Time to Reconsider Evidence for Anaemia Treatment (TREAT) = Essential Safety Arguments (ESA)

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Introduction

TREAT: A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease (ClinicalTrials.gov number NCT00093015), published recently by Marc Pfeffer and colleagues, may rank as one of the most important clinical trials in nephrology [1]. As well as being important, it was one of the largest, best conceived, designed, executed and expensive (a conservative estimate would be $300 000 000) trials in patients with chronic kidney disease.

In this commentary, we will set out what we believe has now changed as a result of the TREAT and how we might have to adapt our thinking and our clinical practice in the future as a result. We believe that clinical nephrologists, anaemia coordinators, clinical practice and guideline setters, and patient registries, will need to re-address anaemia treatment paradigms and, in so doing, reappraise our clinical use of those expensive and powerful medications—erythropoiesis-stimulating agents (ESAs).

Why was TREAT undertaken? What did we not know when it was designed? Why was it special?

The underlying assumption that the marked increase in adverse outcomes seen where anaemia, chronic kidney disease and diabetes co-localize, shown nicely in the Atherosclerotic Risk in Communities study (ARIC) study [2], can be reversed by correction of anaemia using (iron and) ESAs, was an assumption that required a major trial to confirm. In addition, despite much effort, there were no trials to show the ‘ideal’ haemoglobin (Hb) target for treatment of anaemic chronic kidney disease (CKD) patients. Although now, as we discuss later, we need to add the information from TREAT to that derived from the two other recent large anaemia trials—CHOIR [3] and CREATE [4], at the time TREAT was conceived and designed, neither of those two trials had been reported.

This chronically sick type 2 diabetic CKD population is an important population to study, as type 2 diabetes is rapidly increasing in prevalence globally [5], and with that increase there is a parallel increase in the incidence of micro- and macro-vascular complications of diabetes. Knowing how best to prevent or reverse the very significant cardiovascular burden these patients present is a key objective for the coming decades.

Cochrane reviews [6] and meta-analyses [7] suggested that the impact of anaemia correction might not be as favourable as the interpretations from epidemiological risk association studies from large CKD databases [8]. As TREAT was placebo controlled (the first time a large anaemia study had included a placebo arm since 1997 when guidelines suggested target haemoglobin levels in CKD [9]), there was an opportunity to finally demonstrate the clinical benefits of anaemia correction in CKD. Recent trials (including CHOIR and CREATE) did not include a placebo arm, and so there was potential inbuilt bias favouring intervention with ESAs. This, we believe, is the pivotal and important difference in how we should examine and interpret TREAT. If ‘some’ and ‘more’ ESAs appeared to be in clinical equipoise, ‘some’ would win out. Clearly, if ‘more’ meant ‘better’ then ‘more’ would be the way forwards. In both cases, drug-driven changes in haematocrit would be the outcome of the studies.

TREAT: design, execution and main results

The TREAT involved 4038 patients with anaemia, chronic kidney disease and type 2 diabetes [1]. The study was supported and financed by Amgen Inc but run by independent academic steering and drug safety and monitoring (DSM) committees. Patients were recruited from 26 countries, between 2004 and 2007, though 58% of the patients were American.

The design of the trial was simple—recruitment was done by diagnosis of diabetes, by estimated glomerular filtration rate (eGFR) (to include CKD stages 3 and 4 patients) and by haemoglobin (with a caveat to exclude significant iron deficiency). One group was intended to be a placebo arm, with Hb levels allowed to fall to around 9 g/dL, but with pre-specified rescue therapy if needed to restore Hb to above 9 g/dL. The active treatment arm comprised darbepoetin alfa given subcutaneously with the aim of achieving Hb values >13 g/dL. Interestingly, 46% of the placebo group did receive, at one time or another, some ESA, but, in both duration and dose, this was miniscule compared to the...
active treatment arm (median monthly doses 0 mcg in the placebo arm compared to 176 mcg in the active treatment arm—subcutaneous administration taking place at monthly intervals in around 85% of patients). The trial could only be terminated by achieving the necessary number of events (so it was event driven, not money or time driven) or by a safety signal alerting the need for premature discontinuation [1]. As both the Normal Haematocrit study [10] and the CHOIR study [3] were stopped prematurely, it was important that the results of this study would not be undermined by underpowered conclusions.

The main findings from the study were that, in the sustained presence of around a 2-g/dL difference in Hb levels between the two arms (mean Hb 10.6 g/dL placebo and 12.5 g/dL active treatment), there was no evidence of any overall cardiovascular (CV) or renal benefit as a result of anaemia correction. Follow-up was long—median length 29.1 months/patient and in total 9941 patient-years—making this one of the largest single pieces of clinical evidence about ESA use we have. Indeed, it stands as the largest interventional study in nephrology to date, and this trial will dominate the outcomes of subsequent meta-analyses, as by treated patient numbers this one trial exceeds all cumulated previous anaemia trials. Sophisticated use of several different quality of life (QoL) measures (once, at 24 weeks) also showed a clinically small difference between the two groups. Importantly, transfusion requirements were halved in the treatment arm (but were still needed in around 20% of the active ESA-treated patients).

