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Anaemia correction in diabetic patients with chronic kidney disease: lessons from the TREAT study

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One of the most important therapeutic advances in controlling anaemia in patients with chronic kidney disease (CKD) was the synthesis of recombinant human erythropoietin (rHuEPO) in 1985. The only option for those of us who were treating dialysis patients with a haemoglobin level of 5 or 7g/dl at that time was to perform multiple transfusions, which not only increased the probability of viral infections, but also created sensitivities in patients who might eventually undergo a kidney transplant, or produced an iron overload. The clinical trials produced such favourable results[1,2] that rHuEPO was accepted by health regulation agencies as a treatment agent in 1988, only three years after its discovery.

It was soon noted that correcting anaemia in CKD patients not yet on dialysis also produced beneficial effects. A meta-analysis of the data published in randomized studies with more than 200 pre-dialysis patients up to 2001 showed, as others, that early treatment with rHuEPO corrected anaemia, eliminated the need for transfusions and improved quality of life and capacity for exercise.[3]

The effect of correcting renal anaemia on mortality was studied retrospectively. One retrospective longitudinal study carried out on 44,550 haemodialysis patients (Fresenius Medical Care, USA) showed that survival rates were lower in patients with haemoglobin below 9g/dl and higher in patients whose haemoglobin was at or higher than 13g/dl.[4] Furthermore, data from the Spanish prospective study MAR, which included 1,428 patients from 119 centres[5] and from the American organisation DaVita, with 58,058 patients,[6] supported the observation that haemoglobin values below 12g/dl increased mortality of patients on haemodialysis.

Therefore, rHuEPO was shown to be an effective drug which improved the clinical profile and survival rates in retrospective studies carried out on CKD patients.

But…

The first troubling observations arrived with Besarab's prospective study[7]: in haemodialysis patients with clinical signs of congestive heart failure or ischaemic heart disease, administering rHuEPO in order to raise haematocrit to 42% was associated with more deaths due to all causes than was predicted for the group with normal (39-45%) or low haematocrit levels (27-33%). Two simultaneous, prospective, randomised studies from Europe (CREATE) and the United States (CHOIR) in pre-dialysis patients concluded that the target haemoglobin level of 13-15g/dl vs. 10.5-11.5g/dl[8] and 13.5g/dl vs. 11.3g/dl[9] was associated with increased cardiovascular risk, and that complete, early resolution of the anaemia did not reduce the risk of cardiovascular episodes. It is true that the three mentioned studies may be subject to critical analysis due to having some methodological weaknesses,[10] but they were followed by safety warnings issued by the FDA in the United States and by the EMEA in Europe. Both stated that in CKD treatment, haemoglobin levels higher than 12g/dl were associated with an increase in severe cardiovascular complications and mortality due to all causes.[11] Furthermore, these safety warnings included important references to cancer patients treated with rHuEPO: "tumour progression time in patients with head and neck cancer receiving radiation therapy is shortened, survival

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rates decrease and mortality attributed to disease progression in patients with metastatic breast carcinoma on chemotherapy increases".

As a result of the above observations, the clinical practice guidelines changed the haemoglobin recommendations for CKD patients treated with rHuEPO. The European anaemia group made the following recommendation in 2009: "In the opinion of the ERBP Work Group, it appears reasonable to maintain the lower limit of the target, although the actual evidence for choosing this value is also very limited. On the basis of new evidence, Hb values of 11–12g/dl should be generally sought in the CKD population without intentionally exceeding 13g/dl".[12]

The results of the TREAT study were subsequently published and presented in the U.S. conference held at the end of October 2009, on the same day that they appeared in the *New England Journal of Medicine*.[13] In summary, the study analysed 4,038 patients with diabetes, CKD and anaemia. 2,012 patients were randomly assigned treatment with darbepoetin alpha in order to reach a haemoglobin level of approximately 13g/dl and 2,026 patients were treated with a placebo, although they were able to receive rescue darbepoetin alpha when their haemoglobin level dropped below 9.0g/dl. The primary end points were the time to the composite outcome of death from any cause or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and the time to the composite outcome of death or end-stage renal disease.

