

Haemoglobin targets in CKD patients: the state of play

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This editorial overviews the current state of play in anaemia correction but bucks medical tradition by invoking not Hippocrates but Keats (1795-1821), poet and physician, whose muse was Apollo, the god of poetry and medicine. Interestingly, Keats was a medical student at Guy's Hospital about 150 years before J. Stewart Cameron, author of another editorial in this issue, was a professor there!

■ "I KNOW THE COLOUR OF THAT BLOOD."

The availability for clinical use of recombinant human erythropoietin from the late 1980s made it possible to correct the anaemia CKD patients develop as they underproduce endogenous erythropoietin. In addition to making blood transfusions unnecessary, it is widely recognised that correcting anaemia improved intellectual and physical capacities while reducing morbidity and mortality and is thought to slow down progression to end-stage renal disease. In short, it increases quality of life.

■ "PHYSICIAN NATURE! LET MY SPIRIT BLOOD!"

Indeed. Physicians have been gaining experience as to the goal or gold standard to aim for since the early days of anaemia treatment. We started cautiously with a partial correction and have progressively approached normalisation, with several observational and retrospective studies correlating raised Hb levels

with decreased hospitalisations and morbidity, coupled with better quality of life, in dialysis patients.

A check to this progress came in the shape of the 1998 Besarab trial results¹, the findings of the 2006 CREATE² and CHOIR³ studies, the Phromminkul meta-analysis⁴ and Strippoli's 2007 Lancet editorial⁵. Their opinion is that normalising haemoglobin in these patients does not confer cardiovascular advantages on them as previous observational studies showed. Moreover, total correction can even cause harm – myocardial infarction, stroke or even fatality.

There is space here in this overview for a cautionary word. These studies are weighty, but, just as there are 'partial apologists', there are also 'partial sceptics' and in particular those such as Levin⁶, Carrera and Macdougall⁷, Carrera⁸, and Fishbane and Nisenson⁹ who are dubious about the studies in question, detailing several issues arising from them which need to be addressed before the haemoglobin target is finally settled. Let us deal with these above reference studies and trials in chronological order.

The flaw in the population selected for the Besarab trial was that they were patients presenting a higher cardiovascular risk, the idea being this would lengthen the odds of beneficial events occurring. What it meant was that these patients were already in a higher cardiac risk category, presenting congestive heart failure or ischemic heart disease.

This editorial now briefly considers the less than optimal design and conduct of the CREATE study. It randomised pre-dialysis patients into either a higher group of 13.0 – 15.0 g/dL or a lower of 10.5

– 11.5 g/dL and the protocol did not specify when dialysis should be initiated. It was seen that more patients in the higher Hb arm received dialysis than in the lower (127 vs. 111; $p=0.03$). Observers wonder if the open-label design was at fault here, occasioning a delay in starting dialysis, as patients' symptoms were mistakenly seen as anaemia as opposed to uraemia. Additionally, this open-label design brought a possible bias into the study in the non-intentional choice of healthier patients enrolled because of concerns about cardiovascular disease.

A more serious criticism is that the study was not sufficiently powered to demonstrate any difference between the two randomised treatment groups, as evidenced by the observed annual event rate of 6% for the composite cardiovascular disease endpoint being significantly lower than the expected 15%.

Interestingly, CREATE documented no harm coming to higher Hb target group patients and no significant difference from one group to another in terms of combined incidence of adverse effects. Similarly to the greater part of studies, patients' overall health and physical condition showed significant improvement in the 13.0 – 15.0 g/dL group over those in the 10.5 – 11.5 g/dL group ($p=0.003$ vs. $p<0.001$ respectively).

The Singh *et al.* CHOIR study randomised 1432 pre-dialysis patients to either a higher arm of 13.5 g/dL or a lower one of 11.3 g/dL. Again it was open-label, which, as stated above and as is widely known, can add distorting bias, this time by again enrolling healthier patients to preclude possible problems with cardiovascular disease. CHOIR had a high drop-out rate – 38% - and there was no justification offered for more than 50% of these. Not all randomised patients were included in the analysis; patients who had no event at trial-end were left out.