Importantly also, though renal function change with treatment was only a primary end point in TREAT (and a secondary end point in CHOIR and CREATE), we can now say with more confidence that with the data of nearly 6000 patients to examine, there is no convincing evidence that anaemia treatment impacts beneficially or negatively on the rate of renal function decline in both diabetic and non-diabetic CKD.

TREAT: safety issues

There was some reassurance on safety—hypertension was not significantly worse for example—a statistically significant but clinically modest 2-mmHg rise in diastolic blood pressure (BP) being seen in the higher treatment arm—but a significant new safety concern was the doubling of stroke rates in the treated arm (from 2.6% in the placebo group to 5% in the ESA-treated group); stroke was not common per se, but the difference between the arms in the trial was striking. This was apparently NOT associated with a difference in Hb or BP between those with and without strokes (M. Pfeffer, personal communication). Another real concern was a tendency towards increased malignant events and death from malignancies in a small subset of patients with a prior history of malignancies. Among patients with a history of a malignant condition at baseline, there were 60 deaths from any cause in the 188 patients assigned to darbepoetin alfa and 37 deaths in the 160 patients assigned to placebo (P = 0.13 by the log-rank test). In this subgroup, 14 of the 188 patients assigned to darbepoetin alfa died from cancer, as compared with one of the 160 patients assigned to placebo (P = 0.002 by the log-rank test). This is especially worrying as cancer was a theoretical concern at the beginning of the epoetin era. It should be pointed out that both stroke and cancer were not primary end points, but given the size of this trial and its placebo design, these findings must be significantly concerning.

It is important also to note safety concerns from other patient populations exposed to ESAs—first raised particularly in the CHOIR study. Thrombotic complications are especially concerning as they may accelerate cerebrovascular or cardiac events and may threaten precious vascular access. Though not conducted in CKD cohorts, a recent German study of the acute administration of IV ESA in the setting of acute stroke, with a near doubling of mortality (16% versus 9%) in ESA-treated patients [11], is troubling, as are the meta-analyses of ESA use in cancer patients [12], which also report a ‘balanced’ outcome with more morbidity with higher treatment Hb levels.

TREAT: limitations

No trial is perfect; so, as in CHOIR [3,13], there was some imbalance in distribution of heart failure in the baseline patient data across the two arms (with the placebo arm having 66.9% of patients with a history of CV disease compared to 64% of the active arm subjects, P = 0.05)—but this is not in our view a major flaw, since previous post hoc analyses raised worries about treatment with ESAs in cardiovascularly compromised patients.

When CREATE and CHOIR were published in November 2006, the FDA issued a ‘black-box’ warning for ESAs and were criticized by many for doing so. Forensic analysis of CREATE showed that it was underpowered [4,13] and that CHOIR was idiosyncratic in some ways [3,13]; their messages nevertheless were consistent but blunted. Now with TREAT, a much larger, better executed and more persuasive study than either of the previous ones, we can reach conclusions with greater confidence. This trial, with its placebo design, was wisely allowed to be continued even after the results of CREATE and CHOIR were reported in 2006, as it had already been criticized by some for being unethical by exposing patients to the absence of epoetin, while other commentators were just as critical of the design for potentially ‘over-treating’ other patients.

Some will say that, because the patients studied had type 2 diabetes as the cause of their CKD, these findings really only apply to type 2 diabetic patients with CKD and cannot readily be extrapolated to non-diabetic cohorts or to dialysis patients. We feel this is too cautious; if one takes the three trials together—CHOIR, CREATE and TREAT—there are around 1200 non-diabetic subjects and 4700 mainly type 2 diabetic subjects. The only trial of significance to examine high versus low targets in HD patients, the Normal Haematocrit study from 1998 [10], showed a similar message, again with a high proportion of diabetic subjects.

TREAT: additional thoughts and implications

We now know that in the case of type I diabetes, simultaneous attention to multiple interventions is crucial [14], and it is important to acknowledge in this report just
how well similar interventions were deployed in the TREAT patients. Blood pressures of around 135/70 mmHg, extensive use of ACEI, ARBs and other blockers of the RAS, extensive use of lipid-lowering agents and anti-platelet agents and excellent metabolic control, all suggest that the other ‘diabetes and chronic kidney disease’ guidelines were being well executed. This is important, as, with the inclusion of any patient into a trial, very often clinical care improves substantially as protocolization of good practice ensures achievement of therapeutic recommendations. This effect should of course occur equally between placebo and active groups, but it may reduce the likely hard end point event rates (as was seen for example in CREATE [4,13] where expected event rates of 15% per annum were actually 6%). There were, despite the excellence of medical care already referred to above, a lot of primary vascular and renal events in this study—1234 in total (death or non-fatal CV event), showing that even with the best of modern medical interventions, progression to dialysis and death are common fates for these patients (31% or thereabouts for the overall TREAT population).

