Chairman’s Workshop Report

How should anaemia be managed in pre-dialysis patients?

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Abstract Anaemia is a common problem in patients with renal failure, whether or not they are on dialysis. There is a continuum of declining renal function. In addition, the creatinine clearance at which dialysis is initiated varies widely between institutions and between studies. The term ‘progressive renal insufficiency’ is therefore preferable to ‘pre-dialysis’. The adverse effects of renal anaemia on left ventricular mass become apparent early in the course of progressive renal insufficiency; 75% of patients starting dialysis already have left ventricular hypertrophy (LVH). Correction of anaemia in patients with progressive renal insufficiency has been shown to improve physical function and anaemia-related symptoms, but no controlled studies have yet been conducted to determine its effects on LVH. Although one animal study generated some concern that epoetin may exacerbate a decline in renal function, there is no evidence from human studies for any such effect. Treatment of anaemia with epoetin in anaemic patients with progressive renal insufficiency is therefore recommended, provided blood pressure is controlled. To date, however, there are insufficient data to determine whether normalization of haemoglobin is advisable in this patient group. Detection and correction of iron deficiency is important to achieve the full benefits of epoetin, though recommendations cannot yet be made regarding the optimum route and timing of iron supplementation in patients with progressive renal insufficiency. In these patients the role of other adjuvant therapies, such as L-carnitine, vitamin B₆, vitamin B₁₂, and folic acid, also requires further investigation.

Key words: anaemia; blood pressure; epoetin; iron deficiency; pre-dialysis; renal function

Introduction

Before attempting to discuss the management of anaemia with epoetin in ‘pre-dialysis’ patients, it is essential to define the terms. There are two important reasons for insisting on a precise definition of ‘anaemia’ and ‘pre-dialysis’. Firstly, in the research situation, only studies in well-defined patient groups are likely to yield reliable, clinically applicable results. Secondly, rational, evidence-based guidelines for everyday clinical practice can only be provided if the patients to whom they apply are clearly defined.

‘Anaemia’

Unfortunately, even the term ‘anaemia’ is ill-defined with regard to chronic renal failure (CRF). In virtually every other disease area, physicians routinely define anaemia as a haemoglobin less than the normal physiological value: 12–16 g/dl for pre-menopausal females and 13.5–17.5 g/dl for males and post-menopausal females [1]. It is remarkable that in patients with CRF, anaemia is typically defined as a haemoglobin < 11 g/dl for both men and women. As discussed elsewhere in this Supplement, the assumption that CRF patients do not need a ‘normal’ haemoglobin is highly debatable. This workshop recommended that anaemia for CRF patients be defined relative to normal haemoglobin for both genders.

‘Pre-dialysis’

The term ‘pre-dialysis’ is similarly ill-defined. In the literature on epoetin, pre-dialysis has been used to describe patients with a wide range of creatinine clearances, from near-normal to almost pre-terminal. In fact, many of the pre-dialysis patients included in older studies had creatinine clearances as low as 10 ml/min. According to current recommendations, these patients would already have been on dialysis.

The term pre-dialysis therefore implies a rigid cutoff between patient groups, which simply does not exist in real life. Furthermore, whether a patient is categorized as ‘pre’ or ‘post’ dialysis is not wholly determined by his or her clinical condition, but is also influenced by local resources. The physiological reality is a progressive continuum of chronic renal insufficiency.
Canadian Multicentre Study in Early Renal Disease

The existence and relevance of a progressive continuum of renal insufficiency is illustrated by the findings of the Canadian Multicentre Study in Early Renal Disease [2–5]. This is an ongoing, prospective, longitudinal cohort study of the progression of renal disease prior to intervention, conducted at eight academic nephrology centres across Canada. All patients with creatinine clearances of between 20 and 75 ml/min are evaluated serially for renal function. Cardiac status is evaluated using annual two-dimensional echocardiograms to measure left ventricular mass index (LVMI), and cardiac symptoms and events are recorded. Serial measurements are performed for standard laboratory variables, and for haematological, biochemical and endocrine parameters. Clinical records are also kept of blood pressure, medications and body weight.

