CORRESPONDENCE

Darbepoetin Alfa and Chronic Kidney Disease

TO THE EDITOR: Pfeffer et al. (Nov. 19 issue)[1] report on the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) (ClinicalTrials.gov number, NCT00093015), involving patients with chronic kidney disease. This trial, which sought to clarify the effects of darbepoetin alfa replacement therapy on clinical outcomes, examined the effect of darbepoetin alfa versus placebo on the composite end points of death or a cardiovascular event, and death or end-stage renal disease. The target hemoglobin level was 13 g per deciliter, and the median hemoglobin level achieved in the intervention group was 12.5 g per deciliter (interquartile range, 12.0 to 12.8), as compared with 10.6 g per deciliter (9.9 to 11.3) in the placebo group.

The normal range of hemoglobin levels is 20 to 30% higher in men than in children and women. The levels achieved in the TREAT study were in the lower quintile of the range for men but in the mid-normal range for women. We wonder, therefore, whether the significantly increased risk of stroke in the intervention group (hazard ratio, 1.92) was disproportionate among women, who accounted for 58.5% of the intervention cohort.

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No potential conflict of interest relevant to this letter was reported.

1. 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.

TO THE EDITOR: The TREAT study by Pfeffer et al. unexpectedly revealed more strokes in the patients assigned to darbepoetin alfa (5.0%) than in the patients assigned to placebo (2.6%). In the Discussion section, the authors cite a recent study,[1] indicating that erythropoietin treatment in general might be associated with more strokes. The question is, however, what type of strokes may erythropoietin induce?

The German Multicenter EPO Stroke Trial (ClinicalTrials.gov number, NCT00604630) showed an increased rate of hemorrhagic strokes after erythropoietin treatment, resulting in an increased rate of death.[1] This effect was pronounced in patients who received a combination of erythropoietin and recombinant tissue plasminogen activator (rt-PA); surprisingly, in patients who did not receive rt-PA, erythropoietin also induced more hemorrhages as compared with placebo. In light of the TREAT data, this increased rate of hemorrhage appears puzzling because one would ex-

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pect more thromboembolic events in the latter group. Unfortunately, the TREAT outcome data provide just a crude differentiation into fatal and nonfatal strokes. Information about whether the strokes of patients in the TREAT study were hemorrhagic would link those events to one of the recently discovered regenerative mechanisms of erythropoietin — angiogenesis — and it would be essential for a better risk estimation when treating with this factor.[2]

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No potential conflict of interest relevant to this letter was reported.

1. Ehrenreich H, Weissenborn K, Prange H, et al. Recombinant human erythropoietin in the treatment of acute ischemic stroke. Stroke 2009;40(12):e647-e656.
2. Minnerup J, Schäbitz WR. Multifunctional actions of approved and candidate stroke drugs. Neurotherapeutics 2009;6:43-52.

TO THE EDITOR: We take issue with the presentation and interpretation of the TREAT results. In the placebo group, the mean hemoglobin level increased gradually but consistently from 10.4 to 11.4 g per deciliter over 4 years despite worsening renal function. Without the use of darbepoetin alfa, this substantial improvement of anemia is probably due to 30% more administration of intravenous iron in the placebo group. Insufficient iron therapy despite high doses of darbepoetin alfa may have led to iron depletion and reactive thrombocytosis.[1] In a recent study involving 40,787 patients undergoing hemodialysis, a higher platelet count (>300,000 per cubic millimeter) was associated with a higher prescribed erythropoietin dose and lower iron stores, and a hemoglobin level of 13 g per deciliter or greater was associated with an increased rate of death only in the presence of relative thrombocytosis.[2] Erythropoiesis-stimulating agents (ESAs) are known to increase the platelet count.[3,4] In the TREAT study, iron depletion and associated thrombocytosis and enhanced platelet function might have contributed to an increased risk of stroke in the darbepoetin alfa group and masked the potential benefits of higher hemoglobin concentrations. The normalization of hemoglobin levels with adequate iron repletion without excessive doses of ESAs warrants further investigation.

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Dr. Kalantar-Zadeh reports receiving consulting fees from manufacturers or distributors of intravenous iron products (Feraheme, Amag; Venofer, Fresenius Medical Care; and Ferrlecict and Infed, Watson). No other potential conflict of interest relevant to this letter was reported.

