Debate: CON Position

Should Hemoglobin Targets for Anemic Patients with Chronic Kidney Disease Be Changed?

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The results of the TREAT study have been warmly awaited from the nephrological community as the last most important piece of the puzzle in defining optimal hemoglobin (Hb) target to aim for with erythropoiesis-stimulating agents (ESAs). In support of this, the next global clinical practice guidelines on anemia in CKD patients, under the aegis of Kidney Disease Improving Global Outcomes (KDIGO), have been planned after the evidence coming from this study [1].

Do we believe that the findings of the TREAT study will substantially change the way we correct anemia in CKD patients? In our opinion, not substantially, and there are several reasons for this. The first reason is that we should never forget where we come from. Medicine is a fast evolving branch: what seems obvious today was completely different two decades ago. Younger doctors did not experience the era preceding the introduction of recombinant human erythropoietin and have no idea how CKD patients felt those days. Despite being younger and having much less comorbidities, the majority of uremic patients were only ‘survivors’, experiencing shortness of breath even after short walking. Anemia was only slightly and temporary improved by giving iron, frequent blood transfusions (with the risk of infections and iron overload) or even high-risk androgen hormones. The availability of ESAs has completely revolutionized the management of anemia. Doctors living those days do not

want to see CKD patients suffering that way anymore in the name of over-interpretation of ‘evidence-based medicine’ or of ‘p values’ used in a wrong way.

The association between anemia and negative outcome is consistent but overemphasized. Analysis of registry data found an inverse relationship between Hb levels and mortality. This was confirmed by data from the Dialysis Outcomes and Practice Patterns Study (DOPPS), a large prospective observational study involving patients randomly selected from representative dialysis facilities worldwide [2].

From these findings, the hypothesis was generated that complete anemia correction with ESAs could improve patient outcome. However, these studies included a small percentage of subjects with high Hb/hematocrit levels. Data that is more recent indicates that the relationship between anemia and mortality may be not linear, but U-shaped. Anyways, data coming from observational studies should only be considered as hypothesis-generating. This is also so because they only considered achieved Hb levels, while paying little attention, if any, to the ESA doses.

Additionally, partial anemia correction improves or prevents left ventricular hypertrophy. Small, mainly uncontrolled studies showed partial regression of left ventricular hypertrophy after anemia correction. According to a very recent meta-analysis, anemia correction with

ESA was linked to a significant reduction in the left ventricular mass index among patients with severe anemia at baseline [3]. In patients with moderate anemia at baseline, including many with left ventricular mass index values in the normal range, anemia correction did not lead to a significant reduction of the mean values of the left ventricular mass index (let me say that it is very difficult to normalize what is already normal!), although it prevented a possible development of left ventricular hypertrophy.

Early trials compared ESA to placebo in severe anemic patients. According to a meta-analysis, treatment with ESA did not significantly reduce the risk of death or myocardial infarction compared to placebo [4]. However, these trials had been designed to test the safety of ESA or the need for blood transfusions and not mortality. Given their short follow-up, they were inadequate to test the effect of treatment on hard end points. Thus, we should look critically to meta-analysis results where the primary end point is different from the end points of the included trials.

Later on, clinical trials compared two Hb targets with ESA treatment: complete versus partial anemia correction. However, their results have been disappointing in high-risk [5] as well as in less complicated patients [6] undergoing dialysis (i.e. a population not included in the present controversy).

In 2006, two randomized trials testing complete vs. partial anemia correction on cardiovascular events and mortality in patients not undergoing dialysis were published [7, 8]. The Cardiovascular Reduction Early Anemia Treatment Epoetin beta (CREATE) [7] did not show any difference in the risk of reaching the primary composite cardiovascular end point after a mean, planned follow-up of 3 years. The event rate was half than expected, thus reducing the statistical power of the study.

The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial [8] enrolled patients with a higher burden of cardiovascular disease at baseline and diabetics in a higher percentage (48 vs. 26%) compared to the CREATE trial. After a mean follow-up of 16 months, the study was halted for futility and a higher number of composite primary end points in the higher Hb target group.

The evidence coming from these studies have been summarized in two K-DOQI meta-analyses [9]. Combining cardiovascular events in nearly 3,000 CKD patients not undergoing dialysis showed a 24% significantly higher risk among the patients assigned to the higher Hb targets (the CHOIR and CREATE studies contributed to

most of the weight of these meta-analyses). Surprisingly, combining separately mortality in dialysis and nondialysis patients, as well as cardiovascular events in dialysis patients, no significant difference between the higher and lower Hb target was found.

The TREAT trial confirms that complete anemia correction has a neutral effect at best or may be even harmful, also in CKD patients with type 2 diabetes, while consuming more health resources. According to Dr. Singh, 'the TREAT study has turned the world of anemia upside down' [10].

In our opinion, this is an over-interpretation of the TREAT trial results. While acknowledging that this is the largest double-blind placebo-controlled trial performed in the field so far, we do believe that it does not add anything new to our knowledge.

Based on the review of existing evidence, in 2007 the last update of the K-DOQI guidelines already recommended in general an Hb target between 11 and 12 g/dl to aim for with ESAs, without intentionally exceeding the value of 13 g/dl [9]. The recent position papers of KDIGO [1] and of European Renal Best Practice (ERBP) agreed with this recommendation [11]. The European Best Practice Guidelines (EBPG) suggested caution already in 2004, avoiding raising Hb concentrations to levels of more than 12 g/dl with ESAs in patients with diabetes and/or severe cardiovascular disease [12].

