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Epoetin trials: randomized controlled trials don't always mimic observational data

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The medical management of stage 3 and 4 chronic kidney disease (CKD) attempts to both slow the rate of progression towards dialysis and prevent the development of secondary complications associated with worsening uraemia. Clinicians attempt to achieve this by targeting blood pressure, lipids, calcium-phosphate imbalance (mineral metabolism) and anaemia.

Over the past 20 years, there has been a wealth of publications reporting on the associations between uraemic anaemia and the development of left ventricular dilatation and left ventricular hypertrophy (LVH) [1–4], reduced quality of life [5,6] and mortality rates [7], both in the CKD non-dialysis and dialysis populations. In the pre-epoetin era, Silberberg reported an association between the degree of anaemia and LVH and differential mortality rates in dialysis patients in the late 1980s [8]. These findings were extended by Foley and Parfrey *et al*. [9,10] in a number of publications describing the association of anaemia with LVH, congestive heart failure and mortality. Levin *et al*. [1–3] extended those observations to patients with varying degrees of renal dysfunction, demonstrating increasing prevalence of LVH, dilatation and heart failure as kidney function declines. In addition, numerous other authors have described the association of haemoglobin and outcomes in CKD populations, prior to dialysis, on dialysis and even post-transplant [11].

Given the biological plausibility that anaemia impacts cardiac structure and function, and outcomes, as well as large amount of observational data that suggested a 'cause and effect' between the presence of uraemic anaemia and cardiomyopathy, a series of interventional trials were undertaken. Commencing in the late 1990s, a range of themes were applied to clinical trials to examine different hypotheses: 'early' *vs* 'late' correction of anaemia and 'lower' *vs* 'higher' haemoglobin levels in both 'pre-dialysis' and 'dialysis' populations.

Two published trials have examined whether prevention of anaemia could reduce or reverse the development of LVH in the non-dialysis CKD population, maintaining appropriate attention to other modifiable risk factors. Despite maintaining haemoglobin higher than 120 g/l in the active group and allowing for a progressive decline in haemoglobin in the control group (90–100 g/l), there was no statistical difference in the left ventricular mass between the groups after 2 years [12,13]. Of note, both studies found relative stability of haemoglobin in the control group, despite previous observations which would have suggested decline. Within the context of the trial, a number of parameters were attended to: blood pressure control, mineral metabolism balance and iron status. The findings suggest that even at relatively advanced stages of renal dysfunction, multiple clinical parameters within the context of a trial may cancel out the impact of anaemia on LVH. An editorial by Strippoli and Craig [14], of the Cochrane Renal Group, referred to this as a potential example of the Hawthorn effect, where patients in trials tend to do well. Nonetheless, it is important to note that in the observational studies, no treatment interventions were undertaken. The observations were undertaken in an unselected population, either in the pre-epoetin era, or prior to the acceptance of multiple risk factor intervention in CKD. Thus the randomized controlled trials have included a group of patients who are different from those on whom the original observations were made.

In this edition of NDT, Macdougall and co-investigators [15] applied a different model to pre-dialysis anaemic patients, whereby the control group's haemoglobin concentration was allowed to decline to lower levels (90 g/l), but were subsequently rescued to the same haemoglobin concentration as the active group. They too were unable to demonstrate

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a difference in left ventricular mass index (LVMI), between the two groups.

The authors highlight the limitations of the study which became evident as both anaemia management and study designs evolved over time: assessment of those who never received epoetin to correct anaemia and the timing of analysis of echocardiographic data.

All three trials have separated the haemoglobin values, but have done so by raising the haematocrit in the control group, not by having the haemoglobin fall in the control group, as the observational studies and others would have suggested [2,16]. Interestingly, in the paper by Levin *et al*. [2], and subsequent publication on the Roger data by McMahon *et al*. [17] in those patients who, irrespective of treatment group assignment, did demonstrate a decline in haemoglobin, there was a change in LVMI.

There are three other large trials that have explored normalization *vs* partial anaemia correction in non-dialysis CKD patients. The first study was designed to assess the effect of early and complete correction of anaemia using recombinant human erythropoietin (epoetin) alfa on the progression of CKD [18]. Unfortunately, it suffered from early termination by the sponsor because of the appearance of pure red cell aplasia associated with subcutaneous use of epoetin alfa (EPREX, Janssen-Cilag). The end point in this study was progression of CKD, and the study duration was insufficient to derive any conclusions.