The Spanish Society of Nephrology (SEN) was invited to participate in this study three years before. After the meeting with the study coordinators in Madrid, we decided not to participate due to our opposition to having patients in the placebo group who would not receive rEPO treatment until haemoglobin levels dropped below 9g/dl. This decision did not seem ethically acceptable to the nephrologists who met at that time.

This issue also contains an excellent structured analysis by members of NEFROLOGÍA's editorial team which addresses the results from this study, in which the risks of rEPO treatment in diabetic patients with CKD without replacement therapy and anaemia overshadow the potential benefits.[14]

OUR OPINION ON THE TREAT STUDY

This study will undoubtedly have an impact on clinical practice. However, some points must be clarified:

1. According to the *Real Academia Española de la Lengua* (Spanish Language Royal Academy), placebo is defined as follows: "Substance lacking any inherent therapeutic properties which produces a curative effect in a patient if he/she is convinced that the substance is actually able to produce such an effect". In the TREAT study, the placebo group received three interventions that have therapeutic properties:
   a) 46% of the patients assigned to the placebo received at least one dose of darbepoetin as a rescue treatment.
   b) The placebo group received more intravenous iron (20.4 vs. 14.8%; $p < 0.001$).
   c) The placebo group required more transfusions (24.5% vs. 14.8%; $p < 0.001$), thus receiving even more iron.

   These interventions led to a progressive increase in haemoglobin throughout the study, with a median of 10.6g/dl (IR: 9.9-11.3) in the placebo group. Therefore, many of the patients reached levels recommended in the guidelines for optimum treatment of diabetics. This bears little resemblance to the intention for this group according to the initial design. It seems obvious that TREAT's initial proposal was to create a clear difference in haemoglobin levels between the two groups, and this aim was not completely accomplished (the group treated with darbepoetin reached a median of 12.5g/dl; IR: 12.0-12.8). One adequate strategy for the design of the study might have been if all of the patients had begun the study after receiving adequate iron replenishment, most likely by the intravenous route. Only after verifying that all of the patients presented iron levels within the recommended targets by guidelines (ferritin > 100ng/ml and transferrin saturation index [TSI] >20%)[12] would the sample have been randomised. This would have help to define a more clear difference in haemoglobin between both arms.

2. Another factor that we should consider is the median of the darbepoetin doses used in the intervention group: 176μg/month (IR: 104-305). These doses are very high. In studies that aimed to maintain haemoglobin within the recommended ranges by the monthly administration of darbepoetin to Australian patients with CKD (mean haemoglobin of 11.4g/dl), mean doses of 80μg were necessary.[15] In American studies of non-dialysis CKD patients, the mean darbepoetin dose during the study period was 124.4μg/month (106.2-140.0).[16]

   This is important, since doses of ESA can intensify complications. Szczech et al.[17] performed a secondary analysis of the CHOIR study to evaluate the relationship between the erythropoietin doses and evolution with death, hospitalisation, heart failure, stroke and myocardial infarction as the primary compound objective. In the adjusted model, the risk associated with high haemoglobin levels was not significant ($p = 0.49$), while a high dose of erythropoietin was associated with a 57% higher risk of

the main evaluated variable (HR = 1.57; CI: 1.04-2.36; p = 0.03). The Spanish study ANSWER[18] also found such a relationship between high doses of erythropoietin and mortality in non-responders. However, when we adjust for comorbidities, malnutrition, vascular access and iron deficiency, the high doses of ESA do not increase the morbidity/mortality RR. We must examine whether or not the comorbidities are causes that would require the administration of high doses in order to achieve a sufficient response. That is, some of the results found by TREAT could have more to do with the excessive doses of darbepoetin received by patients than with their haemoglobin levels. It is clear that we must examine whether this is due to the high doses alone or if, as we have suggested, it is due to underlying causes that require high doses to be administered in order to obtain a sufficient response. Other actions of erythropoietin differents from erythropoiesis, such as angiogenic, anti-apoptotic, haemostatic actions, etc. on erythropoietin receptors in non-erythropoietic cells and tissues,[19] could explain its harmful effect when administered in high doses.