The intention-to-treat analysis of the TREAT study has the potential for the misleading interpretation that we should treat CKD patients with ESAs only if they have an Hb level below 9 g/dl that cannot be managed with repeated blood transfusions [10]. And this because the so-called 'placebo group' experienced a similar primary end point event rate, together with a significant lower risk of stroke and a significant lower risk of death from malignancies in patients with a previous history of malignancies than the group administered darbepoetin- α aiming for a Hb value of 13 g/dl. However, according to evidence-based medicine, the results on strokes and malignancies should only be considered hypothesis-generating because the study was not powered for testing these outcomes. A statistical fluctuation is always possible. For this reason, p values should not be used in these secondary analyses. In support of this, the significant higher mortality and cardiovascular risk demonstrated by the CHOIR study as a primary end point in more than 1,400 patients (48% were diabetics) was not confirmed by the TREAT study in more than 4,000 CKD type 2 diabetic patients. Moreover, the placebo was not a 'true' placebo group [13] since 46% of the patients received at least one

administration of darbepoetin- α (the mean dose only considering treated patients is not reported). Even more importantly, despite a rescue value of 9 g/dl (strangely enough), achieved Hb values progressively increased in the 'placebo group'. Starting from a median baseline value of 10.4 g/dl, at the end of study the mean Hb value was 11.4 g/dl (the median value during the trial follow-up was of 10.6 g/dl). Thus, the Hb range value was very close to the target range suggested by the current guidelines. This positive trend is clearly against the common notion that the majority of CKD patients experience a decrease in Hb values during the course of their disease [13].

Interestingly, there has been more concern [10] since the publication of TREAT regarding increased cardiovascular risk than the CHOIR or CREATE studies. This is in spite of the fact that the relative mortality risk for cardiovascular events in the higher Hb group was 34% higher in CHOIR, and 22 and 5% higher in the CREATE and TREAT, respectively, and not significantly different from the lower Hb group. However, we should point out the consistency of the results toward a higher cardiovascular risk in patients randomized to the higher Hb target range than that suggested by the current guidelines.

How can we reconcile all these data? Following the hypothesis that full anemia correction would have led to greater benefits in the early phases of CKD, the authors of TREAT decided to also enroll patients with relatively well-preserved renal function (stage 3 CKD). Even though these people had diabetes, it would have been difficult to enroll an adequate number of patients with Hb values ≤ 11 g/dl with that degree of renal function. Possibly in trying to partially overcome this problem, the investigators did not exclude patients who were relatively iron-deficient (serum transferrin saturation levels $>15\%$ without any limit for serum ferritin were allowed). Strangely enough, while the percentage of patients receiving oral iron was not significantly different, a significantly higher percentage of patients in the 'placebo group' received IV iron (20.4 vs. 14.8%) compared to the 'darbepoetin- α group' with the higher Hb target. Given that many patients were possibly not fully iron replete at baseline, iron administration, together with blood transfusions (significantly more frequent in the control group: 24.5 vs. 14.8%), had been successful in many of them in obtaining and maintaining partial anemia correction without the need for darbepoetin- α .

However, this cannot be considered an alternative treatment of anemia, especially in the later stages of CKD, including stage 5D (as strongly testified by the pre-ESA era experience). The risk of a higher number of blood

transfusions, above all for the patients on a waiting list or possible future candidates for transplantation, should always be considered.

It is a matter of fact that the key point for correcting anemia in CKD patients has been (and is) to give the elements the patients are deficient in, including adequate diet and iron. This is mandatory before administering any pharmacological supplement including ESAs.

Therefore, it is not surprising that giving iron to patients with CKD not undergoing dialysis improved their anemia without any ESA administration in 54% of them: iron supplementation is a well-known prerequisite for a successful treatment with any kind of ESA in order to use the lowest dosage for reaching and maintaining the desired Hb target.

The main message from TREAT is the importance of appropriate iron use in correcting anemia (particularly in relatively iron-deficient patients), which is a well-established approach in everyday clinical practice and already clearly indicated by all the current guidelines.

The TREAT study would have been more informative if it had compared lower Hb target values with those recommended by current guidelines (11–12 g/dl) because the possibility of a 'U curve' (that is higher risk aiming at both higher and lower Hb target ranges than those suggested by current guidelines) had not been ruled out by the TREAT study. The possibility that a modest increase in the Hb level (obtained with ESAs), in comparison with the Hb value of the TREAT placebo group, could be beneficial is still open.

In conclusion, the TREAT results only apply to CKD patients with type 2 diabetes and moderate anemia who are not undergoing dialysis. Thus, the Hb target range suggested by current guidelines should not be modified for the CKD population as a whole. Given the suggestions coming from this study, caution is recommended in those with CKD secondary to type 2 diabetes not undergoing dialysis to avoid Hb levels higher than those suggested by current guidelines. In patients at risk of strokes and with a history of malignancies, we should probably aim for the lower edge of the Hb target range, considering the possible higher risk of strokes and deaths for cancer, respectively, in these selected populations. We should balance them with the higher risk of transfusions and cardiac revascularization together with a lower quality of life. The cost-effectiveness evaluation should be part of this decision.

Finally, after underlining that 'the results of TREAT will influence practice guidelines', the accompanying editorial comment of the TREAT paper [14] surprisingly

concluded (in agreement with our comments) that TREAT ‘reinforces the idea that secondary outcomes and subgroup analyses are best viewed as hypothesis generating’. Consequently, we cannot agree with Dr. Singh’s statement ‘that avoiding the use of the drugs in kidney patients not undergoing dialysis is now the soundest approach given’ by the TREAT study [10]. Thus, the ques-

tions as to what the maximal iron dose is that can be safely given to patients to maximally reduce the ESA dose and what the highest doses of iron and ESA are that can be safely administered for reaching and maintaining the Hb target range proposed by the current guidelines are still open.

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