Trends-in-Medicine

November 2007
by Lynne Peterson

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

FDA Tightens the Labels on EPOs

On November 8, 2007, the FDA strengthened the boxed warnings for erythropoiesis-stimulating agents (ESAs) – Amgen's Epogen, Johnson & Johnson's Procrit/Eprex, and Amgen's Aranesp – and made other safety labeling changes to the drugs. ESAs are approved to treat anemia in patients with chronic kidney failure and in certain cancer patients with anemia caused by chemotherapy. Epogen and Procrit are also approved to reduce blood transfusions in certain patients with anemia who are scheduled to undergo major surgery, and they are approved to treat anemia caused by zidovudine (AZT) therapy in HIV patients.

Two FDA Advisory Committees earlier this year both recommended stronger labels for ESAs, though the oncology panel was more specific in what it wanted.

1. **Oncology.** In May 2007, the FDA's Oncologic Drugs Advisory Committee (ODAC), citing concerns about safety, voted 15-2 that the FDA should impose additional restrictions on use of ESAs. The panel also voted unanimously that additional safety trials are needed. Panel members expressed dismay at the dearth of valid data from any trials and expressed concern at the evidence that showed ESAs decrease survival and, in fact, may promote tumor growth. One oncologist described ESAs as "Miracle Gro for tumors."
2. **Renal.** In September 2007, the FDA's Cardiovascular and Renal Drugs Advisory Committee (CRDAC), in a joint meeting with the Drug Safety and Risk Management Advisory Committee (DSaRM), rejected an FDA staff proposal to establish a hemoglobin ceiling "not to exceed ~11 g/dL," largely because panel members did not like the "not to exceed" language. However, the FDA's take-away message from the panel was: "The language (in the current labeling) can be improved. There was a variety of opinions as to how that could be improved. A number of advisers thought we should go the route of target range. They were giving credence to some of the observational data to make that statement."

This is the fifth time since Epogen was first approved that the FDA has revised the product labeling for ESAs. ***What's new now:***

- An advisory that there is **no proven quality of life benefit** to ESAs in cancer or HIV patients, and no proven benefit on fatigue, the symptoms of anemia, or overall patient well-being. An indication section has been added to address this. Any reference to ESAs affecting happiness and well-being have been deleted.
- A **Medication Guide** (MedGuide) is being prepared that pharmacists will give to every patient with every prescription. The FDA is still trying to figure out how patients in the hospital or in doctors' offices will get the MedGuide, but FDA officials cited the example of Biogen Idec/Elan's MedGuide for

Tysabri (natalizumab) use in multiple sclerosis, where every patient gets a MedGuide at the time of every infusion.

- The FDA set a **Hb range of 10-12 g/dL** in both cancer and chronic kidney disease (CKD) patients, but the Agency also warned that:
  - Targeting Hb ≥12 g/dL in certain cancer patients has been shown to shorten survival or cause tumor progression.
  - Maintaining higher Hb levels in CKD patients increases the risk for death and serious cardiovascular (CV) events, such as stroke, MI, or heart failure.
  - Dosing in CKD patients should be individualized to achieve and maintain Hb in the range of 10-12 g/dL.
- The Agency is advising that ESAs should be **used in cancer patients only when they are on *myelo-suppressive* chemotherapy** and discontinuation of the ESA when the chemotherapy is finished – and not for anemia of other causes in cancer patients.
- The FDA is ***strongly*** recommending that **prescribers talk to cancer patients** about the risk that ESAs might cause their cancer to grow more quickly or shorten survival before they start ***or continue*** ESA therapy. The Agency also wants doctors to warn about the risk of pure red blood cell aplasia (PRCA).
- The FDA is warning that even a hemoglobin ceiling of 12 g/dL is not necessarily safe. The risk of serious adverse events in dosing to a level less than 12 g/dL cannot be excluded – and needs to be studied.
- Specific instructions were included for **dosage adjustments and hemoglobin monitoring** for CKD patients who do not respond to ESA treatment with an adequate increase in Hb.
- **Dosage as well as Hb level** could be a factor in adverse events, and Amgen will be required to **conduct new studies** to investigate both of these issues.

In a teleconference with reporters, FDA officials discussed the new warnings and labels. FDA officials said the Agency "will continue to monitor these drugs" and is "working with Amgen to develop different dosing regimens and tumor types to further characterize cancer progression" and to "design and conduct clinical trials of different dosing regimens and tumor types to further characterize potential tumor progression associated with ESAs."

What trials is the FDA working on with Amgen? How many trials will there be? Will they compare dosing? What is the timing?