To date, 446 patients (mean age: 56 years) have entered the study. Approximately half the patients have moderate renal insufficiency (creatinine clearance of 25–50 ml/min), ~30% have a creatinine clearance of 50–75 ml/min and ~20% have a creatinine clearance of <25 ml/min. Just over two-thirds (68%) of the patients are male, which is typical of the dialysis population in Canada. In this cohort, 30% of the patients are diabetic and 86% are hypertensive (i.e. have a mean arterial pressure of >105 mmHg at entry, or are receiving antihypertensive therapy); the mean creatinine clearance is 36 ml/min (corrected for age and weight), the mean haemoglobin is 12.6 g/dl and the mean parathyroid hormone (PTH) is 11.7 pmol/l (twice the upper limit of normal), despite a normal mean calcium (2.3 mmol/l).

One of the most striking findings so far is that many of the patients already have a marked degree of left ventricular hypertrophy (LVH) at baseline. The prevalence of LVH is related to the degree of renal dysfunction (Figure 1): 26% at a creatinine clearance of 50–75 ml/min; 33% at 25–50 ml/min; and 41% at <25 ml/min (P < 0.01 vs 50–75 ml/min). For comparision, the incidence of LVH in patients commencing dialysis is 75% in Canada [6].

Patients who have LVH at baseline are significantly older (mean age 59 years vs 53 years, P < 0.003), have significantly worse renal function (mean creatinine clearance of 33 ml/min vs 39.2 ml/min, P < 0.002) and have a significantly lower haemoglobin (12.1 g/dl vs 13.1 g/dl, P < 0.001). As might be expected, these patients have significantly lower plasma calcium and greater systolic and mean arterial pressures.

However, it is important to note that LVH is defined on a population basis (LVMI > 131 g/m² for men and > 100 g/m² for women) and is simply a categorization of a continuous variable. Perhaps a more clinically relevant measurement is change in LVMI. A clinically significant increase in LVMI can be defined as an increase of > 20% from baseline, or an absolute value of > 20 g/m². Based on these criteria, a significant increase in LVMI occurred during the study in 23% of patients. At baseline, those patients who did and those who did not have a subsequent increase in LVMI showed no significant differences in age, serum creatinine, creatinine clearance, haemoglobin, mean arterial pressure or the use of angiotensin-converting enzyme (ACE) inhibitors or calcium-channel blockers.

After 12 months, haemoglobin and systolic blood pressure were the only variables that differed significantly between patients with and those without an increase in LVMI. Haemoglobin had decreased by a mean of 0.75 g/dl in patients with an increase in LVMI, compared with 0.1 g/dl in patients with no increase in LVMI (P < 0.001). Contrary to expectations, it appeared that treatment with ACE inhibitors did not have a protective effect against an increase in LVMI.

These findings demonstrate that the cardiovascular consequences of renal anaemia begin relatively early in the course of renal failure, and that an increase in LVMI is closely linked to the change in haemoglobin over time.

Recommendations regarding definitions

Based on the evidence presented, the workshop participants concluded that the term ‘progressive renal insufficiency’ is more appropriate than ‘pre-dialysis’. Furthermore, it was recommended that anaemia itself should be defined as any haemoglobin less than the normal physiological range (gender-adjusted). In addition to the absolute haemoglobin, the rate of decline in haemoglobin may also be important. However, defining anaemia relative to normal haemoglobin does not necessarily mean that haemoglobin should be normalized. As discussed below, the optimum target haemoglobin for patients with progressive renal insufficiency remains as controversial as that for patients on dialysis.

Benefits of treating anaemia in patients with progressive renal insufficiency

Having established that the adverse cardiovascular effects of anaemia are apparent quite early in the
course of renal failure, the workshop participants then considered the potential benefits and risks of correcting the anaemia of progressive renal insufficiency with epoetin.

Studies have demonstrated that epoetin can be used safely and effectively to increase the haemoglobin in anaemic patients with progressive renal insufficiency [7–9]. What effect, however, does increasing haemoglobin have on the clinical manifestations of anaemia?

