Erythropoietic response to erythropoiesis-stimulating agents and outcome: should we give up the haemoglobin target approach?

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The hypothesis that complete anaemia correction with erythropoiesis-stimulating agents (ESA) would reduce the risk of death and cardiovascular and renal endpoints among patients with chronic kidney disease (CKD) has been largely tested in the last 15 years. Despite expectations, no study has demonstrated any clinical benefit except some improvement in quality of life by targeting at high haemoglobin (Hb) levels in comparison to partial anaemia correction. Some of these studies even found a trend towards increased risk of cardiovascular endpoints (i.e. death, stroke, acute myocardial infarction and hospitalization for congestive heart failure in different combinations) at primary or secondary analyses [1–4]. A lively debate has developed focussing on possible explanations why clinical trials have not confirmed what has been shown by observational studies: the higher the Hb the better the outcome.

The Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) study randomized 4038 patients with Type 2 diabetes and CKD Stages III–IV to darbepoetin alfa (Hb of 13 g/dL) or to placebo (with rescue darbepoetin alfa for Hb <9.0 g/dL) [5]. Results were neutral on primary composite cardiovascular and renal outcomes, but a higher risk of stroke, death for cancer in patients with previous history of malignancies and thromboembolic events were found at secondary analyses in those randomized to complete anaemia correction. This paralleled a reduction in cardiac revascularization procedures, transfusion rates and improvement in quality of life in this group [6]. Possible implications of these findings have already been discussed [7].

In this editorial, we would like to examine carefully and comment on the recent secondary analysis of the TREAT data by Solomon et al. [8], which investigated the relationship between initial response to darbepoetin alfa, patient characteristics and outcomes.

For this purpose, patients in the darbepoetin-alfa group having a Hb change <2% in the first month after the initial weight-based two doses of darbepoetin alfa were defined as having a poor response and compared with the remaining ones (upper three quartiles of Hb changes). After adjusting for outcome-related covariates, this subgroup had a higher risk of reaching the cardiovascular composite endpoint or death from any cause than the better Hb responders who had an event rate similar to the placebo group. Conversely, both subgroups had similar stroke rates that were higher than the placebo group.

This post hoc analysis suggests that after just two doses of darbepoetin alfa, it is possible to classify the patients in good and bad responders and this may translate into a different outcome risk. This may be an easy method to identify high-risk patients and tailor ESA treatment accordingly, avoiding excessive doses. However, as admitted by the authors, these findings cannot identify the culprit of increased cardiovascular risk following ESA treatment. Is this a consequence of too high ESA doses especially in those who are hyporesponsive to treatment or does this merely reflect patient characteristics?

Unfortunately, no information is available about initial haematopoietic response according to baseline comorbidities in the so-called placebo group for testing the hypothesis generated in the darbepoetin-alfa group. In this group, almost half of the patients were treated with darbepoetin alfa as a rescue therapy because their Hb values had dropped <9 g/dl, although the median dose was zero. This means that the patients received just one or two doses of darbepoetin alfa and very quickly recovered from Hb levels <9 g/dl, possibly reached because of underrcurrent comorbidities and not necessarily related to anaemia of the level of CKD per se alone. Despite these limitations, it would be interesting to compare the outcomes of the patients of the placebo group receiving darbepoetin alfa with those remaining untreated because it may give a possible clue to a better understanding of the relationship between baseline characteristics and initial haematopoietic response on patient outcome, leaving aside the effect of prolonged ESA exposure or excessive doses.

Are high ESA doses toxic?

In an attempt at explaining the unanticipated results of previous clinical trials aiming at complete anaemia correction [1,3,4], it has been hypothesized that ESA-hyporesponsive patients were exposed to higher ESA doses in order to
reach the Hb target with possible negative effects. It is known that ESA do not only stimulate erythropoiesis but also have pleiotropic effects on other organs/tissues where the EPO receptor is expressed. These pleiotropic effects may be beneficial but also harmful and they may be enhanced in patients receiving high doses in a somehow unpredictable way. Accordingly, a number of observational studies found that for every range of achieved Hb levels, higher ESA doses were associated with negative outcome [9]. Similarly, a secondary analysis of the correction of hemoglobin and outcomes in renal insufficiency trial found that, after adjusting for several covariates (although it is well known that it is impossible to adjust for everything including the intensity of the comorbidities), high-dose epoetin alfa was associated with a significant increased risk of a primary endpoint [10].