Advancing certain recommendations that support a prudent strategy seems to be necessary. These recommendations limit the ESA dose in those special cases that do not reach the target haemoglobin levels, and in cases in which raising the dosage without limits would be ineffective, expensive, and with real side effects. One idea of where the ESA upper dose limit may be considered can be found in two studies: one is an observational study by Regidor et al.[6] and the other is Szczech's secondary analysis of the CHOIR study;[17] they advice an upper dosage at 48,000 and 80,000U per month, respectively.

3. Although there were no statistically significant differences in the primary objective (31.4 vs. 29.7%) and cardiac revascularisation procedures were significantly less frequent in the group treated with darbepoetin, there were differences in the number of cerebrovascular accidents. In the study, we can see an increase in strokes, although there were very few cases (101 vs. 53; 5% in the treatment group vs. 2.6% in the placebo group). The HR was 1.92, although the main difference was observed in patients with previous history of strokes: 12% of the patients in the darbepoetin group compared with 4% in the placebo group. It is important to remind that patients with strokes have a higher risk of repeat strokes, and thus a higher overall risk than a person who had not previously suffered a stroke. Among patients without a previous history of strokes the difference although significative was much lower: 4% in the darbepoetin group versus 2% in the placebo group. The increase in the risk of strokes was not found in either the CHOIR or the CREATE studies of CKD patients, containing 48% and 26% diabetic patients respectively.[8,9] This increase in the risk of strokes was neither found in Strippoli's metaanalysis. 20 This increase cannot be explained by differences in systolic blood pressure. We need a secondary analysis of these populations to address the following questions: What haemoglobin level was reached? What dose of ESA did patients receive? What was the distribution by race? By sex? Are there differences between the American and European populations?

4. For some time now, we have known that correcting renal anaemia improves quality of life.[21-23] This improvement in physical exercise, vitality and mental state was observed in the CREATE study. With the use of three validated instruments (LASA, KDQ and SF36), the CHOIR study also observed an improvement in quality of life when anaemia was treated with erythropoietin, but this improvement did not occur when the target haemoglobin level was raised to 13g/dl. Supporting this conclusion are a recent review and a meta-analysis[24] that find a slight, clinically insignificant difference in quality of life when haemoglobin is raised to levels above 12g/dl.

   In the TREAT study, there is only a slight, clinically insignificant improvement in the FACT-Fatigue score, and no improvement in other tests that measure energy and physical function. In fact, this is compatible with findings from previous studies. It is possible that since the window between the haemoglobin groups was too narrow to establish clear differences between the two groups (iron was administered in the placebo group, reaching median levels indicated by guidelines); the difference between the groups was unremarkable due to an improvement in the placebo group. A recent study of patients with heart failure and an iron deficit clearly showed that the replenishment of iron alone, whether or not patients had anaemia, improved symptoms, functional capacity and quality of life.[25]

   In summary, it is difficult to observe differences in quality of life when iron deficiencies are corrected and median haemoglobin levels are at 10.6g/dl. It is necessary, however, to point out that in our normal clinical practice, we often find differences in iron repleted patients' well-being when we use erythropoietin to raise haemoglobin levels from 10.5g/dl to 12g/dl.

5. It is a well-known that administration of ESA to cancer patients is associated with an increase in the risk of thrombosis and mortality.[26] But anaemia from cancer differs from anaemia accompanying CKD: the endogenous EPO levels are normal, the inflammatory component is very important and patients receive drugs that interfere with erythropoiesis. In addition, the cancer patient has a significant predisposition toward

venous thrombosis. The TREAT study showed significant differences between episodes of venous thromboemboli (2 vs. 1.1%) and arterial thromboemboli (8.9 vs. 7.1%), with a higher frequency in the group treated with darbepoetin than in the placebo group. These significant differences were not found in the CHOIR and CREATE studies, even as complications of arteriovenous fistulae. Once again, we need specific complementary analysis of this group in order to learn about its characteristics regarding maximum haemoglobin, EPO dose, age, race, sex, prothrombotic factors, type, etc.

