Rebuttal: CON Position

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

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We agree with Dr. Singh that at least part of the higher morbidity and mortality associated with the randomization to higher Hb target may be related to the higher ESA dosage used when aiming for these targets. The association between higher ESA dosage and higher morbidity and mortality in patients randomized to lower Hb levels [1] supports this. However, we should avoid misinterpreting the association data for ESA doses as we did for Hb levels. Higher Hb values are mainly a marker of good health (less inflamed patients are more likely to require lower ESA dosages and achieve the desired Hb target range). Conversely, 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). Thus, as Dr. Singh acknowledged, 'there is a relationship between ESA dosages and adverse outcome, but since confounding cannot be excluded, causality cannot be established'.

We do not agree with Dr. Singh that 'there is no evidence to indicate risk with other intervention in targeting a higher Hb – blood transfusion or iron'. Avoidance of transfusions is particularly important in patients eligible for renal transplantation, where exacerbation of HLA sensitization should be avoided; infections and reactions secondary to blood transfusions are rare events, but still possible, and continuative transfusion use may cause iron overload. We still do not know if high-dose iron admin-

istration is completely safe, particularly in patients with functional iron deficiency (with very high ferritin levels); intravenous high dose or rate iron administration may cause increased oxidative stress, possibly contributing to cardiovascular disease development. In CKD patients not on dialysis, the use of IV iron therapy should be balanced against the risk of destroying the veins, which is important in the light of possible future need for vascular accesses in hemodialysis. These three therapeutic strategies (iron, ESAs and transfusions) cannot be considered equivalent options to increase Hb levels at all CKD stages.

The Normal Hematocrit study [1] was stopped because of futility and safety; the fact that the morbidity and mortality were higher in the higher hematocrit group, at the same hematocrit levels, points more to the rate of hematocrit correction and related consequences (including higher ESA dosages) than to hematocrit values per se.

It is not true that all the three trials [2–4] in nondialysis patients 'demonstrated increased risk with targeting on higher Hb'. Only the CHOIR study [3] showed a significant risk difference in reaching the primary composite end point and higher ESA dosages being just a result.

Strangely enough, a secondary analysis of the CHOIR study [5] did not find any difference in mortality and cardiovascular events between diabetic patients randomized to higher or lower Hb values, the significant difference being just related to nondiabetic patients. This informa-

tion is in agreement with the results of the TREAT trial [4] showing no significant difference on primary outcome in diabetic patients randomized to the two arms. It would be interesting to know possible differences in ESA dosages between diabetic and nondiabetic patients of the CHOIR study. However, considering that there are no clear advantages, potential risk and higher costs aiming for higher Hb values, we (and guidelines) suggest to aim for partial anemia correction and carefully consider the patient's feeling [6]. In diabetic patients with a history of strokes and malignancies, a target range of 10–12 g/dl is probably more suitable, balancing the risk-benefit of treatment in the single patient.

According to Dr. Singh, 'targeting a higher Hb with ESA is the problem'; in our opinion determining the ideal Hb target range and with which iron and ESA dosages this ideal target range should be aimed for is the real problem.

In conclusion, anemia management consists of iron supplementation, ESA therapy and red cell transfusions, and requires considering all the aspects, including quality of life [6] and costs. Avoidance of transfusions is particularly important. The TREAT study reinforces the guidelines' message on the importance of an integrated

approach, using iron first for correcting iron deficiency and ESA when needed, aiming for a partial anemia correction (Hb target range 11–12 g/dl). The use of a high ESA dose in patients who are hyporesponsive to treatment should be carefully evaluated. It seems wise not to increase the ESA dose progressively in those patients who do not respond to treatment as expected. However, it is still a matter of debate as to how much iron can safely be given to the patients to reduce the ESA dose as much as possible. The other question is determining the highest dose of IV iron and ESAs that can safely be administered for reaching and maintaining an ideal Hb target range.

Disclosure Statements

Dr. Locatelli was a member of the steering committee and an author of the CREATE study, an investigator of the TREAT study, and a liaison member of anemia K-DOQI guideline group. Dr. Locatelli is a member of the ERBP Advisory Board and of the board of directors of KDIGO, a member of an advisory board of Affimax, Amgen-Dompé, Merck, Janssen-Cilag and Roche, and of a safety committee of Sandoz.

Dr. Del Vecchio was a member of the 'anemia Italian guideline group' and has held lectures for Amgen-Dompé and Roche.

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