Another grey area is the statistically significant differences in baseline incidences of coronary artery bypass grafting ($p=0.05$) and hypertension ($p=0.03$) found in the higher group. There were 125 events in the higher group vs. 97 in the lower: could this have impacted on the differences found in outcomes? It is worth noting here that improvements

in quality of life were similar across both groups. In addition, despite the administration of significantly high mean epoetin alfa doses of 11,000 Units, a significant number of patients did not achieve haemoglobin targets, leading to suspicions that these enrolled patients were considerably less well at study-beginning than a typical CKD population would have been.

While CHOIR did not evidence any benefit to patients in the higher Hb target group, it, like the CREATE study, found no concrete proof of harm to patients in this 13.5 g/dL arm. All of the above shows that while the CHOIR conclusions may have been valid for *CHOIR* patients, as the study cohort and medication dosing did not reflect a true CKD population, it is impossible to apply the study's conclusion to the CKD population as a whole.

Turning to the Phromminkul *et al.* meta-analysis⁴, it must be said that its inherent flaws are those common to any meta-analysis, mainly, that no analysis of this type can hope to replace adequately powered, randomised, double-blinded trials. Specifically here, the different studies analysed use a selection of different reporting methods and it was impossible to combine the various composite endpoints due to the inconsistencies in the components of the end-points.

Despite the less than universal acceptance of these findings, their impact has been quickly felt. The FDA has warned physicians to administer the lowest possible erythropoiesis-stimulating agents (ESA) dose to raise the haematocrit to the lowest level necessary to avoid transfusions¹⁰. Further, new K/DOQI guidelines available on their website recommend a range of 11.0 to 12.0 g/dL in dialysis and non-dialysis CKD patients¹¹, with a final publication on this due to appear soon.

In tandem with the FDA, the EMEA has also issued a public statement¹² following their epoetin safety review. Citing 'evidence that, in the treatment of patients with chronic renal failure, aiming at a target haemoglobin concentration above 12 g/dL is associated with an increase in serious cardiovascular morbidity and all cause mortality' their interim recommendations are that '...physicians should exercise caution when considering raising haemoglobin concentrations above 12 g/dL'¹².

Is it cynical to wonder if health economics play a role here? In assessing the financial burden inherent in ESA prescription, a brief glance at the scale involved shows us that global ESA sales were US\$10 billion in 2006 for CKD and cancer patients and that it is estimated that the USA will have over 700 000 CKD patients by 2015. The number will also, of course, increase world wide and have knock-on attendant effects on health care budgets: **“Faded, far-flown Apollo!”**

Despite all this food for thought, I firmly believe questions on the benefits and risks of treatment to correct anemia in CKD patients – and of the optimal target Hb level – still remain to be answered by further large, appropriately powered randomised, controlled trials. The current TREAT (Trial to Reduce cardiovascular Events with Aranesp Therapy) study has almost concluded recruiting 4000 Type II diabetes patients for the largest RCT in renal anaemia to date. One arm will be given darbepoetin alfa to raise their haemoglobin to 13 g/dL while the placebo arm will maintain patients' haematocrit at 9 g/dL, with rescue therapy available. This sufficiently powered study has met with no objections from ethics, steering or data and safety monitoring committees so far and is expected to produce solid results, given time.

To finish, while K/DOQI has already pronounced, the EBPG (ERA-EDTA) has yet to make a statement: no decision was taken on this matter at the latest meeting (June 2007, Barcelona). As separate responses tend to come from both sides of the Atlantic, it begs the question: is it time for scientists to cast aside their team colours and work together to produce Global Guidelines? The Kidney Disease Improving Global Outcomes (KDIGO) has indeed invited all members of all previous regional guideline committees to sit down together to discuss precisely this issue. Our first meeting is scheduled for October 15th-16th in New York. It seems it is early days yet, or yet again: **“Young Apollo! The morning-bright Apollo!”**

Conflict of interest statement.

Dr Fernando Carrera is a scientific consultant, member of steering committees for international clinical trials and/or member of international advisory boards for the following companies: Amgen (Europe), Roche (International) and Shire (International).

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