Anaemia has well-known negative effects on physical, cognitive, emotional and sexual function. Equally important, however, are its effects on the cardiovascular system, which may ultimately result in LVH and its consequences, myocardial infarction and heart failure. The importance of anaemia as a risk factor in patients on haemodialysis has been clearly demonstrated [10,11]. Haemoglobin concentrations of ≤8 g/dl are associated with a 2-fold increase in the odds of death when compared with haemoglobin of 10–11 g/dl [12]. Furthermore, anaemia predicts mortality independently of age, diabetes mellitus, cardiac failure, hypoalbuminaemia, serum creatinine, mean arterial pressure or echocardiographic heart disease.

LVH is already present in 75% of patients starting dialysis and, like anaemia, is an independent predictor of mortality [6]. Anaemia during the pre-dialysis period is believed to be a key factor in the development of LVH in patients with renal failure [4,13]. Since there is a continuum of renal failure, treating anaemia should be beneficial, whether or not the patient is on dialysis. One would also expect that correction of anaemia would at least partially reverse the adverse consequences of anaemia in all patients with renal failure.

This hypothesis is supported by the finding that correction of anaemia with epoetin brings about partial regression of LVH in patients with end-stage renal disease (ESRD) [14]. While regression of LVH has yet to be demonstrated for patients in the pre-dialysis phase, beneficial cardiovascular effects have been shown in terms of exercise capacity [8,15–18]. Furthermore, dialysis patients treated with epoetin are less likely to be hospitalized than those who are not receiving this therapy [19].

In addition to positive effects on the cardiovascular system, correction of anaemia with epoetin results in many other benefits. In patients with progressive renal insufficiency, the effects on energy levels and work capacity are similar to those seen in haemodialysis patients (Figure 2) [8]. Treatment of anaemia has been shown to improve cognitive function not only in dialysis patients [20,21] but also in progressive renal insufficiency patients [16]. Likewise, sexual function improves in both patients on dialysis [22] and those with progressive renal insufficiency [16]. This effect is probably a result of beneficial effects on pituitary–gonadal feedback [23]. Epoetin has also been reported to enhance immune responses in patients with ESRD [24].

The overall effect of improvements in physical function, energy, cognitive function, sexual function and other parameters is an increase in health-related quality of life. This applies not only to dialysis patients but also to those with progressive renal insufficiency [16]. However, demonstration of beneficial effects in patients who are not yet on dialysis is not sufficient. It must also be established that administration of epoetin does not accelerate the decline in renal function in this patient group.

**Does epoetin accelerate renal failure?**

To understand the issues surrounding the effects of epoetin on renal function, both animal and human studies must be considered.

**Animal studies**

Animal data from a study by Garcia et al. in 1988 have generated some concern regarding a potential adverse effect of epoetin treatment on renal function [25]. In a rat model of chronic renal insufficiency, the researchers found that preventing anaemia with epoetin increased systemic and glomerular hypertension and glomerular injury. In contrast, renal function was actually preserved by anaemia in this study.

The study used 5/6 nephrectomized rats, divided into three groups: controls (nephrectomy only); epoetin-treated anaemic (nephrectomy plus epoetin treatment to maintain a stable haematocrit); and untreated anaemic (nephrectomy plus bleeding and a low-iron diet). The animals were monitored for 12 weeks.

As expected, the control rats showed a reduction in haematocrit from 50 to 42%. In the untreated anaemic rats, haematocrit was reduced to ~30%, while in the epoetin-treated animals it remained stable at 50%.

Striking differences were found between the groups with regard to systolic blood pressure (measured by the tail cuff method) and urinary protein excretion (Figure 3) [25]. In the epoetin-treated anaemic animals, blood pressure was highest at baseline and increased sharply during the first 6 weeks of the study (after which the animals died). Blood pressure also increased in the control group, levelling off at ~6 weeks, with the animals surviving to 12 weeks. In the untreated anaemic group, blood pressure was initially low and showed little increase during the study.

