

The future of intravenous iron in nephrology

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Abstract

Management of anaemia in chronic kidney disease (CKD) patients can be difficult and expensive. The recently completed Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), the largest double-blinded trial of erythropoiesis-stimulating agents (ESA) treatment in CKD to date, provides us with a wealth of new information on the natural history of anaemia in Stage 3 and 4 CKD and the risks and benefits of use of ESAs. This section will discuss some of the TREAT trial results in the context of other recent studies of ESAs and intravenous iron in CKD patients. It will also review applying those results when choosing anaemia goals for an individual, and determining if iron therapy might improve anaemia.

Keywords: Iron; anemia; chronic kidney disease; epoetin; stroke; transfusion

The primary result of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trial is that an increase in median haemoglobin (Hgb) with darbepoetin from 10.4 to 12.5 g/dL in type II diabetics resulted in no reduction in cardiovascular (CV) events or mortality compared to placebo treatment [1]. This study disproves the hypothesis that raising Hgb towards the normal range reduces CV risks. This conclusion is consistent with results from three previous large studies testing this hypothesis or the surrogate of left ventricular regression in haemodialysis and chronic kidney disease (CKD) patients [2–6].

The TREAT trial also showed harm from routine use of erythropoiesis-stimulating agent (ESA) therapy with the risk of stroke almost doubling, and a disturbing association of ESA use with cancer recurrence and progression [1]. Recently, Solomon and others reported in TREAT that there is an increased risk of CV events and deaths among those with a poor haematologic response to ESA initiation compared to others receiving ESA or placebo-treated patients [7]. Among patients responding well to ESA initiation, there was no reduction in the risk of CV events and death compared to placebo, disproving again the hypothesis that higher haemoglobin would be protective [7]. In contrast to CV events and deaths, stroke risk is increased

in the ESA-treated patients regardless of the initial response to ESA [7]. This suggests that use of ESA regardless of Hgb target likely increases the risk of stroke in patients [8].

The earlier Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial of higher vs lower Hgb targets found higher ESA doses correlated with increased CV events and death, while the Normal Hematocrit Cardiac Trial found highest cumulative ESA dose related to increased risk of death [2,3,9]. Many experts believe that some risks of ESA are related to the dose rather than targeted or achieved Hgb.

Many experts encouraged to wait for the TREAT trial results before altering Hgb target in CKD and dialysis [10,11], while others counselled to adopt lower Hgb targets based on the results of earlier trials [9,12–14]. With these cumulative trial results, there is some justification in concluding that we did have the target Hgb ‘wrong for years’ for many patients, and provided marginal benefits with measurable harm at unnecessary high costs [11,12].

Several trials indicate that an Hgb target in the range of 9–11 g/dL is safer than higher targets [1–3,5]. We can now feel confident that accepting a lower Hgb target is not increasing CV events or deaths. Yet, most of these trials found a reduction in the proportion of patients transfused when higher Hgb targets were chosen [1,2,15]. Transfusions can result in adverse reactions and carry a low risk of virus transmission. In the critically ill, use of ESAs to reduce adverse reactions or virus transmissions from transfusions has been found to be prohibitively expensive [16], but similar analyses in using data from CKD patients are lacking. Additionally, repeated transfusions may sensitize patients, making organ transplantation more difficult. Most CKD and dialysis patients are not candidates for transplants, but among those who are, maintaining a somewhat higher Hgb may be worth the cost and risks, though studies are needed to prove this.

Based on the above, I believe that we should use the lowest ESA doses possible and choose a target Hgb that takes into account the patient’s potential harm from transfusion [13]. In transplant-eligible patients, that means initiating ESA therapy earlier to maintain an Hgb of 11–12 g/dL. For all other patients, I try to defer ESA therapy and accept lower Hgb levels as sufficiently beneficial. Patients should