1. Hampl H, Riedel E. Cardiac disease in the dialysis patient: good, better, best clinical practice. Blood Purif 2009;27:99-113.
2. Streja E, Kovesdy CP, Greenland S, et al. Erythropoietin, iron depletion, and relative thrombocytosis: a possible explanation for hemoglobin-survival paradox in hemodialysis. Am J Kidney Dis 2008;52:727-36.
3. Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease: results of a phase III multicenter clinical trial. Ann Intern Med 1989;111:992-1000.
4. Vaziri ND. Thromobocytosis in EPO-treated dialysis patients may be mediated by EPO rather than iron deficiency. Am J Kidney Dis 2009;53:733-6.

TO THE EDITOR: The TREAT study showed a neutral effect in aiming at a hemoglobin level of 13 g per deciliter as compared with a rescue value of 9 g per deciliter in the primary end point in patients with chronic kidney disease and type 2 diabetes. The group with high levels of hemoglobin had more strokes and deaths related to cancer and mild improvement in quality of life. Should we stop treating our patients?

Despite a rescue value of 9 g per deciliter, strangely enough, the achieved values progressively increased in the control group. This result could be because iron administration was not controlled by the protocol and more patients in the control group than in the experimental group received intravenous iron and transfusions. Nearly half these patients received darbepoetin alfa (the mean dose was not reported); this cannot be considered true "placebo."

Finally, given that the mean achieved hemoglobin level in the control group (10.6 g per deciliter) was in the range suggested by the Food and Drug Administration[1] and similar to mean values

of registry data, there is no evidence that we should stop treating anemia.

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1. FDA strengthens boxed warnings, approves other safety labeling changes for erythropoiesis-stimulating agents. Silver Spring, MD: Food and Drug Administration, November 8, 2007. (Accessed January 28, 2010, at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109024.htm.)

THE AUTHORS REPLY: We acknowledge the comment by Wright et al. that since women have lower normal hemoglobin values than men, targeting the same hemoglobin level could be considered relatively more intense for female patients. In reply to their requested analysis of the treatment: the sex interaction for stroke was not significant (P=0.21). The similar hazard ratios for women and men in the primary composite cardiovascular and renal outcomes in our trial also provide support for the lack of a differential influence of darbepoetin alfa according to sex.

In response to Minnerup and Schäbitz: in the TREAT study, nonhemorrhagic strokes were most common. Among the 101 strokes that occurred in patients in the darbepoetin alfa group, 74 were categorized as nonhemorrhagic, 13 were categorized as hemorrhagic, and 14 were unknown, whereas in the 53 strokes that occurred in patients assigned to placebo, 38 were categorized as nonhemorrhagic, 8 were categorized as hemorrhagic, and 7 were unknown. We cited the German trial of erythropoietin during acute ischemic stroke to highlight another disappointing recent finding with these compounds.[1]

Regarding the comments of Hampl et al.: aside from the protocol-directed use of darbepoetin alfa, clinical care of the patients was individually managed by their physicians. Patients who were selected on a clinical basis for intravenous iron tended to have lower hemoglobin values throughout the study and, although highly confounded, more adverse cardiovascular and renal events. We agree that other strategies of addressing anemia warrant further investigation and underscore the importance of rigorous, double-blind, placebo-controlled clinical-event trials.

Locatelli and colleagues also raise concerns about the uneven clinical use of intravenous iron and red-cell transfusions after randomization. Consistent with clinical practice, the patients who received these additional treatments for anemia had lower hemoglobin levels during the trial. The intermittent treatment of patients in the placebo group for hemoglobin values of less than 9 g per deciliter resulted in a mean dose of 5±11 μg in the placebo group and 225±208 μg in the darbepoetin alfa group.

The most clinically relevant and important question posed was "Should we stop treating our patients?" Clearly, treatment decisions must be individualized. However, in this patient population, for this therapy that is not superior to placebo and is associated with risks, we respond: Why treat?

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Since publication of their article, the authors report no further potential conflict of interest.

1. Ehrenreich H, Weissenborn K, Prange H, et al. Recombinant human erythropoietin in the treatment of acute ischemic stroke. Stroke 2009;40(12):e647-e656.

Vaccination against HPV-16 for Vulvar Intraepithelial Neoplasia

TO THE EDITOR: In the study by Kenter et al. (Nov. 5 issue)[1] regarding vaccination for the treatment of grade 3 vulvar intraepithelial neoplasia caused by type 16 human papillomavirus (HPV-16), it would have been interesting if the investigators had included a placebo group. The authors state that the rate of spontaneous regression of such lesions is low, around 1.5%. These lesions include those associated with both Bowen's disease and bowenoid papulosis. In Bowen's disease, sponta-