Urinary protein excretion mirrored systolic blood pressure, being very marked in the epoetin-treated anaemic animals, very slight in the untreated anaemic group and intermediate in the controls. Filtration pressure followed the same pattern. There was very early glomerular sclerosis in the epoetin-treated anaemic animals; 33% of glomeruli were found to be sclerosed after 6 weeks. The control group took 12 weeks to reach 30% sclerosis, whereas the untreated anaemic animals showed only 6% sclerosis after 12 weeks.

The authors concluded: ‘these results suggest that
anemia is a hemodynamically favorable adaptation to chronic renal disease and that its overly vigorous correction may have adverse renal hemodynamic and structural consequences. In a later study, however, Ruedin et al. showed that control of systemic hypertension could completely prevent any adverse effect of epoetin treatment in rats [26].

**Human studies**

Despite the somewhat disturbing results of the animal study reported above, several human studies provide no evidence to suggest that treatment with epoetin may accelerate renal decline [15,18,27–30].

Teehan et al. found no effect of epoetin on creatinine clearance in a 6 month study of 12 pre-dialysis patients [15]. In a study of 26 patients followed-up for a period of 2.4–24 months, Lim et al. found that neither epoetin administration nor a normal haematocrit accelerated the deterioration of renal function (measured by the slope of 1/serum creatinine vs time) [27]. In a study of 16 patients (follow-up: 12–65 weeks), Abraham et al. found no adverse effect of epoetin administration either on glomerular filtration rate (GFR) (measured by inulin clearance) or on the slope of 1/serum creatinine vs time [28].

In a 12 week study of eight pre-dialysis patients, Frenken et al. [29] found no effect of epoetin treatment on GFR, renal blood flow or filtration fraction. Similarly, in a 12 week study of 12 patients, Clyne and
Jogenstrand [18] found no adverse effects of epoetin on GFR. The Austrian Multicenter Study of 123 epoetin-treated patients found no alterations in the slope of the curve of renal decline (1/serum creatinine) over a 12 week follow-up period [7].

More recently, Roth et al. [30] conducted the first large-scale study of the effects of epoetin on renal function in a large number of patients with progressive renal insufficiency, using a reliable measure of GFR ([¹²⁵I]iothalamate clearance). This 48 week, randomized, open-label, multicentre study included 83 anaemic patients with a serum creatinine of 3–8 mg/dl (265–707 μmol/l) who were not yet on dialysis. At entry, patients were required to have a haematocrit of ≥30%, a mean arterial pressure of <114 mmHg, a daily protein intake of 0.8 ± 0.32 g/kg/day, and good control of serum phosphorus (<5.5 mg/dl); these parameters were controlled within the same range throughout the study.

A 2 month stabilization phase (for control of blood pressure and nutritional parameters) was followed by a 48 week treatment phase. Forty patients were randomized to the untreated arm and 43 patients to the treatment arm (50 IU/kg epoetin subcutaneously (s.c.) three times weekly). When the haematocrit reached 36%, the epoetin dosage was titrated to maintain a haematocrit of 35%. GFRs were measured at intervals throughout the study (weeks 1, 8, 32, 48 or early termination).

The majority of epoetin-treated patients (79%) achieved the target haematocrit of 36% (average just under 35%). In contrast, the haematocrits of untreated patients did not change significantly during the study. GFR, mean arterial blood pressure and daily protein intake did not differ significantly between the two groups during the study. The statistically significant increase in haematocrit in the epoetin-treated group was not associated with any acceleration of deterioration in GFR (Table 1) [30], nor was there any difference between the groups in time to initiation of dialysis (Figure 4) [30]. The authors concluded that epoetin therapy improves anaemia in pre-dialysis patients and does not accelerate progression to ESRD.

Recently, it has actually been claimed that correction of anaemia with epoetin can retard the progression of renal failure in pre-dialysis patients [31]. In this study, untreated anaemic controls (n = 31) were compared with anaemic patients treated with epoetin (n = 42) and with non-anaemic controls (n = 35). The primary end point for each patient was a doubling of the baseline creatinine, yielding cumulative renal survival rates plotted against time. Cumulative renal survival in the epoetin-treated patients and non-anaemic controls was significantly better than in untreated anaemic patients, a difference which seemed to indicate better renal survival in non-diabetic epoetin-treated patients. The authors suggested that ‘reversal of anemia by epoetin can retard the progression of renal failure, especially in non-diabetic patients, provided that blood pressure control, rate of increase in hematocrit, and dietary protein restriction are appropriate’.