The secondary analysis of the TREAT [8] study does not seem to support that high ESA doses are toxic; the difference in darbepoetin alfa doses between the ‘good’ and ‘bad’ responders was not very impressive (only 65 µg monthly) with a substantial overlap between the two groups [11]. Moreover, the group having a good initial response to darbepoetin alfa had similar event rates as the placebo group. Again, this would stand against a dose-related toxicity of ESA. Even more importantly, this analysis was unable to fully differentiate the risk of strokes between good and bad responders, although the difference in stroke was the secondary endpoint that caused more concern to nephrologists.

What is the role of pre-existing clinical conditions?

It is well known that response to ESA is somehow unpredictable in the single patient. However, the burden of patient comorbidities largely influence ESA dose needs and achieved Hb levels [12]; this has also been related to patient outcome [13,14].

As suggested by Solomon et al. [8], the poor initial response to ESA is probably a marker of illness severity. Patients of this group were more likely to have previous cardiovascular disease or receive treatment for heart failure, have higher C-reactive protein (CRP) levels and be overweight. Interestingly, ESA hyporesponsiveness has been linked to insulin resistance [15], which is more likely to occur in overweight patients and is a well-known cardiovascular risk factor [16]. The worse outcome of patients with poor initial haematopoietic response may be the result of more inflammation and more severe cardiovascular disease rather than the effect of anaemia treatment [8]. However, these are only speculations, since it is difficult to ascertain, even after adjusting for comorbidities, whether the increased outcome risk was due to pre-existing clinical conditions or to higher ESA dose or an interplay of both.

Oddly, as reported above, the initial haematopoietic response to darbepoetin alfa was not able to discriminate the risk of stroke, which was the main outcome difference in the original paper. Considering that strokes were more frequent in those already having such events previously, it is likely that patient characteristics are a major cause of negative outcome [17]. These patients may have a particular hypercoagulable state, perhaps genetically determined [18], that may be exacerbated by ESA treatment independently from patient predisposition to increase Hb levels. Indeed, the stroke risk was comparable in patients having a good or a bad response to ESA but was higher than that of placebo. Given that the patients in the darbepoetin alfa group had similar systolic blood pressure values during follow-up than those in the placebo group [5], it is unlikely that the increase in stroke risk was mediated by a pressure response following ESA therapy.

Further studies are needed to identify factors influencing ESA hyporesponsiveness and their possible link with patient outcome, considering that knowing initial haematopoietic response to darbepoetin alfa improves the predictive value of the Cox’s model by only 7% for both the cardiovascular composite outcome and death [8]. We wonder whether using inflammation markers such as CRP may have a similar or even better predictive power in the model.

Is iron balance the key factor?

Iron is a prerequisite for treatment success with any kind of ESA. Unfortunately, the design of the TREAT study did not adequately exclude patients who were relatively iron deficient [19]. It has been hypothesized that following ESA-induced erythropoiesis, iron depletion may occur or be exacerbated and this may be associated with relative thrombocytosis possibly contributing to increased mortality [20]. In the secondary analysis of the TREAT [8] study, the patients having poor initial haematopoietic response to darbepoetin alfa were more likely to be iron deficient than the others. This is in line with previous observations showing that iron deficiency is one of the first causes of ESA hyporesponsiveness [12]. However, platelet levels were similar in the two groups. It is possible that initial higher ESA doses given to hyporesponsive patients may have further reduced iron stores and induced thrombophilia. Unfortunately, we do not have enough information to support or deny this hypothesis.

Should we give up the Hb target approach?

The TREAT study has not substantially changed the way we correct anaemia in CKD patients. However, more attention has been focused on the risk-benefit balance in the single patient [17]. In the absence of clear benefits on hard endpoints when aiming towards high Hb levels, the possibility that treatment choices may also be driven by symptom relief independently of Hb levels has arisen.

A major limit of previous studies is that they only considered Hb levels, while paying little attention if any to ESA doses. The possibility that a subset of patients who are hyporesponsive to ESA may be exposed to negative effects following ESA treatment cannot be ruled out at present and has pointed the finger towards the target Hb approach. This is why the position statement of the European Renal Best Practice (ERBP) clearly underlined that the target Hb should be weighed with the ESA dose (and iron dose) needed to achieve it [7].
In conclusion, while the general approach to anaemia management in CKD patients should be aiming at Hb levels of 11–12 g/dl [7], the secondary analysis of the TREAT [8] study remind us of the importance of individualized treatment according to patient characteristics and comorbidities and that the target Hb should be weighed with the ESA and iron doses needed to achieve it.

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References

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