One useful thing TREAT helps to challenge is the concern that aggressive iron supplementation itself is driving potential adverse outcomes from anaemia therapy, as, unlike in both CREATE and CHOIR, in TREAT more placebo-treated patients received iron (either IV or oral) than did the ESA-treated group. The role of iron supplementation, which is an essential facet of efficient erythropoiesis, is difficult to dissect away from the effect of the ESAs themselves—in our view, it is more important to understand the effect of a suite of interventions, as seen in this trial, than to know the individual value of each component. This is now very topical and potentially highly relevant, with the demonstration in the Ferinject Assessment in patients with IRon deficiency and chronic Heart Failure (FAIR-HF) trial that treatment with intravenous ferric carboxymaltose in patients with chronic heart failure and iron deficiency, with or without anaemia, improves symptoms, functional capacity and quality of life—with these clinical changes not linked to subsequent alterations in Hb levels [15].

ESAs themselves, it is speculated, might have direct vascular/endothelial toxicity, and this must be one possibility to explain the increased rate of events with higher Hb levels; recently, greater interest has arisen in the role of thrombocytes perhaps allied to increased blood viscosity driving the atherothrombotic events. This aspect of the use of ESAs deserves urgent further attention and analysis (but no published data are available from TREAT on this point). The median monthly darbepoetin alfa dose in the treatment arm was around 180 mcg (mostly monthly), translating to around 45 mcg/week, or the equivalent of say 8000–9000 IU epoetin-alfa or -beta equivalence. This is higher than that reported in CREATE (which had only around 20% diabetic subjects [4]) but lower than the doses reported in CHOIR (around 50% diabetics, but the huge doses used, around 12 000 IU epoetin alfa/week, were unexplained, especially as they were accompanied by a markedly blunted response in terms of haemoglobin rise [3]). Again, given the difference in ESA dose ranges used in these three major studies of ESAs in CKD (low in CREATE, intermediate in TREAT and high in CHOIR) leading to similar achieved Hb levels in the higher/treatment arms of all three studies, we can speculate whether this can explain the outcome differences seen in these trials.

It is worth repriming what the benefits and harm of ESA therapy are for CKD patients. No one will doubt, even without any formal randomized controlled trial (RCT) proof, that very low Hb levels (e.g. <8 g/dL) will be dangerous for CKD patients. TREAT does not address this. Transfusion avoidance is important, reducing the risk of iron overload, infection and allosensitization, and is shown well in TREAT [1], though ESA use does not abolish the need for blood transfusion. In terms of quality of life (QoL), whose metrics remain underdeveloped [16–18], it is fair to say that in relatively healthy pre-dialysis CKD patients [4], comorbidity stressed haemodialysis patients [10] and healthy haemodialysis patients [16] there is evidence for some reduction in fatigue scores on ESA administration (one of typically 20–36 QoL domains). However, some of this could potentially have been the result of IV iron therapy [15]. Several studies have also suggested that the LV remodelling which occurs with ESA-mediated anaemia correction is modest in scope [4,19–21]—in part no doubt because there are many factors of influence for cardiac structure and function in CDK, not just one, and the Hb range studied is not wide. What ESAs can also do is increase morbidity—including arteriovenous (AV) fistula thrombosis [10] and other atherothrombotic events such as stroke [1,10,12], and with TREAT there is some real concern for their use in subjects with prior malignancy [1]. ESA treatment is a multi-billion-dollar industry. We have to ask if the clinical benefit derived can justify the money spent. Would this money convey better QoL improvements more safely if used for other interventions?

Conclusions

We believe that for the sick comorbid majority of patients with CKD (on dialysis or not), ‘we need to use ESAs more sparingly, and with care’. A new Hb target of 10 or 10.5 g/dL or a range of 10–12 g/dL might be more appropriate, affordable and safer than target thresholds of 11 g/dL and more pragmatic than an unfeasibly narrow Hb range of 11–12 g/dL. TREAT, as it did not specifically examine this Hb range, cannot directly confirm the validity of this potential change to the clinical recommendations, but this comment applies also to many other studies recently reported (and implicitly, therefore, the current recommendations are a blend of knowing that ‘too low’ is harmful and that ‘too high’ is also harmful).

So—what should nephrologists, and others who care for CKD patients, do differently in the light of TREAT? Clinicians, we feel, should now consider that ‘ESAs are not mandated for all patients with CKD and moderate anaemia’, though they remain a useful option for symptomatic patients, alongside other measures to improve erythropoiesis, and use of IV iron may well be as effective in symptom relief and be safer and cheaper—this now needs testing by RCT in CKD patients. We know that better dialysis strategies are a good way to improve erythropoiesis in CKD 5 D, and more attention on achieving these is warranted [22]. Clinical prac-
tice guideline bodies, clinical patient registries and practice pattern groups dealing with CKD patients (e.g. European renal best practice ERBP, KDIGO, DOPPS) now need to reflect further on this ever-changing area, emphasizing the option of assessing the effects of the use of iron to replete iron stores before embarking on ESAs and perhaps now adding cautionary notes about when, how and to what extent such ESA-based treatment strategies may be needed, and sanctioning greater ‘bespoke’ individualization of ESA use better to fit recipients’ clinical characteristics [23]. This would certainly change the therapeutic landscape for good.

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References

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