### Table 1. Glomerular filtration rate (GFR) ([¹²⁵I]iothalamate clearance) in 83 anaemic pre-dialysis patients followed up for 48 weeks with and without epoetin treatment (mean ± SD)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Epoetin-treated</th>
<th>Untreated</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>GFR (ml/min)</td>
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<tr>
<td>1</td>
<td>41</td>
<td>10.2 ± 4.1</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>9.7 ± 4.2</td>
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<tr>
<td>16</td>
<td>33</td>
<td>9.3 ± 3.3</td>
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<tr>
<td>32</td>
<td>19</td>
<td>9.1 ± 3.7</td>
</tr>
<tr>
<td>48</td>
<td>15</td>
<td>9.5 ± 4.4</td>
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</table>

There was no significant effect of epoetin treatment on renal function. (Data from [30]).

### Need for further studies

To date, there is no evidence from human studies indicating that treating anaemia with epoetin in progressive renal insufficiency patients has any detrimental effect on progression of renal failure. However, most studies have included relatively small numbers of patients, and have had short follow-up periods. Under these circumstances, and given the usual wide variability in baseline renal function, correction of anaemia would have to exhibit a marked effect on renal survival in order to become apparent [32]. The number of patients required to demonstrate a difference in renal survival of 10% would range from 80 (for a 15% coefficient of variation in renal function) to 600 (for a 50% variation). Further studies are therefore needed to confirm the encouraging data obtained so far.

### Importance of controlling blood pressure

Any potential adverse effects of epoetin on renal function are likely to be mediated via effects on blood pressure. The majority of epoetin-treated patients (79%) achieved the target haematocrit of 36% (average just under 35%). In contrast, the haematocrits of untreated patients did not change significantly during the study.

[Figure 4. Survival function for time to initiation of dialysis in 83 anaemic pre-dialysis patients followed up for 48 weeks with and without epoetin treatment. There was no significant effect of epoetin treatment on survival function. P-values for comparing equality of survival curves: log-rank test, P = 0.9955; Wilcoxon test, P = 0.8613. (Reproduced with permission from [30]).]
pressure. In the rat study by Garcia et al., for example, there was a sharp, uncontrolled increase in blood pressure in epoetin-treated animals, which probably caused the acceleration in renal failure [25].

Partial correction of anaemia with epoetin in CRF patients causes hypertension in ~20% of patients [33]. However, most studies have found that an epoetin-induced increase in blood pressure can be controlled readily with antihypertensive medication in the majority of patients.

Nevertheless, certain reservations must be borne in mind. For example, it is becoming increasingly evident that the optimum target blood pressure for patients with progressive renal disease may be much less than the currently accepted 140/90 mmHg [34]. No study has yet shown that blood pressure can be reduced to less than this in epoetin-treated pre-dialysis patients. Furthermore, none of the studies conducted so far has used 24 h blood pressure monitoring to ascertain adequate blood pressure control.

In addition, successful reduction of blood pressure in essential hypertension has not resulted in as large a reduction in cardiac mortality as might be expected on the basis of epidemiological studies. In hypertensive patients with progressive renal insufficiency, as in other categories of hypertensive patients, it is unclear whether effective treatment of hypertension will offer protection against cardiac events. In the Modification of Diet in Renal Disease (MDRD) study [35], it was not possible to demonstrate a protective effect of low-protein diet or aggressive blood pressure therapy in a cohort of several hundred patients who were followed for many years. Finally, it is not known how the different therapeutic agents that may be used in progressive renal insufficiency patients interact. For example, the study by Frenken et al. demonstrated that the efferent renal vasodilative response to an ACE inhibitor is blunted in patients treated with epoetin [29].