6. In both the darbepoetin and the placebo groups, a high transfusion rate was recorded (14.8 vs. 24.5%), and the percentage of patients receiving intravenous iron was significantly higher in the control group (20.4 vs. 14.8%).

   Despite the fact that the ferritin and IST data are recorded as a mean and interquartile range (values between the first and third quartile, the range in which 50% of the data falls), we do not know what percentage of patients presented an iron deficiency at some time during the study. Mean ferritin at the beginning of the study, 131 and 137ng/ml in the treatment and placebo groups respectively, was below the limit recommended in guidelines particularly when we consider that patients were to receive ESA and would probably present an iron deficiency during the course of their condition.

7. One particularity of the TREAT study is its high population of patients from the United States (more than 50%). It is well-known that mortality rates and ESA doses are higher in the United States than in Europe, A comparative analysis of the two populations would then be necessary.

8. Finally another aspect that was not clearly explained in the TREAT study is the result for the event "death or end-stage kidney disease" with regard to race. The highest risk was found in the group of non-white, non-black patients (n = 653; HR = 1.46); the next-highest risk was in white patients (n = 2570; HR = 1.05), and the lowest risk was in black patients (n = 815; HR = 0.87). Once more, secondary analyses are needed in order to explain these differences.

   It is quite possible that this study will lead us to redefine overall target levels of haemoglobin in our CKD patients. However, we must consider that it is very difficult to maintain patient levels within a narrow range[27] and those goals must be individualized according to each patient's profile. Recommendations about the correction speed, the maximum doses and adequate control of blood pressure (among other factors) may be as important as redefining haemoglobin objectives.

CONCLUSIONS

1. The TREAT is the first study comparing a placebo treatment (?) with ESA in diabetic patients with anaemia secondary to CKD.

2. No effects of darbepoetin treatment were noted relating to death, end-state kidney failure or cardiovascular events. A significant increase in stroke risk, in the group receiving darbepoetin treatment was observed.

3. TREAT study showed fewer blood transfusions and improvement in some quality of life issues in the group treated with darbepoetin.

4. TREAT data may only be applied to diabetic patients with CKD, and not to those on dialysis or having received a transplant.

5. New secondary analyses of the TREAT study must be carried out in order to clear up certain aspects, particularly those referring to compare patients in the placebo group whose haemoglobin level was below 10g/dl after correcting the iron deficiency with patients in the treatment group whose haemoglobin was above 12g/dl.

RECOMMENDATIONS

Following the TREAT study, the recommendations by the SEN's Anaemia Group for non-dialysis CKD patients in stages 3-5 are as follows:

1. All CKD patients not undergoing dialysis with haemoglobin below 11g/dl and iron deficiency (IST < 20%; ferritin < 100ng/ml) must receive iron orally (CKD 3-4) or intravenously (CKD 4-5) until guidelines targets are met, without allowing ferritin values to exceed 500ng/ml.[12]

2. Once the recommended iron parameters have been achieved and if anaemia is still present we recommend:

   a) For diabetic patients, use ESA provided that haemoglobin is below 10g/dl in order to meet a target between 10 and 11g/dl, and in selected cases without exceeding 12g/dl. For patients with a prior history of stroke we do not recommend treatment with ESA. It should be administered (exceptionally, for symptomatic anaemia) only as a recovery measure when the haemoglobin level is below 9.0g/dl.
   b) For non-diabetic patients, once the iron parameters have been corrected, ESA should be used provided that haemoglobin is below 11g/dl; Target is between 11 and 12g/dl, and the level should not exceed 13g/dl.

3. In any case, the maximum monthly ESA dose for non-dialysis anaemic CKD patients in stages 3-5 are as follows:
   a) 40,000U/month of Epo alpha or beta.
   b) 200μg/month darbepoetin.
   c) 200μg/month CERA.

Although this is not a direct conclusion of the TREAT study, the need for higher doses calls for a more complete study of the potential causes of hyporresponse.

We hope that our recommendations will lead to more secondary analyses of the TREAT study and further studies to clarify these findings.

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