Dr. Richard Pazdur, director of the FDA's Office of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER): "We are in discussions with Amgen at this time about the types of trials we want and the number of trials we want. We believe we would like to see specific trials in specific tumor types, with the clearly outlined endpoints of survival or time-to-progression (TTP). The designs were discussed at the ODAC meeting, and we got very specific advice from ODAC that subsequent trials should focus on specific tumor types and should have specific endpoints of overall survival or TTP or progression-free survival (PFS). We would be asking the sponsor to look at a variety of tumors, especially tumors that experienced a signal such as breast cancer or NSCLC, and we also want to look at a target Hb that is lower than originally studied, which tended to look at Hb >12…We will collect more information on dosing as well as targets in upcoming studies…Frequently when we went back in these studies, some of the important information was not maintained or captured…Because of the safety signals we are seeing now and this issue of target vs. dose as the culprit, this will be adequately captured in the next generation of studies as well as ongoing trials."

He said Dr. Patricia Keegan, director of the FDA's Division of Biologic Oncology Products, CDER, has been negotiating with Amgen and the other sponsors on this.

How is the new labeling expected to impact prescribing?

Dr. Pazdur said, "We really wanted physicians and patients to have very careful discussions about the risk of tumor promotion and overall survival…We think physicians should have very careful discussions with patients about this risk. We think it should be individualized discussions about the purpose the patient is receiving chemotherapy, the type of chemotherapy, and the duration of therapy, but we also believe the labeling gives the physician a degree of flexibility that allows clinical judgment to come into play."

In the past the FDA said CMS coverage of ESAs was consistent with the labeling. Is CMS coverage consistent with this new labeling?

Dr. Pazdur: "Is the total package still consistent with the coverage decision of CMS? Yes. We believe that the changes that we provided in this labeling as well as previous labeling has given the requisite flexibility to practicing physicians to really provide the optimal decision-making in prescribing these drugs, and we do believe this is consistent. We have not stipulated in the labeling a Hb to start ESA. We have in the labeling that Hb should not exceed 12 g/dL. We would like to emphasize that this is not a target; this is an upper boundary for safety."

Dr. John Jenkins, director of the FDA's Office of New Drugs, CDER, added, "We continue to emphasize that ESAs should be used at the lowest doses necessary to avoid blood transfusions…Doctors should have discussions with patients on whether to use them at all, and if they (ESAs) are determined to be used, our concern is to use the lowest dose to avoid blood transfusions since that is the ***only*** identified benefit…

We also added to the label a table that described the six randomized, controlled trials (RCTs) that showed adverse outcomes and tumor progression. One of the columns in that table describes achieved Hb levels in those studies vs. target levels. The targets were all greater than 12 g/dL, but in two of the three studies where we have achieved Hb data, the value was <12…So, this goes to emphasize that the risk of serious adverse events in dosing to Hb ***less than*** 12 g/dL have not been excluded, and we think people should be very aware of that and make very careful decisions about the risk:benefit when using these drugs in individual patients."

The main point of dispute in the Medicare (CMS) coverage decision is a cap on reimbursement at a Hb of 10 g/dL, and the new FDA label gives discretion up to a cap of 12, though the FDA advises keeping it lower. Why is this consistent with CMS's hard cap of 10?

Dr. Jenkins: "We say it is consistent because in both cases the goal is to use the lowest dose to avoid the need for blood transfusions…The CMS coverage decision is based on the knowledge that blood transfusions are rarely provided for patients with Hb ≥10. So, in that way, labeling and CMS are consistent. **We are not in any way suggesting our upper safety limit of 12 is the target for therapy.** There are no controlled trials that Hb in that range have an effect on quality of life…And two of the three studies with adverse events where we have the data – in one, the achieved Hb was 10.5 and in the other it was ~11. **Our view is that it is probably a factor more of ESA dose, and you really should be trying to use the lowest dose possible**."

What about the difference between targeted Hb and achieved Hb?

Dr. Keegan: "We can't really dissect out the contribution of the dose from the target. We need more data for that."

Dr. Jenkins: "We believe it is clear that achieved Hb level has a definite impact on some CV outcomes – MI, stroke, clotting of vascular access in dialysis patients. It is less clear in cancer, whether it is achieved Hb which has the impact or if it is the dose of the ESA used. That is something we still need to tease out…Biologically, **it may be the dose that is more important than the Hb level, but we don't have the data to confirm that**…There are really two sets of adverse events we are focusing on here. One is the CV adverse events, which we think are pretty clearly related to achieved Hb but may also be related to dose. The CV events can also occur in cancer patients receiving these drugs, and with the cancer patients, we don't know if the decreased survival is related to CV-related events or to tumor-related events."

