target hemoglobin group with a hazard ratio of 1.3 [95% CI 1.03, 1.74] (p = 0.03 by log rank test).
- The rates for the individual components of the composite primary endpoint were (high target vs. low):

Death:	7.3% vs 5.0% (p = 0.07)
CHF hosp:	9.0% vs 6.6% (p = 0.07)
Non-fatal MI:	2.5% vs 2.8%
Non-fatal stroke:	1.7% vs 1.7%

- The analyses for this study found no correlation between rate of rise of hemoglobin and adverse cardiovascular events. However, the relationship between seizures and the rate of rise of hemoglobin as reported in the labeling for all three products remains a concern.

The CHOIR and CREATE study findings underscore the importance of the existing warnings regarding cardiovascular risks that include thrombotic events and increased mortality observed in hemodialysis patients with cardiac disease targeted to higher hemoglobin levels (~14 g/dL), and recommendations not to exceed hemoglobin levels of 12 g/dL in approved labeling for Procrit®, Epogen®, and Aranesp®. Please refer to the full prescribing information for additional information. Internet links to the full prescribing information for all approved ESA products may be found at the FDA page for this alert. ●

Report serious adverse events to FDA's MedWatch reporting system by completing a form online (WWW.FDA.GOV/MEDWATCH/REPORT.HTM), by faxing (1-800-FDA-0178), by mail using the postage-paid address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).