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A need for an individualized approach to end-stage renal disease patients

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Abstract
Evidence suggests that an individualized and flexible approach may be beneficial to end-stage renal disease (ESRD) patients. This article discusses this approach in relation to three issues: target haemoglobin (Hb) level, epoetin dosing frequency/administration and patient management/education programmes. Trial data indicate that each patient's condition should be taken into account when assigning target Hb values. Normalization of Hb is unlikely to be protective in patients with well-established cardiac disease. However, in patients without severe cardiac conditions, normalization is associated with benefits, such as reduction of cardiovascular risk factors and improved quality of life. Data are awaited from trials examining the impact of anaemia correction in patients not yet on renal replacement therapy (RRT). Two large, randomized controlled trials of haemodialysis patients have demonstrated that once-weekly epoetin β is as effective and as well tolerated as administration two or three times weekly. Additionally, one of these trials showed that once-weekly and three times weekly administrations were equivalent therapeutically in terms of maintaining both stable haematocrit levels and epoetin β dose requirements. These results suggest that the epoetin β route and frequency of administration can be individualized according to patient/physician preference. Renal management programmes, which incorporate a multidisciplinary team approach, strategies for early referral of patients and patient education, have an impact on patient outcomes and on RRT modality choice. An individualized programme will help to optimize the use of treatments aimed at delaying the progression of renal failure and its co-morbidities. In conclusion, evidence suggests that an individualized and flexible approach to target Hb values, epoetin β route and frequency of administration, and patient education/management programmes may be beneficial to patients with ESRD. As early intervention has an impact on patient outcome and the progression of risk factors, this approach may also be appropriate for patients who are not yet receiving RRT.

Keywords: anaemia; end-stage renal disease; epoetin β; patient education; renal insufficiency; target haemoglobin

Introduction

Despite the availability of US and European Guidelines [1–3], certain issues related to the management of anaemia in end-stage renal disease (ESRD) patients remain to be resolved. The most prominent issue appearing in the recent literature concerns appropriate target haemoglobin (Hb) levels [4–7]. Renal anaemia is an independent risk factor for the development of left ventricular (LV) hypertrophy, heart failure and mortality [8–10]. Consequently, there has been much discussion surrounding the impact of partial or full normalization of Hb levels on progression of renal disease [11,12] and the status of co-morbidities, particularly cardiovascular conditions [4–7].

Recombinant human erythropoietin (rh-EPO, epoetin) has been available for the treatment of renal anaemia for >10 years. During this period, the advantages of subcutaneous (s.c.) epoetin administration over intravenous administration have become apparent [1,3]. However, an outstanding issue has related to the frequency of s.c. epoetin β dose administration, i.e. if it is feasible to administer epoetin β once weekly, as well as twice or three times weekly.

Selecting the infrastructure of the management for ESRD patients, which has an indirect impact on the management of anaemia, is another area of debate. Although it is apparent that renal disease and risk factors should be identified early, before the onset of renal failure and the presence of co-morbidities,

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adequate resources are needed to support such a strategy [13].

This article discusses the issues of target Hb level, epoetin dosing frequency and patient management/education programmes. In particular, the harmonizing theme among these issues is highlighted, i.e. the need for an individualized approach to the management of ESRD patients.

Target haemoglobin

For patients with chronic renal failure, the NKF-DOQI Clinical Practice Guidelines and the European Best Practice Guidelines recommend that the target Hb level should be 12 and >11 g/dl, respectively [1–3]. These targets encompass subnormal physiological values (normal levels 14–16 and 13–15 g/dl in men and women, respectively). Moreover, although target Hb levels have increased over time, in clinical practice they frequently remain lower than recommended. For example, in a cross-sectional analysis of 1449 haemodialysis (HD) patients in the UK, none of the nine renal centres involved achieved the UK Renal Association standard requiring >80% of patients to have Hb levels >10 g/dl [14]. It is logical to expect a definition of the optimal Hb level to result from a process of balancing potential adverse events against potential clinical benefits. However, it is now clear that the components of the balance differ among various patient groups. For example, results from the US Normalization of Hematocrit Trial showed that not all patient types benefit from a normalized haematocrit (Hct) [15]. This study followed outcomes in 1233 HD patients with symptomatic ischaemic heart disease or cardiac failure. The patients had been anaemic for several years and were at high cardiovascular risk. Patients in the higher Hct group (42%) had a trend towards greater mortality than those in the lower Hct (30%) group, and a higher rate of vascular access thrombosis. This study showed that normalization of Hb was not protective in patients with well-established cardiac disease.

More recent studies, however, have shown that normalized Hb levels can provide clinical benefits to HD patients. Three studies, conducted in Canada, Spain and Australia, respectively, found that normalized Hb levels were associated with significant improvements in cardiovascular risk factors and patient quality of life [16–18]. Moreover, the Canadian Normalization of Hemoglobin Trial found that normalization prevented the development of LV dilatation, but did not reverse the progression of established cardiac co-morbidities [16]. These results illustrate the importance of early intervention for the correction of anaemia, i.e. before cardiovascular conditions become established.