Who to treat

The workshop concluded that the evidence from human studies shows epoetin to be effective in correcting anaemia in patients with progressive renal insufficiency. There is no evidence of short-term (up to 48 weeks) adverse effects of correcting anaemia with epoetin in patients with advanced renal insufficiency and a haematocrit of 27–34%, provided that blood pressure is controlled.

Progressive renal insufficiency might be defined in terms of: (i) a GFR of <50% of normal (adjusted for age and gender); and (ii) structural evidence of renal disease. Such patients have an ~80% chance of progressing to end-stage renal failure [36].

Serum creatinine per se is uninformative, and it is therefore preferable to use calculated or measured creatinine clearances. In addition to anaemia, patients considered for epoetin treatment would also be expected to have evidence of other pathophysiological consequences of impaired renal function, such as hypertension, mild or moderate hyperparathyroidism and metabolic acidosis.

Should haemoglobin be normalized in patients with progressive renal insufficiency?

There is a difference between treating anaemia and normalizing haemoglobin. At present, there is no evidence either to recommend or to advise against early treatment to normalize haemoglobin in patients with progressive renal insufficiency. Long-term, randomized, controlled trials are needed to reassess both the optimal timing and the targets for treatment of anaemia in this patient group. In particular, the relative benefits and risks of normalizing haemoglobin in progressive renal insufficiency patients must be evaluated. It is important to identify appropriate end points for such studies, which might include time to renal replacement therapy, rate of progression, exercise capacity, left ventricular growth and geometry, and cardiac events.

Role of adjuvant therapy

Studies on the efficacy and safety of epoetin treatment in patients with progressive renal insufficiency should also investigate the role of adjuvant therapies. The use of appropriate adjuvant therapies could increase the effectiveness of epoetin therapy in those progressive renal insufficiency patients who may require high doses to achieve target haemoglobin.

Iron supplementation

Diminished iron stores and/or decreased availability of iron are the most common causes of relative resistance to epoetin in uraemic patients [37]. Intravenous (i.v.) iron is now widely accepted as the most effective route of administration for iron supplementation for patients on dialysis [38]. However, much less is known about the effectiveness of and optimal route of administration for iron supplementation in patients with progressive renal insufficiency. Bone marrow studies in uraemic undialysed patients show that ~94% have reduced iron stores [39]. Possible reasons for this include reduced iron intake (due to anorexia or a low-protein diet), reduced iron absorption or gastrointestinal blood loss.

Silverberg et al. [40,41] have reported the efficacy of i.v. iron in patients with progressive renal insufficiency, both with and without concurrent epoetin treatment. In a study of 33 anaemic undialysed patients (creatinine clearances of 10–40 ml/min), previously treated with oral iron, 200 mg i.v. iron sucrose was administered once monthly for 5 months [41]. One month after the last dose, the mean increase in haematocrit percentage points was 1.9, compared with baseline values. In the 22 patients in whom haematocrit increased, the mean increase in haematocrit percentage points was 3.0.
A subsequent study was conducted in 93 anaemic undialysed patients (of whom data for 71 have been published [40]). Patients were treated once weekly for 5 weeks with: (i) epoetin 2000 IU s.c. (n = 13); (ii) iron sucrose 200 mg i.v. (n = 52); or (iii) a combination of i.v. iron and epoetin (n = 28).

All patients had initial serum ferritin <600 µg/l and transferrin saturation <35%. Three weeks after the last dose, the mean rise in haematocrit percentage points was 0.46 in the epoetin group, 3.17 in the i.v. iron group and 4.24 in the combination group.

A subset of those patients originally given i.v. iron was then given either a second course of i.v. iron alone or the i.v. iron–epoetin combination. In these two groups, the mean increases in haematocrit percentage points after both treatment courses together were 5.89 and 6.88, respectively. A repeat course was also given to a subset of those who were originally given the i.v. iron–epoetin combination, and the mean increase in haematocrit percentage points after both courses together was 5.34. In total, ~40% of patients who had been given i.v. iron alone and 75% of those who had received the combination of i.v. iron and low-dose epoetin achieved the target haematocrit of 35%.