The other two trials are contemporaneously appearing in the public domain, and scheduled for publication late in 2006. Both CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment) [19] and CHOIR (Correction of Hemoglobin and Outcomes In Renal Insufficiency) [20] were initiated in the context of observational data suggesting a negative impact of anaemia on mortality rates in the CKD population. See also editorial comment in the previous NDT issue: Adeera Levin, Understanding recent haemoglobin trials in CKD: methods and lesson learned from CREATE and CHOIR. *Nephrol Dial Transplant* 2007; 22: 309-312; doi:10.1093/ndt/gfl824.

The CREATE study examined correction of anaemia to high (normalization) *vs* standard-target values with epoetin beta (NeoRecormon, Roche) in 600 patients across Europe and was unable to demonstrate a significant impact on cardiovascular disease events in CKD patients. Secondary end points included the effect of the same strategy on LVMI and progression of kidney disease. Initial echocardiograms did not demonstrate severe LVH and over the 4 years of the trial, there was no significant change in LVMI. As in the nested analysis of the Australian study, those patients who commenced the study with hypertrophied hearts did appear to benefit from early anaemia correction to higher haemoglobin concentrations [17].

The last trial, CHOIR, was an open-label, multicentre study that randomized a total of 1432 patients to achieve target haemoglobin levels of 135 or 113 g/l, respectively [20]. This trial explored the hard end points of time to all-cause mortality or cardiovascular morbidity (myocardial infarction, stroke or heart failure), rather than the surrogate end points of change in left ventricular mass or quality of life. The trial was terminated early (after a planned interim analysis) because of both futility and a suggestion of harm in the treatment group. Hospitalization for heart failure and death appeared to drive the composite event rate (A Singh, NKF Spring Clinical Meeting, Chicago, April 2006).

So, what is the unifying theme as to why these trials have failed to show a benefit in terms of improvement in LVMI? Might it be that patients who are enrolled in clinical trials receive a level of care that surpasses that of routine clinical management, and is certainly different from the care received in the populations on whom the observations were originally made? Yes, most likely. There is close attention to blood pressure, lipids, mineral metabolism and iron supplementation in all the studies. These combined treatment strategies, in addition to close follow-up by nature of being in a trial, may well have contributed to the lack of fall of haemoglobin, the slower rate of progression of CKD, and thus maintenance of effective endogenous erythropoietin production. In combination with the therapies that would also impact on LVH (treatment of blood pressure, use of ACEi, control of hyperparathyroidism) the studies were unable to demonstrate the isolated impact of anaemia correction. Observational data is important for our interpretation of clinical issues; when coupled with sound biological plausibility, that data provides a stepping stone for the design of randomized clinical trials to explore hypotheses.

Observational data had suggested anaemia correction would lead to improvements both in surrogate (LVH) and hard end points (CV events/mortality). However, the trials to date have fallen short of confirming those suspicions. One might suggest that there is a need for more 'real world' designed trials, in which populations are not highly selected (with little comorbidity and demonstrated stability), and in which the treatment paradigms are in keeping with current conventions, and not highly controlled. It is only then that the true impact of an isolated intervention like treatment of anaemia can be determined. There are certainly examples of this in the cardiology literature (HOPE, Heart Protection Study), and in nephrology, the recently commenced study SHARP (Study of Heart which and Renal Protection) which aims to describe the impact of lipid-lowering strategies on patient outcomes [21–23]. All of these studies test the hypothesis that the single intervention in large populations, representative of those patients seen by all medical practioners, is effective.

Perhaps the time has come for nephrologists to design studies based on the clinical observations made, but in the unselected populations in which those observations were made, and enrolling large numbers of patients in multiple centres.

With the appearance over biosimilar epoetins in various western markets over the next few years, necessary pharmaceutical sponsorship of trials

may disappear, but with appropriate collaboration amongst the nephrology community, and pharmaceutical industries including those making the biosimilars, an opportunity may exist to continue to test these hypotheses. Alternatively, it may be that the nephrology community is sufficiently satisfied with the answers to date, and are convinced that there is no additional benefit of normalizing haemoglobin in CKD populations. Correction of anaemia to values over 100–110 g/l as per most guidelines may well be appropriate for this complex patient group.

Conflict of interest statement. Drs Roger and Levin have received funding for investigator initiated and pharmaceutical industry sponsored trials and received honoraria for advisory boards and speaking for Amgen, Janssen-Cilag and F. Hoffmann-la Roche.

(See related article by Macdougall *et al*. Is early treatment of anaemia with epoetin-α beneficial to pre-dialysis chronic kidney disease patients? Results of a multicentre, open-label, prospective, randomized, comparative group trial. *Nephrol Dial Transplant* 2007; 22: 784–793.)

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