A PBB Alliance Briefing:

FDA to Re-evaluate Use of Erythropoiesis-Stimulating Agents in Chronic Kidney Disease

January 20, 2010

The FDA announced plans for an advisory review board in 2010 to re-evaluate erythropoiesis-stimulating agents (ESAs) usage and dosing for the treatment of anemia in chronic kidney disease. This decision followed publication of a report indicating ESAs provide no benefit in outcome compared to placebo, and increases stroke rates (1,2). This news should cause investors to examine their positions in Amgen and Johnson & Johnson whose ESA's had 2008 sales of $6.9 billion according to their annual reports, a significant decline from the 2006 sales of $8.7 billion, and 2007 sales of $7.8 billion. Any further FDA restriction of these drugs could have profound impact on these companies' performance, and on the market potential of next-generation ESAs in these, and other company pipelines.
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The Biological Significance of Erythropoietin

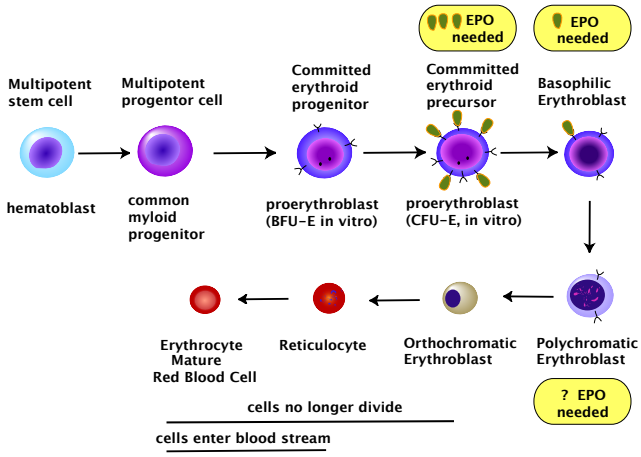
Erythropoietin (EPO) is a (para)hormone that is produced primarily by the kidneys but also in the liver and other organs like the brain. EPO is an important driver of red blood cell (RBC) generation in the bone marrow (erythropoiesis). Although RBCs have a relatively long life span in the blood of about 3 months, the body needs to constantly replenish the supply. This means that a supply of EPO is always needed by the body and this demand for EPO can be different depending on the circumstance. For example, patients with chronic kidney disease undergoing dialysis do not make enough EPO to adequately support their erythropoietic needs, and they become anemic.

RBCs carry hemoglobin which is the molecule that carries oxygen in the blood and releases it to tissues. Without adequate carrier, tissues become starved for oxygen or hypoxic. The number of RBCs relates directly to the amount of available hemoglobin. This is why you'll see the effects of ESAs measured in units of hemoglobin even though their action is to increase the number of RBCs.

Cells have a mechanism for stimulating EPO when hypoxic through the induction of hypoxia-inducible factor-1 (HIF-1). One of the consequences of HIF-1's action is the stimulation of EPO production along with other signals that stimulate blood vessel formation and adaptive metabolic changes to cope with the reduced supply of oxygen. Although the major contribution of EPO as a circulating hormone may come from the kidney, the reality is that probably all tissues produce some localized EPO in response to hypoxia and inflammation through the action of HIF-1.

EPO binding to its receptor on cell surfaces causes a cascade of signaling within the cells that culminates in protection from programmed cell death (apoptosis). EPO must bind cell receptors to prevent the precursors from undergoing apoptosis and thus failing to continue erythropoiesis and generate RBCs (**Figure 1**). Without maintenance of an adequate number of precursors there will be inadequate generation of RBCs and anemia. Recombinant EPO acts by preventing the die off of precursors during erythropoiesis (3). If the receptors of the CFU-E precursors (Fig.1) do not bind enough EPO *in vi-*

Figure 1. Erythropoiesis in the bone marrow



tro, they will undergo apoptosis within 2-8 hours. Clinical results demonstrate a dose-dependent response, i.e., the more receptors likely occupied on the precursors, the greater the overall response, although the rate of response does not change with increasing dosage. What is important to significant RBC generation is maintaining EPO availability.