Taking the need for early intervention into account, the impact of anaemia correction should also be assessed in patients prior to renal replacement therapy (RRT). Such studies are already in progress or in the planning stage. For example, the Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin β (CREATE) trial will investigate the effect of early anaemia correction on cardiovascular risk reduction in patients not yet on RRT [19].

Epoetin dosing frequency

The ability to administer epoetin once *vs* two or three times weekly has advantages in terms of flexibility of dosing, individualization of epoetin dosage regimen, patient preference, facilitation of self-administration and clinical workload. In Europe, there is evidence that nephrologists already adopt a flexible approach to the frequency of epoetin dose administration. Results from the European Survey on Anaemia Management (ESAM) showed that, during the maintenance treatment phase, the mean number of epoetin administrations was approximately evenly distributed between once, twice and three times weekly (Figure 1) [20].

A number of small-scale studies of HD patients have shown comparable efficacy and tolerability between once-weekly and more frequent s.c. epoetin administrations [21–23]. Moreover, results from two large, controlled studies of HD patients showed that once-weekly epoetin β was as effective and as well tolerated as administration two or three times weekly [24,25]. Locatelli *et al.* used a statistically rigorous probe for equivalence between once weekly and three times weekly dose regimens [24]: to establish equivalence, the group difference in mean time-adjusted area under the curve (AUC) for Hct, and its 90% confidence interval (CI), were to be between +2 and −2%. Simultaneously, the group ratio of mean weekly epoetin β dose, and 90% CI, were to be within the range of 0.8 to 1.25. During the evaluation period (weeks 13–24 of the study), the mean Hct and epoetin β dose values, and the 90% CIs, were within the pre-specified equivalence

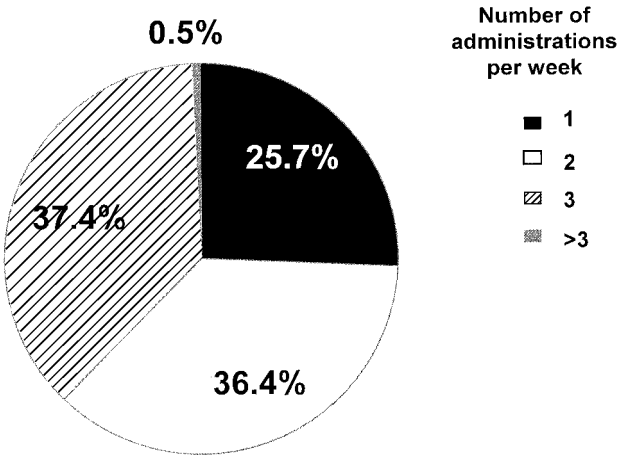

Fig. 1. Mean number of s.c. administrations per week of epoetin (maintenance phase of dialysis; ESAM data) (adapted from Jacobs *et al.* [20] with permission).

ranges. Mean Hct levels in both treatment groups remained stable throughout the study.

Patient management/education programmes

Levin *et al.* [13] showed that an education programme for patients with progressive renal insufficiency had a positive impact on the clinical course of these patients prior to and during RRT (Table 1). The programme, which involved discussions on renal function, blood pressure control, bone disease and dietary advice, used a multidisciplinary approach: patients' time at each clinic visit was divided between a nurse educator, physician, social worker and nutritionist. Moreover, the frequency of clinic visits was adapted according to the level of renal function. A control group of patients did not attend the education programme and were managed according to conventional practice.

As well as the differences in outcomes (Table 1), the mean Hb value of patients on the programme was significantly higher than the mean value in the control group (9.6 *vs* 9.1 g/dl; $P < 0.05$). The authors comment, however, that the success of their programme was dependent on early referral, adequate resources for dedicated programme staff and infrastructure, and available ESRD resources [13].

Patient education has also been shown to have an impact on choice of RRT [26]. As part of the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality study (wave 2), 2400 patients were surveyed in relation to their mode of dialysis [HD or peritoneal dialysis (PD)]. Patients were asked to indicate which modality options were discussed for their initial treatment for ESRD. Of patients treated with PD, 68% reported that in-unit HD was discussed. However, of patients on HD, only 25% reported that continuous ambulatory peritoneal dialysis was discussed. When asked about the process of selecting their method of treatment, among patients receiving PD, the decision was physician-led in 17% of cases and patient-led in 36% of cases (Figure 2). Among those receiving HD, physicians took the lead in 53% of cases and patients took the lead in 17% of cases (Figure 2). Therefore, taking the percentage of joint decisions into account, 84% of patients treated with PD appeared to contribute substantially to the decision, whereas only 47% of HD-treated patients contributed to the decision. These data indicate an overall preference by patients for PD when involved with the decision-making process. This is supported by interim results from the US National pre-ESRD Education Initiative [27,28]. In this on-going programme, >11 000 pre-ESRD patients received comprehensive one-to-one education on kidney function, kidney failure and RRT modality. Preliminary results suggest that this patient education programme led to increased PD utilization [27,28].