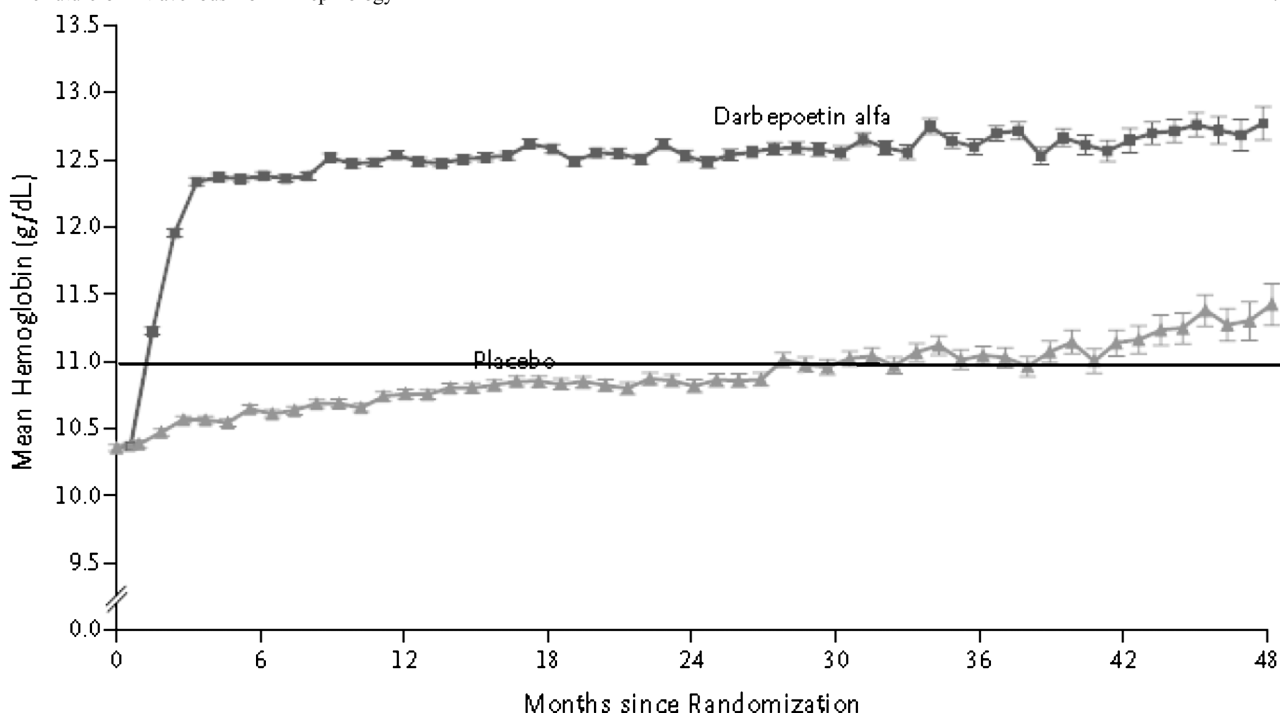


Fig. 1. Mean haemoglobin levels through 48 months among patients who were assigned to receive darbepoetin alfa or placebo [1].

be apprised of the risks and benefits of ESAs, and make the final decision on management goals [8].

The other major findings of the TREAT trial are in the placebo or ‘don’t treat’ arm [1]. All patients entered the trial with a baseline Hgb of 9–11 g/dL and were not receiving ESA therapy. Patients randomized to placebo received saline injections regularly, but were given darbepoetin ‘salvage’ whenever the monthly Hgb fell below 9 g/dL. Once Hgb rose to above 9 g/dL, injections were reverted to placebo [1].

Despite the expectation, anaemia would worsen in the placebo arm over time, the mean Hgb progressively increased from 10.4 g/dL at randomization to 11 g/dL at 30 months, and 11.4 g/dL at 48 months (Figure 1) [1]. ESA salvage therapy does not appear to account for most of the Hgb improvement over time, as more than half of placebo randomized patients never received ESA therapy and just 25% received 5 µg or more per month of darbepoetin during the trial. Use of iron is believed to account for some of the Hgb improvement however. About two-thirds of patients received oral iron, and 20% received IV iron at some point in the trial [1].

The baseline ferritin and transferrin saturation (TSAT) data in TREAT are similar to data from a recent study of iron stores and iron responsiveness in anaemic CKD patients by Stancu and colleagues (Table 1) [1,17]. Stancu assessed bone marrow iron stores in 100 anaemic non-dialysis CKD patients who had not received previous IV iron or ESA therapy. Stancu found that 48% of patients were iron deficient by bone marrow assessment. Neither a ferritin nor TSAT could adequately predict which patients had absent iron stores [17].

Stancu also treated all 100 CKD patients with 1 g of IV iron regardless of bone marrow iron status. The Hgb increased 1 g/dL or more in 63% of the iron-deficient patients and 30% of iron-replete patients [17]. Again, ferritin and TSAT—or even a combination of those tests—could not adequately predict who would respond to IV iron [18]. The authors concluded that 1 g of IV iron was a useful diagnostic and therapeutic test in anaemic CKD patients [17].

In comparing the ferritin and TSAT results from Stancu to TREAT (Table 1), it appears likely that many patients in TREAT were overtly iron deficient. Additionally, the high response rate of anaemic CKD patients to iron observed by Stancu may explain the steady improvement of anaemia in the placebo arm of TREAT, as there was heavy use of oral iron and occasional use of IV iron in the placebo arm [1,17].

