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# Iron treatment and the TREAT trial

Francesco Locatelli

Department of Nephrology, Dialysis and Renal Transplant "Alessandro Manzoni" Hospital, Lecco, Italy

*Correspondence and offprint requests to*: Francesco Locatelli; E-mail: nefrologia@ospedale.lecco.it

**Abstract**

Treatment with erythropoiesis-stimulating agents (ESAs) enables the correction of anaemia in chronic kidney disease (CKD) patients, thus reducing its symptoms and complications. Not only is iron therapy aimed at correcting iron deficiency, but also it is an adjuvant therapy in CKD patients receiving ESAs. Iron stores in CKD patients may be near normal, but there may be insufficient immediately available iron to optimize ESA therapy. In this context, iron therapy significantly reduces ESA dose requirements. Erythropoiesis following ESA therapy may precipitate iron deficiency in association with increased platelet production. In the TREAT trial, the 'placebo group' did not receive a true 'placebo' since 46% of the patients had at least one dose of ESA and achieved progressively increased haemoglobin (Hb) values during follow-up against the common observation. The patients in the 'placebo' group were treated more frequently with intravenous iron than the darbepoetin group. Given that many patients were relatively iron deficient at baseline, iron administration was successful in many of them in obtaining and maintaining partial anaemia correction without the need for ESAs, thus underlining the great importance of iron supplementation in correcting anaemia. The upper safety limit for iron administered to patients in order to minimize, as much as possible, the ESA dose and the upper limit for ESA dosage for maintaining the target Hb range as suggested by the current guidelines are still open questions.

**Keywords:** anaemia; CKD; ESA; iron therapy; TREAT trial

## Anaemia response to erythropoiesis-stimulating agents

Anaemia develops early in the course of chronic kidney disease (CKD) and affects a large percentage of CKD patients; treatment with erythropoiesis-stimulating agents (ESAs) enables the correction of anaemia, thus reducing its symptoms and complications. ESA therapy should be given to treat anaemia in all CKD patients with a haemoglobin (Hb) level persistently below 11 g/dL, from patients in the early stages of CKD to those receiving renal replacement therapy [1,2] after having ruled out all other causes of anaemia. Dose requirements in achieving anaemia correction are quite variable and poorly predictable in the individual patient. However, a number of patients need a greater than usual ESA dose and are defined as hyporesponsives. According to the European Best Practice Guidelines (EBPG) [1], resistance to ESA treatment is defined as a continued need for >20 000 IU/week (300 IU/kg/week) of rHuEPO administered subcutaneously or 1.5 μg/kg of darbepoetin alfa (>100 μg/week); this means that resistant patients require more than 2.5 times the average ESA dose.

The most common cause of incomplete response to ESAs is absolute or functional iron deficiency. According to an Italian cross-sectional study [3], 16% of patients had a transferrin saturation of <15%, which is considerably below that recommended in the EBPG and in the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [1,2]. Angiotensin II-converting enzyme inhibitors and angiotensin II receptor blockers, often used in CKD patients for controlling hypertension and possibly slowing down the progression of CKD, may also play a role. However, compliance should always be checked in patients self-administering an ESA.

## Iron status

Iron status should be checked every 1–3 months according to clinical needs [1,2]. This information should be evaluated together with Hb levels, ESA doses and their trend over time, in order to elucidate the status of both external (gain or losses) and internal iron balance (distribution of iron in stores and erythrocytes) [2].

More widely used iron tests are serum ferritin and transferrin saturation (TSAT) levels. However, these are not optimal tests, as they lack accuracy and stability. Indeed, they are greatly influenced by inflammation and malnutrition, two conditions often affecting CKD patients.

An ideal marker of functional iron deficiency should be independent of erythropoietic activity. New cell counters are able to determine cell volume and Hb concentration separately on reticulocytes and mature erythrocytes.

Evidence for iron target in CKD patients not on dialysis is poor; a target of 100–500 ng/mL[2] for serum ferritin levels should be adequate to ensure effective erythropoiesis with ESA treatment.

## Iron administration

The preferred route of iron administration in haemodialysis patients is intravenous (IV); in PD and CKD patients not on dialysis, it can be either IV or oral [1,2].

Oral iron is best absorbed when given without food; constipation, diarrhoea, nausea or abdominal pain limits compliance.

In CKD patients, not only is iron therapy aimed at correcting iron deficiency, but it is also an adjuvant therapy in patients receiving ESAs, to achieve and maintain the Hb target. In these patients, iron stores may be near normal, but during ESA treatment, there may be insufficient immediately available iron to optimize ESA therapy. In this context, iron therapy significantly reduces ESA dose requirements.

## Iron, ESA and Hb target

One of the hot topics in nephrology recently is the Hb target from treatment with ESAs and/or iron therapy. Given that cardiovascular morbidity and mortality are a major concern in CKD patients and lower Hb levels have been associated with poor outcomes, the most important trials in the field have been designed mainly focusing on this primary end point.

The hypothesis that complete anaemia correction with ESAs would reduce the risk of death, cardiovascular and renal end points among patients with type 2 diabetes and CKD not undergoing dialysis was the rationale of the last trial in the field, the Trial to Reduce cardiovascular Events with Aranesp® Therapy (TREAT) [4]. More than 4000 patients were randomized to darbepoetin alfa to achieve an Hb level of 13 g/dL or to placebo (with rescue darbepoetin alfa for Hb level <9.0 g/dL).

## Criticisms of the TREAT trial

The TREAT trial is the best trial in the field of anaemia published to date. However, at the early stages of the study, many criticisms were made regarding its design, either due to ethical issues (a much lower Hb value than recommended by guidelines was allowed in the control group) or because it was considered of little informative use (the comparison did not take into account the 'gold standard' of treatment, i.e. partial anaemia correction according to current guidelines (Hb 11–12 g/dL)) [1–3,5].

