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Original Investigation

Hemoglobin Stability in Patients With Anemia, CKD, and Type 2 Diabetes: An Analysis of the TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy) Placebo Arm

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Background: Sparse data are available about the natural history of hemoglobin (Hb) level trends in contemporary patients with anemia, chronic kidney disease (CKD), and type 2 diabetes mellitus. We intended to describe Hb level trends over time with no or minimal administration of erythropoiesis-stimulating agents.

Study Design: Prospective clinical trial cohort.

Setting & Participants: 2,019 individuals with type 2 diabetes, moderate anemia, and CKD from the placebo arm of the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) followed up for 2.3 years with an average of 32 monthly Hb level determinations per patient. Darbepoetin alfa was administered only if Hb level decreased to <9 g/dL.

Outcomes & Measurements: Number of protocol-directed doses of darbepoetin alfa received due to an Hb level decrease to <9 g/dL.

Results: 1,106 (55%) placebo patients consistently maintained an Hb level ≥9 g/dL and received no protocol-directed darbepoetin alfa. The other patients received 1 (16%), 2-4 (16%), or 5 or more (13%) doses of darbepoetin alfa. Those who received no darbepoetin alfa doses had higher baseline Hb levels, higher estimated glomerular filtration rates (eGFRs), less proteinuria, and lower ferritin and transferrin saturation values. On average, Hb levels were stable or increased in all groups. Compared with individuals who received no darbepoetin alfa, those who received 5 or more doses were more likely to receive intravenous iron therapy and blood transfusions and progress to renal replacement therapy, but were not at higher risk of death. The strongest predictors of requiring 5 or more doses of darbepoetin alfa were lower baseline Hb level, lower eGFR, and higher proteinuria level.

Limitations: Post hoc analysis of a clinical trial of a specific population with diabetes, anemia, and non–dialysis-dependent CKD.

Conclusions: In the TREAT placebo arm, Hb levels were stable with no or minimal protocol-directed darbepoetin alfa during 2.3 years of follow-up. Most patients with moderate anemia, non–dialysis-dependent CKD, and type 2 diabetes are able to maintain a stable Hb level without implementing long-term erythropoiesis-stimulating agent therapy.

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Editorial, p. 191

Despite the lack of strong evidence that anemia correction yields mortality or morbidity benefits,[1] erythropoiesis-stimulating agents (ESAs) have been a mainstay of anemia management as a way to decrease transfusion requirements and improve quality of life in patients with chronic kidney disease (CKD) undergoing dialysis.[2-4] These generally accepted beneficial aspects of ESAs in dialysis patients led to their use in the broader population of individu-

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als with non–dialysis-dependent CKD and milder anemia. However, randomized controlled trials completed in the last 6 years failed to report clinical mortality or morbidity benefits with higher hemoglobin (Hb) target levels compared with lower targets[5-7] or even placebo.[8,9]

Currently, the US Food and Drug Administration[10] recommends consideration for starting ESA therapy only when Hb level is <10 g/dL and interruption or reduction of ESA dose if Hb level is >10 g/dL in patients with non–dialysis-dependent CKD. These recommendations stemmed from the unfavorable responses to ESAs observed with higher Hb levels and are aimed at balancing the potential benefits of decreasing red blood cell transfusions against the heightened risk of cardiovascular events with ESA therapy. However, there is a paucity of data regarding the natural history of Hb level trends over time in anemic patients with CKD without an intervention.

The Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) is the only large placebo-controlled outcomes trial that assessed the effect of darbepoetin alfa in patients with moderate anemia and non–dialysis-dependent CKD. The study showed no decrease in risk of cardiovascular or renal events or death in patients treated with darbepoetin alfa compared with placebo[8] and reported a nearly 2-fold increased risk of stroke in those assigned to darbepoetin alfa therapy.[11] The inclusion of a placebo arm with protocol-directed ESA administration only when Hb level decreased to <9.0 g/dL offers the opportunity to study Hb level stability in patients assigned to the placebo arm who received no or minimal ESA therapy. Our aim was to identify factors associated with maintaining Hb levels at >9 g/dL and, conversely, factors associated with more frequent Hb level decreases and darbepoetin alfa administration, as well as describe observed clinical events according to Hb level stability. By reporting the natural progression of Hb levels in a large cohort of patients with diabetes, CKD, and anemia receiving no or minimal ESA therapy, our aim was to assist clinicians and their patients in decisions regarding ESA therapy initiation and Hb level monitoring.