Thus, the TREAT trial results paired with Stancu trial results contradict many preconceptions about anaemia in CKD. The natural history of anaemia in CKD is not inexorably worsening. Iron deficiency is far more common in CKD than previously thought and plays a major role in the severity of the anaemia. Ferritin and TSAT are helpful

Table 1. Baseline ferritin and TSAT in TREAT Trial [1] and study by Stancu *et al.* [17]

Baseline data	Trial	Median	Interquartile range
Ferritin (ng/mL)	Stancu <i>et al.</i>	176	79–300
Ferritin (ng/mL)	TREAT trial	134	67–258
TSAT (%)	Stancu <i>et al.</i>	23	13–30
TSAT (%)	TREAT trial	23	18–29

when low, but cannot discriminate between responders and non-responders to iron therapy when tests results are higher. Lastly, treatment with iron can raise Hgb and delay or defer ESA requirements.

The choice of a lower Hgb target is the most effective way to reduce ESA doses. The second most effective way appears to be to administer iron. As demonstrated by Stancu and others in CKD patients, IV iron therapy can significantly increase Hgb in anaemic patients with Stage 3 or 4 CKD [17,19]. Oral iron therapy can be effective in these patients also, though prolonged treatment may be required [19]. In haemodialysis patients, oral iron has been shown to be ineffective, while IV iron can be quite effective even when ferritin is relatively elevated [20–22].

In 2006, KDOQI released practice recommendations which stated ‘When serum ferritin is >500 ng/mL, decisions about IV iron treatment should weigh factors such as patient’s clinical status, ESA dose/responsiveness, Hb level and iron indices’ [23].

Some interpreted this practice recommendation to mean that IV iron should be stopped whenever ferritin exceeded 500 ng/mL, although we lack trial data or observational data supporting that this was an efficacy or safety breakpoint. Also, well known to laboratory medicine experts but not nephrologists, ferritin values vary considerably among assay methods, and there is large short-term intra-patient variability of serum ferritin. Our group found when one method reported a ferritin of 500 ng/mL, two other methods reported 439 ng/mL and another method reported 632 ng/mL [24]. Higher ferritin values led to even greater discrepancies among assays [24].

When our group measured ferritin using a single assay repeatedly over 6 weeks in stable haemodialysis patients, individuals had substantial variation in values. To be 95% confident that a clinical change in ferritin had occurred (as opposed to laboratory and biologic variability), a ferritin value must change by at least 32% [24].

Most importantly, the practice recommendation does not say to halt iron when ferritin is >500 ng/mL. As high ferritin lacks predictive value to exclude a response to IV iron, the guidance recommends examining other factors such as the dose of ESA and severity of anaemia [25]. This recommendation was confirmed by the subsequent DRIVE trial which randomized anaemic haemodialysis patients on high ESA doses with high ferritin values (500–1200 ng/mL) to 1 g of IV iron or no iron [21].

In the DRIVE trial, over the first 6 weeks when the ESA dose was fixed, IV iron led to significantly greater increase in Hgb [21]. Over the next 6 weeks, when ESA doses could be altered and discretionary iron administered, the IV iron group required significantly less ESA and had a higher mean Hgb than the no iron group [26]. In a post hoc analysis, over the 12 weeks of monitoring, those randomized to IV iron had significantly fewer serious adverse events than those randomized to no iron (33% vs 58%; $P = 0.041$) [26]. Additionally, among the no iron group, those who never received iron during the 12 weeks had more serious adverse events than those given discretionary IV iron during the final 6 weeks. A formal pharmacoeconomic analysis of the DRIVE trial results indicate a dra-

matic cost savings when treating such patients with IV iron and ESA rather than ESA alone [27].

Serum ferritin can be valuable in guiding decisions concerning use of IV iron. In patients with CKD Stage 3 and 4, a low ferritin (<100 ng/mL) usually indicates low iron stores [23]. A higher ferritin lacks predictive value, and physicians should use clinical judgement on whether to give IV or oral iron [17]. In this population, IV iron can raise Hgb, delay or prevent the need for ESA therapy, or lower ESA doses [17,20]. In patients on dialysis, a low ferritin (<200 ng/mL) usually indicates low iron stores, while a higher ferritin lacks predictive value [23]. Clinical judgement should be used on whether to give IV iron, as oral iron in this population has not been proven efficacious. Over a broad range of ferritin values, IV iron can raise Hgb, lower ESA dose requirements and lower costs [21,26–29].

Conflict of interest statement. D.W.C. is a consultant and speaker for Pharmacosmos, Abbott, Sanofi Aventis and Watson, is a consultant for INEOS and Shire, and PI in multicentre studies designed and funded by Abbott, Amgen.

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