This study clearly demonstrated that the use of darbepoetin alfa in aiming at an Hb target of 13 g/dL in type 2 diabetic patients not undergoing dialysis does not reduce the risk of the two primary composite outcomes. Besides, secondary analyses showed a higher risk of strokes mainly in patients with a history of strokes and death due to cancer in patients with a history of malignancies, and venous and arterial thromboembolic events in patients randomized to the higher Hb target, associated with a significant reduction in cardiac revascularization procedures, number of transfusions and a mild improvement in quality of life.

The interpretation of the TREAT results is complex [6]. The simplest explanation is that higher Hb levels are the cause of increased occurrence of strokes through an increase of blood viscosity and perhaps blood pressure (median diastolic blood pressure was slightly higher in the darbepoetin alfa group). However, in the Normal Hematocrit Study [7] and in the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial [8], higher achieved Hb levels were associated with fewer cardiovascular events in each study arm. This leads to the hypothesis that the lower the dose of ESAs, the better the outcome [7]. However, the selection bias of survivors may have a role: patients achieving higher Hb concentrations may be healthier and thus more responsive to treatment. A secondary analysis of the CHOIR study [9] clearly pointed out that high ESA doses may be related to increased cardiovascular events not related to high Hb levels. The link between high ESA dose and negative outcomes may be simply explained by the fact that patients with more comorbidities or those who are more inflamed are hyporesponsive to ESA treatment. High ESA dose may stimulate EPO receptors other than those controlling erythropoiesis. This could exacerbate some pleiotropic effects of ESAs on endothelial and muscular cells. ESAs cause thrombocytosis in those patients who are iron deficient. Erythropoiesis following ESA therapy may precipitate iron deficiency. This has been associated with increased platelet production and thus increased thrombotic risk. Therefore, high ESA dosage could cause cardiovascular events not only through high Hb levels.

However, we should not misinterpret the association data for ESA doses. Using higher ESA dosage for achieving the same Hb levels (or even not achieving it) is a marker of comorbidities (inflamed patients reach lower Hb levels despite higher ESA dosages).

In the TREAT study, the median monthly darbepoetin dose in the group randomized to darbepoetin and higher Hb level was rather high (176 μg; interquartile range, 104–305) compared to that used in everyday clinical practice in patients not on dialysis. The fact that the drug was administered once a month in the majority of the patients and above all some of them were not fully iron-replete may have contributed to this high dose requirement. In fact, patients with a transferrin saturation of even 15% were eligible for enrolment, and transferrin saturation and ferritin levels were measured quarterly; moreover, there was no protocol for iron administration, and only 43% of the patients received iron at baseline and 66.8% (14.8% IV) in the darbepoetin alfa group and 68.6% (20.4% IV) in the placebo group, during the follow-up trial.

## Are we going to change the way we treat our patients?

In my opinion, important limitations inherent to the study design reduce the general applicability of TREAT results

and do not support substantial changes in the way we manage anaemia in our patients.

Literally, reading the intention-to-treat analysis of the TREAT, one could draw the misleading conclusion that we should treat CKD patients with ESA only if they have an Hb level below 9 g/dL that cannot be managed with blood transfusions [10]. This is further supported by the results of the secondary analyses (lower risk of stroke, thromboembolic events and death from malignancies in the 'placebo group' with lower Hb target range). Conversely, much less emphasis has been put on other secondary outcomes, i.e. a lower risk of transfusions and cardiac revascularization and a better quality of life in the patients randomized to the darbepoetin alfa and higher Hb level.

Moreover, the 'placebo group' did not receive a true 'placebo' since 46% of the patients had at least one dose of ESA [10]. Even more importantly, despite a rescue value of 9 g/dL, achieved Hb values progressively increased during follow-up (from a median value of 10.4 g/dL at baseline to 11.2 g/dL at the end of the study, with a median value of 10.6 g/dL during follow-up). These achieved values are very close to the target range suggested by current guidelines [1–3,5]. This positive trend is against the common observation that CKD patients show a decrease in Hb values during the course of their disease, and this makes it hard for us to accept the TREAT study as a 'placebo' randomized controlled trial [10]. In addition to rescue treatment with darbepoetin alfa, the patients in the 'placebo' group were treated more frequently with IV iron (and blood transfusions) than the darbepoetin group. Given that many patients were relatively iron deficient at baseline, iron administration had been successful in many of them in obtaining and maintaining partial anaemia correction without the need for ESAs. However, transfusions cannot be considered as an alternative treatment for anaemia, and iron alone is not enough in the later stages of CKD, as strongly demonstrated by the pre-ESA era experience [11].

## Conclusions

The findings of the TREAT study underline the great importance of iron supplementation in correcting anaemia, although this should be a well-established approach in everyday clinical practice and has already been clearly indicated by current guidelines [1–3,5]. The risk–benefit of more transfusions should also be considered carefully, especially for patients who are potential candidates for transplantation.

Finally, the upper safety limit for iron administered to patients in order to minimize, as much as possible, the ESA dose and the upper limit for ESA dosage for maintaining the target Hb range as suggested by the current guidelines are still open questions. Large prospective randomized trials are welcome for clarifying this very important clinical issue.

*Conflict of interest statement.* F.L. was vice-chairman of the steering committee and an author of the CREATE study. He was a Country Principal Investigator of the TREAT study and a liaison member of anaemia KDOQI guideline group, chairman of anaemia EBPG group, and a member of the executive board of directors of KDIGO. He is a member of the ERBP group, of an advisory board of Affymax, Amgen-Dompé, Gsk, Janssen Roche and Takeda, and of a safety committee of Sandoz.

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