Patients who reached the target haematocrit were then followed-up for a mean of 9 months. Almost 30% of those who initially had received the i.v. iron–epoetin combination were able to maintain the target haematocrit for several months without epoetin therapy.

In none of the original three treatment groups did initial serum ferritin, erythropoietin, transferrin receptor protein or parathyroid hormone correlate with haematocrit response. However, in the group that received i.v. iron only, initial and final serum creatinine and initial percentage transferrin saturation values correlated negatively with haematocrit response. The rate of decline in renal function, as measured by the change in serum creatinine over time, improved significantly with treatment of the anaemia.

These results demonstrate not only that i.v. iron therapy and epoetin therapy have additive effects in correcting renal anaemia in patients with progressive renal insufficiency, but also that i.v. iron therapy alone may be sufficient in some cases. These findings are similar to those obtained by the same authors in dialysis patients [42]. It is not necessarily possible, however, to extrapolate from data in dialysis patients. Further studies are therefore needed to compare i.v. iron with oral iron in patients with mild-to-moderate progressive renal insufficiency, and to examine the optimal dose, timing and monitoring of i.v. iron administration in progressive renal insufficiency patients.

In the meantime, the workshop concluded that red blood cell indices should be reviewed regularly in progressive renal insufficiency patients receiving epoetin, with a view to initiating iron therapy whenever necessary. Early iron therapy is important to maximize the effectiveness of epoetin in correcting anaemia, and to allow it to be used in the most economic way possible.

Other adjuvant therapies

Nutritional deficiencies may contribute to anaemia in patients with renal failure, and may limit erythropoiesis in patients on epoetin therapy. The recent literature suggests that some nutritional supplements may enhance the effectiveness of epoetin treatment and improve patients’ well-being and health status. Potential roles have been identified for L-carnitine, vitamin B₆, vitamin B₁₂, folic acid, ascorbic acid and vitamin D (W. H. Hörl, this volume). However, nearly all of the research on nutritional supplements has been conducted in patients on dialysis.

L-Carnitine is perhaps the best-researched of the nutritional supplements in haemodialysis patients. Patients with renal insufficiency are believed to have abnormal renal handling of carnitine; carnitine is also lost during dialysis [43]. Carnitine appears to be necessary for the structure and function of the red cell membrane [44,45], and administration of L-carnitine has been shown to reduce erythrocyte membrane fragility in dialysed patients [46].

In haemodialysis patients, administration of L-carnitine (without epoetin) has been reported to increase haemoglobin, as well as to correct lipid abnormalities, and to improve muscular and cardiac function [43]. The response to epoetin in anaemic patients with ESRD is correlated with serum carnitine [47]. Moreover, L-carnitine administration has been shown to improve the response to epoetin [48,49]. However, until recently, the potential role of L-carnitine in patients with progressive renal insufficiency prior to dialysis had not been examined.

Teplan et al. conducted a randomized controlled trial of the effects of adjuvant therapy with L-carnitine in anaemic patients with progressive renal insufficiency [50,51]. A total of 38 patients (20 men, 18 women) with severe renal insufficiency, aged 32–68 years, were followed for 1 year. All patients had low creatinine clearance rates (12–36 ml/min) and symptomatic renal anaemia (haemoglobin < 10 g/dl, haematocrit < 30%). Patients were given a diet containing 0.6 g/kg body weight protein per day (mean energy value 145 kJ/kg body weight per day). The diet was supplemented with keto amino acids at a dose of 0.1 g/kg body weight per day.

After correcting serum iron, ferritin and transferrin saturation, the patients were divided into two groups: (i) epoetin alfa at a low dose of 20 IU/kg s.c. three times per week (the dose subsequently was adjusted in individual cases), together with L-carnitine at an oral dose of 1.0 g (n = 18); (ii) standard diet but no additional therapy (n = 20).

