Higher target haemoglobin level and early anaemia treatment: different or complementary concepts?

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Abstract There is little doubt that epoetin is a highly effective treatment for renal anaemia. However, it has been used primarily to treat dialysis patients, in whom there is good evidence that it induces significant improvements in cardiac function, exercise capacity, and quality of life. Unfortunately, none of these three major parameters is completely normalized. There are three possible reasons for this: (i) the anaemia is not fully corrected, (ii) too much damage has already occurred by the time the patient starts dialysis, and (iii) other contributory factors may be playing a part. Although the effects of completely correcting renal anaemia have been examined in various studies, the results have not been as positive as expected. It therefore seems appropriate to consider a new strategy in which epoetin therapy is initiated at an earlier stage in the course of the disease, e.g. at a haemoglobin concentration of 11 g/dl or less. It is possible, for example, that earlier treatment of anaemia could prevent many cardiac problems and other morbidities in renal patients. In addition, if epoetin therapy is started in patients who have not been exposed to long-term chronic anaemia, fewer complications may be encountered when reversing the anaemia. Higher target haemoglobin concentrations may also be appropriate in these patients. It would certainly be inappropriate, however, to extrapolate the data on normalization of haemoglobin in dialysis patients to the pre-dialysis population. It is therefore necessary to re-examine the issue of optimal target haemoglobin concentration in pre-dialysis patients. One of the challenges in the new millennium must be to better understand the consequences of initiating treatment of anaemia earlier in the course of chronic renal failure.

Key words: anaemia; early treatment; epoetin; target haemoglobin; treatment strategies

Introduction

There is little doubt that epoetin is a highly effective treatment for the anaemia of renal failure. It has transformed the management of this condition, dramatically reducing the need for blood transfusions, and replacing previously unsatisfactory treatments such as the use of androgens. Epoetin is effective in correcting renal anaemia in 90–95% of patients treated [1–3], and there are considerable secondary benefits in terms of improved cardiac function [4–8], exercise capacity [9–11], and quality of life [12–14].

To date, however, epoetin has been used primarily to treat dialysis patients, many of whom have been exposed to chronic anaemia for a considerable time before epoetin therapy is initiated. A large number of these patients have already developed irreversible, or only partially reversible, changes in cardiac structure, such as left ventricular hypertrophy and left ventricular dilatation [15–17]. It is becoming increasingly apparent that the greater the degree of cardiac damage, the more difficult it is to reverse the damage, even with aggressive anaemia treatment. This observation has stimulated a new approach to the treatment of renal anaemia, i.e. starting epoetin at an earlier stage in the course of the disease. The aim of this article is to discuss not only why this new strategy seems appropriate, but also why the existing strategy of focusing on dialysis patients alone is not the solution if significant improvements in quality of life, morbidity, and mortality are to be achieved in the renal failure population.

Strategies for treating renal anaemia

Strategy 1

Few nephrologists would argue against treating a patient with end-stage renal failure who has recently started dialysis and whose haemoglobin concentration has fallen progressively to around 8–9 g/dl (Figure 1). This course of action is appropriate for two reasons: firstly to improve the symptoms of chronic anaemia, and secondly to slow the progression of cardiac.
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The results of most of these studies have been rather disappointing. The Normal Hematocrit Trial [19] was a randomized, prospective, open-label multicentre study involving 51 centres in the USA. A total of 1233 haemodialysis patients were recruited, all of whom had to have clinical evidence of ischaemic heart disease or congestive heart failure. In the ‘intervention’ group, which comprised 618 patients, the target haematocrit was 42%. The aim in the ‘control’ group of 615 patients was to maintain a haematocrit of around 30%. The primary end-point of this study was death or first non-fatal myocardial infarction, and the intended follow-up was 3 years. There was a clear difference in the achieved haematocrits in the two groups of patients (Figure 3). Nevertheless, the study was aborted prematurely after 29 months due to a borderline damage. There is good evidence that dialysis patients treated with epoetin show major improvements in cardiac function [4–8], exercise capacity [9–11], and quality of life [12–14]. In epoetin-treated patients, the high cardiac output associated with chronic anaemia reverses towards normal [4], peripheral vascular resistance increases [4], anginal symptoms lessen [5, 6], and left ventricular hypertrophy regresses [5,7,8]. Patients also show an increased capacity for exercise, with objective improvements in maximum oxygen consumption and anaerobic threshold [5,9–11]. Quality-of-life parameters, measured using tools such as the Karnofsky Score and the Sickness Impact Profile, also improve significantly [12–14] in patients treated with epoetin.

Nevertheless, most studies fail to show complete normalization of these physiological defects. Although left ventricular mass decreases, some degree of left ventricular hypertrophy is still evident in many dialysis patients [5,7,8]. In most patients, little change is seen in left ventricular dilatation, another abnormality that is known to predispose to cardiac mortality, after anaemia is corrected with epoetin [5,18]. Quality of life and exercise capacity may improve with epoetin, but most patients still have subnormal values as compared with normal, healthy, age- and sex-matched controls.

Why are we unable to normalize left ventricular hypertrophy, left ventricular dilatation, exercise capacity, and quality of life in dialysis patients? There are several possible reasons: (i) the anaemia is not fully corrected, (ii) too much damage has already occurred by the time the patient starts dialysis, and (iii) other contributory factors may be playing a part.

