Against TREATing All Patients Alike: Lessons from an FDA Advisory Committee Meeting

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On October 18, 2010, the Food and Drug Administration (FDA) convened a Cardiovascular and Renal Drug Advisory Committee (CRDAC) meeting to discuss the risks and benefits of darbepoetin or, more broadly, erythropoiesis-stimulating agents (ESAs) for the treatment of anemia in patients with chronic kidney disease (CKD), a subject that was recently debated in JASN.1,2 Dr. Emil Paganini, a nephrologist at the Cleveland Clinic, chaired the panel, which consisted of 17 experts in nephrology, cardiovascular medicine, and quantitative sciences. I had the privilege of representing the American Society of Nephrology to explain its position in the public speaker session.3

From an internal evaluation of evidence before the meeting, the FDA had concluded that for the treatment of the anemia associated with chronic kidney disease, no safe target hemoglobin levels, darbepoetin dosages, or dosing strategies had been established.4 After hearing evidence from Amgen and the FDA and extensive deliberations, a substantial majority of the panel voted against recommending withdrawal of the labeled indication for darbepoetin for the treatment of anemia associated with CKD for patients who are not on dialysis. The panel also did not endorse using the treatment algorithm from the placebo group of the recent Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) for recommended dosing on a revised label. That algorithm called for ESA rescue treatment of patients with anemia once their levels of hemoglobin fall below 9 g/dl, whereas the current label calls for the lowest hemoglobin target necessary to avoid transfusions within a hemoglobin target range of 10 to 12 g/dl.

The meeting was triggered by a previous CRDAC meeting held in September 2007 regarding two large ESA trials5,6 published in 2006. Those earlier trials showed no meaningful benefit or even harm in patients who had CKD and anemia and were randomly assigned to higher versus lower hemoglobin targets. A boxed warning (Black Box) about the specific safety signals was added after the meeting in 2007, and more decisive regulatory action was postponed to await the results from the TREAT study, a much larger ESA trial in patients with diabetes, relatively moderate CKD, and mild anemia. TREAT was published in October 2009, and the investigators found no benefit on the primary cardiovascular end point for patients who were randomly assigned to receive darbepoetin to a hemoglobin target of 13 g/dl compared with placebo injections with blinded darbepoetin rescue at 9 g/dl.7 Some have now argued that these results show that revision of current treatment guidelines is warranted.8

Of particular concern, TREAT patients who were randomly assigned to darbepoetin experienced a doubling of their rate of stroke, and those with a history of cancer had increased mortality. Boxed warnings on the potential of increased risk for stroke had been swiftly added to the labels of epoetin and darbepoetin in late 2009, and the FDA indicated that they would convene the CRDAC again in 2010 to conduct a broader discussion about the safety and continued marketability of ESAs in CKD.9

Not surprising, much of the discussion at the recent CRDAC meeting revolved around the increased risk for stroke in the active treatment arm of TREAT. Although the overall hazard ratio (HR) for stroke was 1.92 (95% confidence interval [CI] 1.38 to 2.68), the risk seemed to be accentuated in patients with a baseline history of stroke (HR 2.91; 95% CI 1.37 to 6.18) compared with patients without such a history (HR 1.69; 95% CI 1.16 to 2.45). The FDA asked the panel whether ESAs should be contraindicated for patients with history of stroke. The panel believed that such action was not warranted, especially in light of a nonsignificant test for interaction (P = 0.21). Additional analyses focused on potentially explanatory factors for the excess stroke risk in the darbepoetin group. Neither Amgen nor the FDA was able to identify from their analyses any specific predictors including treatment-related candidate characteristics such as recent BP, hemoglobin concentration, platelet counts, darbepoetin dosage, or estimated GFR.

The discussion on the findings of increased cancer-related mortality risks among treated patients with a history of cancer was relatively short. The TREAT investigators with a simple checkmark noted history of cancer at baseline, and cancer outcomes were not adjudicated, thus reducing the reliability of their findings. However, in light of the established risk for cancer progression and mortality in multiple oncology trials of ESAs that have led to restricted access to ESAs for treatment of patients with cancer,10 any cancer-related safety signal from ESA treatment is particularly concerning.

The FDA further pointed out that because almost half of the study patients in the placebo group of TREAT were ex-
posed to at least some rescue treatment with darbepoetin (per study protocol), the risks estimated from the trial likely underestimate true risk. The proposed as treated analysis, however, would depart from the internal validity awarded by randomization and render an epidemiologic analysis with a relatively lower level of evidence. The actual exposure in the placebo arm, however, was relatively minimal: Only 46% of patients received any darbepoetin, and of those, more than half received a cumulative dosage of only ≤90 μg. By comparison, the median dosage in the darbepoetin arm was 3920 μg. Thus, the bias toward the null was probably small in TREAT.

Much discussion also focused on the benefits of ESA treatment, transfusion avoidance, and health-related quality of life. Some panelists questioned the relevance of the transfusion benefit. It was noted that infectious risk of transfusions is now almost negligible compared with the 1980s, when epoetin alfa was first approved on its ability to reduce transfusions. As the FDA pointed out, the risk difference was small between darbepoetin, for which the rate of patients who received any transfusion during study was 15%, and placebo, for which the rate was 25%. Prescribing for a hemoglobin target of 13 g/dl did not completely eliminate the need for transfusion. Furthermore, the FDA calculated that for each five patients spared from transfusion, there was one additional stroke event. However, several speakers, including American Society of Nephrology representatives, pointed out that lowering the labeled hemoglobin target range would inevitably increase the risk for transfusion and with it the risk for allosensitization for future kidney transplant candidates, thereby reducing the chances of receiving a transplant as well as the likelihood of maintaining long-term transplant function. Furthermore, the transfusion risk would be disproportionately borne by women and minorities.

Several panelists asked about evidence on the effectiveness of ESA treatment on patient-reported outcomes. None of the large randomized ESA trials demonstrated any meaningful health-related quality-of-life benefits from higher hemoglobin targets. Some data were presented on meaningful benefits among dialysis patients, who exhibited marked anemia, but marginal benefits of ESA treatment, within the range of relatively milder anemia, remain unproven.

The members of the panel were unwilling to support sweeping label changes for ESA treatment of all patients with CKD. After all, TREAT studied patients with diabetes, relatively mild CKD, and mild anemia, or, as one panelist remarked, “TREAT cannot be extrapolated to all CKD.” But to address the obvious concern about the safety of these medications, “a very conservative approach is warranted . . . as close to placebo as possible.” The most immediate result of the meeting was a vote in favor of leaving physician and patient choices intact, thus maintaining individualized anemia management for patients with CKD. The unease accompanying these recommendations, however, was palpable.

REFERENCES


Risks and Benefits of Sweet Pee

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The renal reabsorption of filtered glucose is accomplished by two Na⁺-coupled carriers, SGLT1 and SGLT2, in the apical cell

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W.C.W. represented the American Society of Nephrology as delegate of the Public Policy Board on which he serves.