Overall, a flexible approach to patient management/education appears to provide benefits in terms of patient outcome and improved compliance. Also, choice of RRT appears to be influenced by an individualized approach to patient education.

Table 1. Differences in outcomes during the first month on dialysis between patients who had been on an education programme for progressive renal insufficiency (clinic group) and patients managed according to conventional practice (control group) (Levin *et al.* [13])

	Clinic group	Control group
Number of hospital admissions	17	27
Mean number of days per admission	6.5*	13.4
Urgent dialysis start	4 (13%)*	13 (35%)
Hospitalized for symptomatic uraemia	3*	11

*$P < 0.05$ *vs* control.

Conclusions

Accumulating evidence suggests that an individualized, flexible approach should be adopted for patients with ESRD and renal insufficiency (Figure 3). For target Hb level, it is important to recognize that full correction of anaemia can be beneficial for certain subgroups of patients, such as those without established cardiac complications. This requires that each patient's condition is taken into consideration. Anaemia is a well recognized risk factor for cardiovascular disease, but is

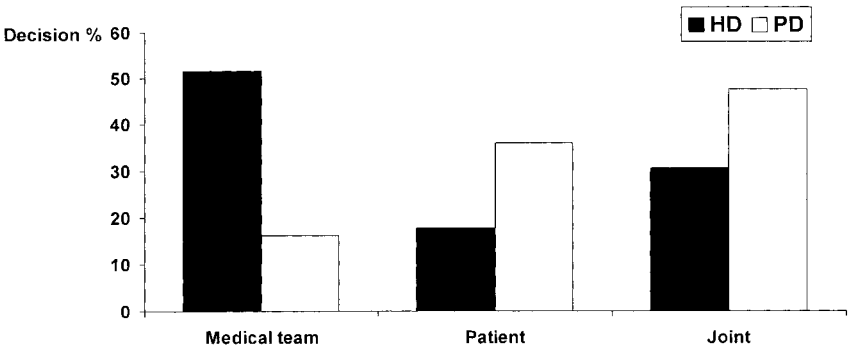

Fig. 2. Patient involvement in selecting mode of RRT (adapted from USRDS [26] with permission).

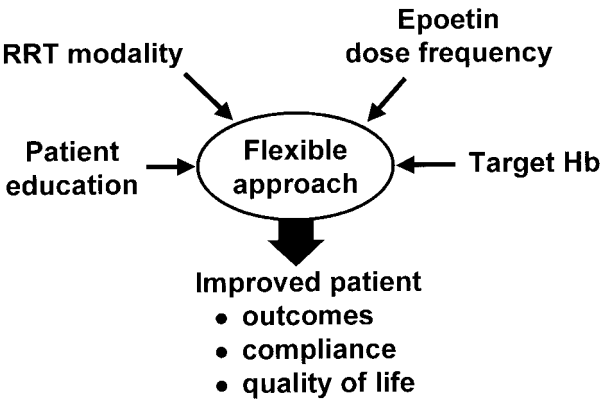

Fig. 3. An individualized, flexible approach is required for patients with ESRD and renal insufficiency.

modifiable, so early identification of subnormal Hb levels is critical. Data from trials, such as the CREATE study, examining the effect of early anaemia correction on cardiovascular risk reduction in patients who are not yet on dialysis, are awaited.

The availability of flexible s.c. epoetin β dose frequencies (once, twice or three times weekly) is consistent with the need for an individualized approach. Data from two large epoetin β trials have confirmed that once-weekly administration is as effective as administration two or three times weekly [24,25]. Therefore, the choice of epoetin β regimen can be based on the preferences of nephrologists and their patients. Additionally, the ability to reduce the frequency of dose administration will have an impact on clinic workload, may improve patient compliance and may encourage patients to self-administer treatment.

Finally, renal management programmes, which incorporate a multidisciplinary team approach, strategies for early referral of patients and patient education, have an impact on patient outcomes and on RRT modality choice. An individualized programme will help to optimize the use of treatments aimed at delaying the progression of renal failure and its co-morbidities. Also, early intervention will allow advance preparation for RRT, including facilitation of informed choice in relation to RRT modality.

In conclusion, evidence suggests that an individualized and flexible approach to target Hb values, epoetin β dose frequency and patient education/management programmes may be beneficial to patients with ESRD. Additionally, as early intervention has an impact on patient outcome and the progression of risk factors, particularly cardiovascular risk factors, this approach should also be considered for patients who are not yet on RRT. The advantages associated with this approach are likely to include improved patient compliance, outcomes and quality of life. However, further data are required to confirm the benefits of an individualized, flexible strategy for the management of renal patients.

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