**Strategy 2**

Several clinical studies [11,18–20] have investigated whether failure to achieve maximum benefit from epoetin therapy might be due to the fact that anaemia is only partially, not completely, corrected. All of these studies recruited dialysis patients in whom anaemia had already been partially corrected with epoetin; a subgroup of patients was then targeted to achieve a normal haemoglobin concentration or haematocrit (Figure 2). The results of most of these studies have been rather disappointing.

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the study provided no evidence to support universal adoption of a ‘normalization of haemoglobin’ strategy.

A Canadian multicentre trial [18] examined changes in left ventricular hypertrophy and cavity volume in two groups of haemodialysis patients. As with the Normal Hematocrit Trial, the target in the ‘intervention’ group was a normal haemoglobin concentration, while the aim in the ‘control’ group was to maintain a conventional haemoglobin concentration of around 10–11 g/dl. Although minor improvements in left ventricular hypertrophy and quality of life were seen in this study, the main conclusion was that left ventricular dilatation could not be reversed, even when anaemia was fully corrected [18]. It was, however, possible to prevent the development of left ventricular dilatation in patients who had a normal left ventricular cavity volume at the start of the study; this was in contrast to the ‘control’ patients, many of whom continued to show progressive left ventricular dilatation (Figure 5). The obvious conclusion from this study is that an attempt should be made to prevent left ventricular dilatation from ever developing, since any intervention, including treatment of anaemia, will be too late to have a positive impact once left ventricular dilatation is present.

In another recent study, McMahon et al. [11] measured exercise capacity following normalization of haemoglobin concentration using a randomized crossover design. All patients in this study were examined at two target haemoglobin concentrations, the first at around 10 g/dl, and the second at around 14 g/dl. Exercise capacity and maximum oxygen consumption were greater at the higher haemoglobin concentration ($P < 0.01$ for all 14 patients) (Figure 6). Even at a normal haemoglobin concentration, however, the exercise capacity of dialysis patients was still considerably lower than that of normal healthy individuals [11]. There are several possible reasons for the difference: (i) acquired abnormalities in muscle function, (ii) general systemic effects from sustained uraemia, or (iii) prolonged exposure to anaemia. Again, this study suggests that a strategy of intervention at an earlier stage in the course of renal anaemia should be considered.

**Strategy 3**

Another strategy to consider is treating renal anaemia at an earlier stage in its development. In many cases, this would mean initiation of epoetin therapy before the patient needs dialysis (Figure 7). As nephrologists currently strive to treat hypertension early, hyperparathyroidism early, and malnutrition early, the obvious question is ‘why not anaemia?’

Unfortunately, most of the studies of epoetin therapy in pre-dialysis patients have involved small numbers of patients and short follow-up periods [22–25], and it is therefore difficult to draw any definitive conclusions from the results. It is known, however,
that epoetin is both safe and effective in treating renal anaemia in pre-dialysis patients. Despite earlier concerns raised by the results of one animal study [26], there is now considerable evidence to show that epoetin does not worsen the decline in renal function in pre-dialysis patients [22–25].

There are also some preliminary data indicating that epoetin improves cardiac function and quality of life in pre-dialysis patients, although evidence from controlled studies is still lacking. Several studies in the UK, Canada, and Australia, however, are currently examining the effects of earlier anaemia treatment on cardiac function, exercise capacity, and quality of life. Data from these studies are expected in the near future.

The study being conducted in the UK—the UK Early Intervention Study—involves 25 centres. This study has recruited patients with a serum creatinine level of between 150 and 500 μmol/l who are not yet on dialysis. The aim in the ‘early intervention’ group is to maintain a haemoglobin concentration of 11 ± 1 g/dl; in the ‘triggered intervention’ group, the haemoglobin concentration is allowed to fall to less than 9 g/dl before epoetin is started. Major end-points in this study include left ventricular hypertrophy, exercise capacity, and quality of life.

**Strategy 4**

The natural extrapolation from a strategy of treating renal anaemia at an earlier stage in the disease process is a strategy aimed at preventing renal anaemia from ever developing (Figure 8). Clearly, the ‘technology’ to achieve this is available, and one of the challenges in the new millennium must be to investigate in a scientific manner the implications of such an approach. While scientific evidence in support of such a strategy is currently lacking, perhaps the popular saying ‘prevention is better than cure’ should be borne in mind.

**Conclusions**

Guidelines that address the following questions are urgently needed:

- What haemoglobin concentration should epoetin treatment be initiated?
- What is the optimal target haemoglobin concentration in pre-dialysis patients?
- How can the benefits of early anaemia treatment in pre-dialysis patients be maximized?
- What impact will early anaemia correction have on healthcare services?

It is possible, for example, that epoetin dose requirements will be lower in pre-dialysis patients than in patients who are already on renal replacement therapy. In the meantime, both the DOQI Guidelines [27] and the European Best Practice Guidelines [28] suggest that the aim should be to maintain the haemoglobin concentration above 11 g/dl in patients with renal failure. It is to be hoped, as data from ‘early intervention’ studies become available, that the scientific rationale for this approach will be strengthened.

In the course of the past 10 years, it has become increasingly apparent that left ventricular hypertrophy and left ventricular dilatation, exercise capacity, and quality of life cannot be normalized if anaemia treatment is started too late in the course of the disease. Therefore, to limit cardiac damage and maximize the improvements in exercise capacity and quality of life, the treatment of anaemia must be initiated earlier in renal failure patients. The results of studies investigating the effects of epoetin therapy in pre-dialysis patients are awaited with much hope and expectation.

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**References**

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