Dr. Pazdur: "(Dose) is one possibility. There is some lack of information that requires study. When targeting a higher Hb, one would generally use higher doses…Is it a reflection of the dose or the target (when there is an adverse event)? They may be related, or there may be some discrepancy."

Why are there different recommendations for renal and cancer patients?

Dr. Pazdur: "For renal patients, we are looking at lifelong, prolonged therapy. In essence, for the renal population this is almost replacement therapy for a hormone – EPO – and a prolonged use of this drug throughout someone's lifetime. With the oncology population, we are really talking about rather episodic treatment, short-term use, and we do recommend that the therapy be discontinued after the completion of a chemotherapy course. So, there is really a dramatic difference in the treatment philosophy and the use of these drugs which led us to the different range in renal and not to specify when these therapies are to be initiated in the oncology population."

Did the FDA consider a lower Hb limit for cancer patients similar to what the CMS national coverage decision (NCD) says? And what is meant by "The FDA strongly recommends doctors talk to patients"?

Dr. Jenkins: "The upper safety limit that is included in the labeling is based on the fact that six studies quoted in the labeling with decreased survival or increased tumor progression were all targeting Hb 12 g/dL or above. That is the basis for the upper safety limit. **We made it very clear that the evidence is not there to say a lower Hb target may not have the same risk**."

Dr. Pazdur said, "We left the level at which to initiate up to the discretion of the physician…We believe it is a relatively complex picture on when to decide to use these drugs that involves consideration of why patients are treated with chemotherapy, how long the chemotherapy is intended to be used, the efficacy of a specific chemotherapy on red cell precursors, the risk for transfusions. It is a very complicated picture, and we didn't set a lower or initiating level." Dr. Jenkins added, "ESAs are only approved to treat anemia in patients with cancer who have anemia on chemotherapy. Anemia is common in cancer. It is only those receiving chemotherapy…We will have a Medication Guide…The FDA approved patient labeling that must be provided to the patient at each time an ESA is administered, so they (patients) can be aware of the risk and participate in making that decision in their own case."

Will the MedGuide be compulsory for every patient when they get an EPO shot? Is that strategy used very often by the FDA?

The MedGuide regulations were written mainly with a focus on outpatient prescriptions…So, it is written so that the MedGuide has to be provided by the pharmacist to the patient with every new prescription and with every refill. We are only now starting to learn how to do this with drugs provided in the physician's office or at infusion centers…We did have a MedGuide with the re-introduction of Tysabri, where patients get a MedGuide every time they come in to get an infusion of Tysabri. I think we need to work out the details for the expectations for patients receiving EPOs, on how they get a

MedGuide, whether it is with every dose infused or some other strategy."

What about hyporesponders in the renal setting?

Dr. Dwaine Rieves, deputy director of the FDA's Division of Medical Imaging and Hematology Products, CDER: "An important new addition to the label is in the dosage and administration section, where there are guidelines – bullets – on how to manage patients who fail to achieve Hb in the recommended range or who fail to maintain a level in the recommended range. For example, dosage should not be increased if a patient's Hb fails to achieve the level of 10-12 g/dL after 12 weeks…We think this text is an important addition to the use of ESAs in CKD anemia treatment."

Will hyporesponders be studied in clinical trials as well?

Dr. Rieves: "That is a complex issue because Hb response to ESA is very difficult to differentiate from dose…The TREAT study may provide useful information on the hyporesponder issue, but at the present time we are working to try to develop study designs, and this is a complex issue…We intend to explore that and get those studies going."

If there are no quality of life data that ESAs improve symptoms of anemia, why do we call them anemia drugs?

Dr. Jenkins: "Because anemia is defined by Hb level, and we know in RCTs that were the basis for approval that they were successful in raising the Hb level and avoiding the need for blood transfusions. That is the basis for their approval."

Is the FDA stopping or changing any ongoing ESA trials?

Dr. Rieves: "TREAT (an Amgen-sponsored, randomized, double-blind trial of Aranesp vs. placebo in anemic diabetic patients, with a primary endpoint of all-cause mortality or CV mortality) is ongoing, and that study is being intensively monitored by the data safety monitoring board (DSMB). The investigators have been made aware of the risk of ESA usage, but that study is continuing, closely watched."

Dr. Jenkins: "We are not aware of any other studies that have been halted or changed."

What will the FDA do if ESA use does not decline after these label changes?

Dr. Pazdur: "Our emphasis is on safety, not how widely they are prescribed. We want to be sure that patients are adequately informed of the risk, that the types of patients receiving these are the appropriate patients. It does not have anything to do with the usage, but with safety concerns the Agency has."

♦