Dose tailoring strategies in haemodialysis patients: a discussion of case histories

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Abstract

Tailoring of the epoetin dose to the needs, clinical condition and circumstances of individual patients with renal anaemia offers potential for optimizing the benefits and costs of epoetin therapy. This can be achieved through alterations to dosing frequency, administration route and/or delivery device. Two case histories are presented to illustrate dose tailoring of epoetin therapy in daily clinical practice. The first patient was a man aged 23 years with renal failure secondary to vasculitis. Haemoglobin (Hb) levels were stable during treatment with subcutaneous (s.c.) epoetin-β. Switching to intravenous (i.v.) epoetin-β required, after a 5 month period of complex dose adjustments, a 50% increase in the dose of epoetin-β to maintain Hb levels. The second patient was a woman aged 50 years with diabetic nephropathy. She self-administered epoetin-β via the Reco-Pen® device to maintain stable Hb levels. Epoetin-β is approved for administration at dosing frequencies ranging from three times weekly to once every 2 weeks, is safe and effective whether administered by the s.c. or i.v. route and is available in a range of delivery devices. Epoetin-β therapy can be easily tailored according to the needs, preferences and circumstances of individual patients, thereby maximizing treatment outcomes.

Keywords: administration route; anaemia; device; dose tailoring; epoetin

Introduction

Recombinant human erythropoietin (rhEPO; epoetin) is a well-established treatment in patients with anaemia secondary to chronic renal failure. Epoetin treatment in these individuals has been shown to reduce fatigue, improve exercise capacity and enhance health-related quality of life [1–3] and may also have potential for partial reversal of left ventricular hypertrophy [4]. Guidelines advising on the treatment of renal anaemia have been published in the USA [5] and in Europe [6], and it is increasingly recognized that tailoring the epoetin dose to reflect the needs, clinical condition and circumstances of the individual patient offers potential for optimizing the benefits of epoetin therapy.

Approaches to dose tailoring include alteration of the dosing frequency, selection of administration route and choice of administration device. Early studies showed that subcutaneous (s.c.) epoetin-β could be administered once weekly instead of three times weekly with no loss of efficacy [7]. More recently, the efficacy and safety of epoetin-β have been demonstrated during randomized studies at dosing frequencies ranging from three times weekly to once every 2 weeks (in patients who are stable on the once weekly dose) [8–10].

Epoetin can be administered via intravenous (i.v.) or s.c. injection. The s.c. route is favoured in many European countries [11], reflecting recommendations in current European and US guidelines for s.c. injection in pre-dialysis, peritoneal dialysis and haemodialysis (HD) patients [5,6]. Unlike epoetin-α, which is contraindicated for s.c. administration in Europe owing to product-specific safety concerns regarding the incidence of pure red cell aplasia, epoetin-β can be administered by either route [12].

Epoetin has traditionally been administered from single-dose vials, a potentially wasteful strategy as unused solution must be discarded. In recent years, epoetin-β has become available in a range of
devices, including multidose vials, pre-filled single-dose syringes with low injection volumes, and a pen delivery device (Reco-Pen®; F. Hoffmann-La Roche, Basel, Switzerland), providing a wide choice of devices to meet individual patients’ needs.

This article will describe the case histories of two patients with renal anaemia and contrasting clinical circumstances in whom tailoring of epoetin-β dosing strategies has been employed to maximize treatment outcomes.

Case history 1: switching from s.c. to i.v. epoetin in a young dialysis patient

Case description

The patient was a man aged 23 years with renal failure resulting from vasculitis. His vasculitis was immunologically mediated, as shown by the presence of anti-neutrophil cytoplasmic antibodies (P-ANCAs) reactive to myeloperoxidase. The patient changed from his normal dialysis routine (HD for 5 h three times weekly) to ‘long slow HD’ given overnight for 8 h three times weekly, which was administered using a single-pass batch-type dialysis machine (GENIUS™; Fresenius Medical Care). The GENIUS is able to deliver individual dialysis, and this form of HD is characterized by prolonged treatment time using a submaximal dialysate flow rate. When used with individually composed dialysis fluid and ultrapure water, it permits dialysis of high quality and has been associated with therapeutic benefits [13].

After switching to long slow HD, the patient showed an increase in total weight and maintained his dry weight (Figure 1). His Kt/V increased significantly, and there was also an increase in serum albumin, a positive sign as low serum albumin (<4.0 g/dl) is known to be a strong predictor of mortality risk in dialysis patients [14]. He had been receiving epoetin-β s.c. at a stable dose of 8000 IU/week for >3 months, and his haemoglobin (Hb) level was stable at ~11.8 g/dl.

In October 2002, the patient was switched to i.v. epoetin-β at a dose of 8000 IU/week to allow night-time dialysis during sleep. Prior to the switch, both his Hb level and epoetin-β dose had been stable (Figure 2). On switching to i.v. administration, his Hb level fell to 10.5 g/dl, and the dose of epoetin-β had to be increased to regain control of his anaemia, reaching a maximum of 15 000 IU/week. After 5 months of dosage adjustments, during which Hb fluctuated between 10 and 11.8 g/dl, both Hb level and epoetin-β dose were eventually stabilized. An Hb level of 11 g/dl was successfully maintained with a dose of i.v. epoetin-β of 12 000 IU/week. This was 50% higher than the 8000 IU/week dose that had been required during s.c. administration.