Man-made recombinant erthyropoietins are called epoetins. Some refer to the entire class of erythopoietic molecules as ESAs. Most, but not all ESAs are biotechnology versions of erythropoietin. Recombinant human erythropoietins (rhEPO) were first approved by the US Food and Drug Administration (FDA) in 1993. In the US, there are two first-generation rhEPOs commercially available: epoetin alpha known as Procrit® (Johnson & Johnson) or Epogen® (Amgen), and epoetin beta or Recormon® (Roche Diagnostics).

Native EPO has a half-life of 8.5 hours. In contrast, epoetins have half-lives of up to 24 hours (4). With a half-life of hours and the need to maintain adequate levels of circulating EPO measured in days, this presents a dosing challenge (5). Clinically, the dose of rhEPO has to be high to allow for the short half-life. Achieving a 1,000-fold increase in circulating EPO, translates clinically to a 5-fold increase in hemoglobin levels (related to RBC numbers) (3). The duration of the dose is more important than the size of the dose. This has led to modifications of the epoetin molecule to produce second-generation epoetins with extended half-lives.

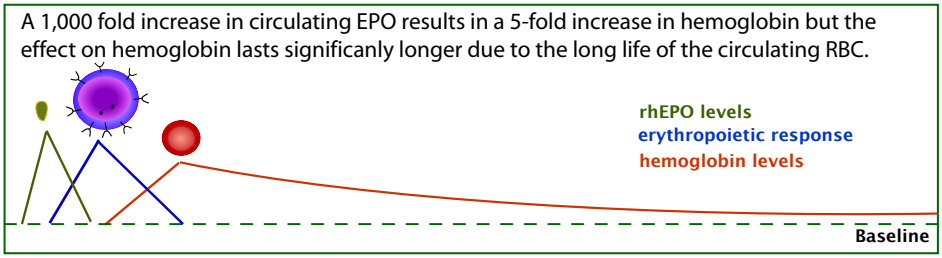
EPO is a glycosylated protein, which means it consists of both protein and sugar molecules. The strategy behind the development of darbepoetin alpha, also known as Aransep® (Amgen) was to increase glycosylation, which would decrease the rate of clearance and thus be able to maintain an effective serum level longer. Compared to epoetin alpha, darbepoetin has up to a three-fold longer half-life. Although the affinity to the EPO receptor is not as strong, the ability to prolong the effective dose of ESA is sufficient to increase the length of effectiveness of darbepoetin compared to epoetin alpha (3). An alternative to glycosylation is pegylation. Pegylated epoetin is available in Europe (Micera, CERA, Hoffmann-La-Roche) but is not yet on the market in the US (6).

Figure 2 illustrates the relationship between a dose of ESA to the final outcome of increased circulating hemoglobin. RBCs generated from a single dose can persist up to 3 months. With patients receiving doses as frequently as several times per week, one can appreciate that prolonged, or frequently repeated ESA stimulation of erythropoiesis could lead to higher than normal numbers of RBCs per unit volume at a point during the course of treatment (unless counterbalanced by a more rapid depletion of RBCs due to other factors) (5). A higher number of RBCs increases the viscosity of the blood (7) and thus increases the risk of stroke and thrombosis. Irrespective of hemoglobin concentration, rhEPO can also add to the thrombotic risk via increased inflammation and antifibrinolytic activity (8). Only Procrit®, Epogen® and Aransep® (see below) will be re-evaluated by the FDA. Since all epoetins will follow the same path to RBC formation and raising levels of circulating hemoglobin, it is possible that the decision by the FDA will impact the entire market.