METHODS

The design and results of TREAT (ClinicalTrials.gov identifier NCT00093015) have been reported previously.[8,12,13] Briefly, TREAT was a randomized double-blind placebo-controlled trial that enrolled patients with type 2 diabetes, non–dialysis-dependent CKD (estimated glomerular filtration rate [eGFR] of 20-60 mL/min/1.73 m^2), moderate anemia (Hb ≤11.0 g/dL), and transferrin saturation (TSAT) ≥15%. ESA administration within the prior 12 weeks of screening was an exclusion criterion.

Patients were randomly assigned to receive either darbepoetin alfa (Aranesp; Amgen) or placebo in a one-to-one ratio. Randomization was stratified according to study site, baseline presence of marked proteinuria (>1 mg/dL of protein per 1 mg/dL of creatinine in a spot urine sample), and history of cardiovascular disease. Darbepoetin alfa was supplied in prefilled syringes with matching placebo. In the active arm, the initial dose of darbepoetin alfa was 0.75 μg/kg rounded to the nearest prefilled syringe concentration, with this dose repeated after 2 weeks if Hb values did not exceed 14.0 g/dL. After randomization, a point-of-care device was used to monitor Hb levels and a computer algorithm was used to assign subsequent doses (after 1 month), with the aim of achieving and maintaining Hb level at ~13.0 g/dL. Hb measurement was performed every 2 weeks during the study drug titration period and monthly thereafter.[8,14]

To maintain the double-blinding process, an interactive voice-response system determined the vehicle dose to be administered based on a blinded Hb level obtained through a third-party point-of-care device. If an Hb level decreased to <9 g/dL at any point during follow-up (not requiring confirmation), darbepoetin alfa was given at an initial dose of 0.45 μg/kg. Placebo participants who received darbepoetin alfa because Hb level decreased to <9 g/dL could not receive more than one monthly dose before their achieved Hb level and rate of increase were determined at the following visit[8,13] (Table 1). Administration of placebo vehicle was resumed if Hb level reached ≥9 g/dL. For this study, we performed an analysis of the 2,019 placebo-arm–assigned participants in TREAT who received at least one dose of placebo vehicle. The 9-g/dL cutoff for administration of protocol-directed darbepoetin alfa was selected prospectively to balance between perceived concerns for safety and statistical feasibility.[13] Investigators were encouraged to administer iron according to standard clinical care reflected in a provided algorithm to ensure that participants were iron replete as defined as TSAT >20% or ferritin level >300 μg/L (Item S1, available as online supplementary material).

On average, 32 Hb level determinations per patient were performed by the HemoCue B-hemoglobin Photometer (HemoCue, Inc, Cypress, CA) at monthly intervals during a mean follow-up of 2.4 years. HemoCue performance parameters include a reportable range of 0-23.5 g/dL, within-run precision of 1.6% (Hb range, 10.1-12.0 g/dL), and between-day precision of 1.2% (Hb range,

Table 1. Algorithm for Darbepoetin alfa Rescue in TREAT Placebo Participants

Hb (g/dL)	Hb Rate of Increase (g/dL per 2 wk)	Dose Adjustment
<9.0	<0.5	Initiate or increase to next higher prefilled syringe[a]
<9.0	≥0.5 but <1.0	Maintain dose
<9.0	≥1.0	Decrease to next lower prefilled syringe[a]
≥9.0	Any	Resume placebo administration

Note: If Hb level was <9.0 g/dL at any time for placebo participants, therapy with darbepoetin alfa was instituted with a single dose of 0.45 μg/kg rounded to the nearest prefilled syringe. At the next monthly visit, if Hb level was <9.0 g/dL, an additional dose of darbepoetin alfa was administered as above. This process continued until Hb level was >9.0 g/dL, at which time placebo injections were resumed.

Abbreviations: Hb, hemoglobin; TREAT, Trial to Reduce Cardiovascular Events With Aranesp Therapy.

[a]Darbepoetin alfa was given in prefilled syringes with the following concentrations: 10, 15, 20, 30, 40, 50, 60, 80, 100, 150, 200, and 300 μg. Initial dose any time Hb level decreased to <9 g/dL was 45 μg/kg.