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Fig.1. Weight gain, Kt/V and serum albumin in a patient switched from normal HD (5h three times weekly/75 I dialysis fluid consumption) to long slow HD (8 h overnight three times weekly/91 I dialysis fluid consumption).
Case discussion

The observed requirement for an increase in epoetin-β dose on switching to i.v. dosing is consistent with the literature. In a study comparing i.v. and s.c. epoetin in 208 patients receiving long-term HD, the mean weekly dose of epoetin required to maintain haematocrit (Hct) in the range of 30–33% was 32% lower in the s.c. group than in the i.v. group ($P < 0.001$) [15]. This difference in dose has an important impact on costs. In a meta-analysis of 27 prospective clinical studies, Besarab et al. [16] found that the average epoetin dose was 48 IU/kg/week lower in patients treated with s.c. epoetin than in those receiving i.v. epoetin ($P < 0.001$). This was estimated to result in a substantial average cost saving of US$1761 (SD US$1080) per patient per year [16], which amounts to a reduction of 30% in direct drug costs. Applying these results to Italy, Fraticelli et al. [17] estimated that switching all the HD patients in Italy from s.c. to i.v. epoetin administration would cost an extra US$15.6 million per year.

It is becoming widely recognized that, compared with i.v. administration, less epoetin is required to treat the same number of patients via the s.c. route. This case report suggests the need for careful follow-up after a switch to s.c. from i.v. dosing, even in a young patient with no co-morbidity. In an older patient with other concomitant diseases, it is likely that the dose adjustment process would be more complex. Any costs associated with such dose adjustment could further add to the increase in cost already incurred by the need for a higher epoetin dose with i.v. dosing.

Case history 2: self-administration of epoetin-β in a dialysis patient with diabetic nephropathy

Case description

The patient was a woman aged 50 years, who was diagnosed with type I diabetes in 1974 and with diabetic nephropathy in June 1991. In August 1998, she began HD (5 h three times per week) because of progressive renal failure. Her Hb level was $\approx$9.9 g/dl at this time. She was well treated with a $Kt/V$ of 1.24, and her serum albumin and total protein were within the normal ranges (4.9 and 6.1 g/dl, respectively). In order to maintain glycaemic control, the patient was self-administering insulin 3–4 times daily with an injector-pen delivery device.

The patient chose to self-administer epoetin-β using the Reco-Pen device as she was already familiar with s.c. self-administration and dose tailoring (in conjunction with the physician) as a result of her insulin therapy. She required three concomitant antihypertensive medications to control her blood pressure. Epoetin-β administered via the Reco-Pen successfully maintained stable target Hb levels over a 14 month period. In April 2002, the patient underwent a successful kidney and pancreas transplant and now does not require either HD or insulin treatment.

Case discussion

Intensive insulin treatment designed to maintain blood glucose as close to normal as possible has been shown
to be more effective than conventional insulin therapy in type I diabetes. For example, in the secondary prevention cohort of the Diabetes Control and Complications Trial [18], patients receiving intensive insulin therapy were significantly (P = 0.002) less likely to develop microalbuminuria (albumin excretion rate of >70 mg/min) than patients receiving conventional therapy (Figure 3). The possibility of achieving similar improvements in outcome in renal anaemia by use of individualized erythropoietic therapy is an exciting one.

The Reco-Pen has been designed specifically to allow self-administration of individualized doses of epoetin-β, and consists of an injector pen delivery device used in conjunction with a convenient multidose formulation that can hold up to 1 month’s dosage of epoetin-β. In a multicentre trial, the Reco-Pen was rated as easy to use by 92% of patients, and pain-free by 81% [19]. A total of 89% of patients considered the Reco-Pen easier to use than their previous self-administration device [19]. This increased patient satisfaction may contribute to improved adherence to treatment.

Individualized therapy with epoetin-β and the Reco-Pen previously has been shown to be effective and well tolerated. An open, multicentre study investigated the efficacy of the Reco-Pen device in 406 adult patients who were switched to it from either i.v. or s.c. epoetin-β [20]. The initial epoetin-β dose was reduced by 25% from pre-study levels in patients switching from i.v. treatment, and was unchanged from the pre-study level in patients switching from s.c. treatment. Iron supplementation was given as required, and the epoetin-β dose was adjusted throughout the study to maintain constant Hct levels. On average, the mean weekly epoetin-β dose was reduced by 31% in the patients switched from i.v. epoetin (Figure 4a). Furthermore, the mean weekly epoetin-β dose was significantly (P = 0.0001) reduced by 28% in the patients switched from s.c. epoetin (Figure 4b), even though a dose reduction had not been intended in this group [20]. This might reflect the greater ability to individualize dosage with the Reco-Pen.

In this case, the Reco-Pen device allowed the patient to take control of her own epoetin-β treatment, along with her insulin treatment. Individualized self-administered epoetin-β successfully maintained stable Hb levels. Unique delivery systems, coupled with flexibility in dosing frequencies, allow the dosing regimen of epoetin-β to be precisely tailored to take account of individual patients’ preferences, circumstances and needs. This should help to improve adherence to treatment and encourage self-administration of epoetin by patients, thus contributing toward achieving successful treatment outcomes.

**Conclusions**

These two case histories illustrate some of the possibilities for epoetin dose tailoring in daily clinical practice. The main factors in epoetin dose tailoring are the dosing frequency, the route of administration and the choice of delivery device. Epoetin-β is approved for administration three times weekly, once weekly and once every 2 weeks in patients who are stable on the once weekly dosing schedule. It is safe and effective given by either the i.v. or s.c. route, and is available in a range of devices. Dose tailoring of epoetin therapy, with s.c. administered epoetin-β, allows anaemia
treatment to be adjusted according to individual patient needs, preferences and circumstances. Moreover, Hb stability is maintained using lower doses of epoetin-β compared with i.v. administration, thereby optimizing treatment outcomes cost-effectively.

Conflict of interest statement. None declared.

References

2. Bárány P, Pettersson E, Konarski-Svensson JK. Long-term effects on quality of life in haemodialysis patients of correction...