Clinical Indications

The first clinical indication for ESAs was in chronic kidney disease, more specifically, the kidney dialysis

Figure 2. The Dosing Challenge



Based on Elliott et al. Exp. Hematol. 2008, 35:1573.

patient. These patients not only lack adequate EPO production but are exposed to increased RBC loss due to the dialysis treatment. Kidney dialysis patients are unable to maintain adequate EPO concentrations and suffer from anemia. Since dialysis can continue over years, this is an ongoing problem. While some have linked anemia with increased morbidity and mortality, the primary clinical benefits are a reduction in the need for blood transfusions, and quality of life issues like having adequate energy and being able to undertake physical exercise. Since some kidney dialysis patients may also be transplant candidates, limiting the risk of sensitization to foreign antigens from a blood transfusion is also a medical consideration favoring the use of ESAs. However issues have arisen in the risk to benefit of ESAs, particularly as applications expand to other causes of anemia and clinical studies examine benefits beyond increased energy.

Statistics

The FDA's decision to convene a review panel was triggered by the publication of the TREAT Study (Trial to Reduce Cardiovascular Events with Aranesp Therapy), a double blind, randomized study of ESA in chronic kidney disease. The goal of TREAT was to increase hemoglobin levels to avoid anemia, a biomarker of risk for higher rates of cardiovascular and renal events. While it has been shown that ESAs do increase hemoglobin, it was not known whether using ESAs also reduced cardiovascular and renal events. Therefore, the two primary outcomes in TREAT were a composite of death by any outcome plus cardiovascular event, and death by any outcome plus end stage renal disease.

The TREAT study failed for both primary outcomes. With 2,012 patients randomized to ESA, and 2,026 randomized to placebo, the first outcome of death and cardiovascular event occurred in 632 (31.4%) of the ESA treated patients, and 602 (29.7%) in the placebo group. The data showed a higher percentage of events in the treatment group, though not statistically significant (HR = 1.05; 95% CI, 0.94-1.17; P = 0.41). A similar pattern was found for the outcome death and end stage renal disease, as well as in the subset analysis of end stage renal disease only.

But these failings alone did not lead the FDA to call for a re-evaluation of ESAs. Rather two other factors did, one from the TREAT study, and one from the history of ESAs in medicine.

Within TREAT was the unexpected, or perhaps hopefully not desired, increase in stroke in patients on ESA. There were 101 (5%) of the 2,012 treated patients and 53 (2.6%) of the 2,026 placebo patients with fatal or non-fatal strokes with a reported $P<0.001$. (The actual P value using a Fisher's exact test is 0.000072.) ESA results in a 92.3% increase in strokes over placebo.

But TREAT was not the first study to show problems with ESA in chronic kidney disease and other diseases. The CHOIR study compared low and high hemoglobin level targets in a randomized study and was terminated early after the second interim analysis (9). For the composite event death, myocardial infarction, hospitalization for congestive heart failure, and stroke, in the high hemoglobin group 17.5% had the event versus 13.5% in the low hemoglobin group (HR = 1.34; 95% CI, 1.03-1.74; P=0.03). In ESA versus transfusion for treatment of anemia in cancer, a meta-analysis of 53 trials involving 13,933 patients showed an increased mortality (HR = 1.17, 95% CI 1.06–1.30; P=0.003). In a German study of ESA for treating acute ischemic stroke (10), there was an increase in mortality in ESA treated patients (16%) versus the placebo group (9%). Other studies have raised concern as well (11).

Discussion

From sales in 2006 of $8.7 billion to 2008's $6.9 billion, a dramatic 21% drop, the FDA's announcement may produce even more drastic declines in sales in the next several years. We can expect a strong response in favor of ESAs to come from industry, and come quickly. For example, it is interesting that the advisable level of hemoglobin is now 11-12 g/dL for the ESAs to avoid the thrombosis risk (5). The definition of anemia by The World Health Organization is a hemoglobin concentration of less than

13 g/dL and The National Kidney Foundation defines anemia at less than 12 g/dL (8). With an FDA mandate of levels not to exceed 10-12 g/dL in renal failure patients (5), ESAs safely improve levels to borderline anemia levels. That puts into question whether given the limitations needed to reduce risk (i.e., lower hemoglobin target) if the improvements can impact the other clinical factors in a way that will be both safe (4) and statistically significant.

No matter how industry counters this announcement and these results, the evidence against ESAs is strong enough for the FDA to take significant action, and investors should thoroughly familiarize themselves with the biology, clinical trial history, and statistical results to protect their investments.

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