Over a follow-up period of 1 year, patients receiving epoetin plus L-carnitine showed significant increases in albumin, body mass index, and transferrin, and decreases in Whitehead quotient and the phenylalanine:tryptophan ratio compared with baseline. Lipid metabolism also improved in this group of patients. During the study, the mean dose of epoetin alfa declined from an initial value of 3900 IU/week to
2500 IU/week (P < 0.01). Significant decreases were noted in triglycerides (from 4.26 to 2.24 mmol/l), total cholesterol (TC) (from 7.31 to 5.82 mmol/l) and low-density lipoprotein (LDL) cholesterol (from 5.24 to 3.75 mmol/l). There were significant increases in high-density lipoprotein (HDL) cholesterol (from 0.92 to 1.4 mmol/l), the HDL:TC ratio (from 12 to 24%) and the HDL₂: cholesterol: HDL₃ cholesterol ratio (from 5.69 to 2.06).

These findings suggest that, in patients with progressive renal insufficiency, concomitant administration of l-carnitine might reduce the dose of epoetin required and have beneficial effects on lipid metabolism. However, it should be noted that the beneficial effects seen in this study may also have been due to the overall metabolic stabilization of patients (including enhanced metabolism of amino acids and saccharides) and the concomitant administration of keto amino acids. A study comparing epoetin therapy alone with epoetin plus l-carnitine is needed to establish whether l-carnitine supplementation adds to the efficacy of epoetin in progressive renal insufficiency patients.

Workshop recommendations

There is reasonably good evidence for the usefulness of iron supplementation in progressive renal insufficiency patients prior to dialysis. There is also some evidence for adjuvant therapy with l-carnitine in this patient group. Other nutritional supplements, such as folic acid, ascorbic acid and vitamins B₆, B₁₂ and D, have yet to be investigated in progressive renal insufficiency patients.

It cannot be assumed that findings from patients on dialysis can be extrapolated to this patient group. For example, the effects of dialysis itself may influence the nutritional status of dialysis patients in a way that does not apply to undialysed patients. In addition, a significant proportion of patients with CRF will be anaemic for reasons other than erythropoietin deficiency. The workshop participants therefore recommended that all anaemic patients be evaluated routinely for folic acid, thyroid hormone and B₁₂ deficiencies, as well as iron status.

Conclusions

The conclusions of this workshop may be summarized as follows.

- The term ‘pre-dialysis’ is unhelpful; there is a continuum of renal insufficiency from normal renal function to end-stage renal failure.
- The term ‘progressive renal insufficiency’ is therefore more appropriate to describe patients not yet on dialysis.
- Anaemia in patients with renal insufficiency should be defined in the same way as in other conditions (i.e. haemoglobin less than normal physiological values).
- In an individual patient, the amount of the decrease in haemoglobin may be as relevant as the absolute haemoglobin.
- The adverse effects of haemoglobin on left ventricular mass are apparent early in the course of progressive renal insufficiency, and become more severe as renal function declines.
- Correction of anaemia in progressive renal insufficiency patients improves physical function, energy, cognitive function, sexual function and other parameters, though effects on LVH have yet to be demonstrated in controlled studies.
- Although a study in 5/6 nephrectomized rats has suggested that administration of epoetin may accelerate a decline in renal function, no evidence for any such adverse effect has been seen in human studies lasting up to 48 weeks.
- Treatment of anaemia with epoetin may be considered in patients with progressive renal insufficiency (GFR of < 50% of normal and structural evidence of renal disease), provided blood pressure is well controlled.
- There is no evidence either for or against increasing haemoglobin to normal in this patient group.
- Unrecognised ‘iron-responsive’ anaemia may occur in patients with progressive renal insufficiency; early iron therapy is important to achieve the full benefits of epoetin.
- Adequate nutrition is important in progressive renal insufficiency; the role of supplements such as l-carnitine, B₆, B₁₂ and folic acid requires further investigation.

There is still a great deal to be learnt about the management of anaemia in patients with progressive renal insufficiency. However, studies of this patient group have already been initiated. There is clearly a role for epoetin in ameliorating the symptoms of anaemia in these patients, and good theoretical reasons to believe that early correction of anaemia may help to reduce the toll of anaemia-related cardiac disease.

References


