Triggering Erythropoiesis: New Developments

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Introduction

Up until recently, the best option for treating anaemia in renal failure patients was recombinant human erythropoietin (epoetin alfa or beta), which was most commonly administered twice– or thrice–weekly. There were, however, a number of studies which examined the potential for giving epoetin once-weekly (1–11), although most nephrologists continued to recommend the use of two or three injections a week, and the small number who ended up on once-weekly dosing were generally those who were responding well to epoetin therapy in the maintenance phase of treatment. It was certainly less common to start such patients on once-weekly administration, although a large Austrian multicentre study in pre-dialysis patients did utilise a treatment regimen of 10,000 units of epoetin once weekly (6).

There is little doubt that the fairly recent introduction of darbepoetin alfa once again focused our minds on the concept of once-weekly dosing (12). This product represented a new class of erythropoietic agent with a longer duration of action, with one of its main aims to allow less frequent dosing both intravenously and subcutaneously. This was achieved by adding an extra two N-linked glycosylation chains to the protein backbone of the molecule (which, in turn, required five amino acid substitutions) (13), and the extra sialic acid residues that were conferred on the new molecule produced an intravenous half-life of 25.3 hours compared with 8.5 hours for epoetin-alfa (14). The pharmacokinetics of a drug, however, do not always predict the pharmacodynamics or biological response, since the latter may be dependent on more than an ambient circulating level of the drug. Thus, some biological effects may require continuous receptor occupancy, while others may be driven by intermittent receptor occupancy.

Nevertheless, a number of efficacy studies of darbepoetin alfa have confirmed that the drug is effective with a once-weekly dosing schedule (15-20), and indeed some patients have managed to get away with once every 2 weeks (18) (or even once every 4 weeks (21)) administration. The aim of the present review is to examine the medical literature regarding once-weekly administration of the various erythropoietic agents available to us, and to ascertain the potential differences between these products.

Once-weekly administration of epoetin

Beginning in the early 1990's, various reports of once-weekly treatment with epoetin appeared (1-11). In a small, uncontrolled study, Saleh et al (1) treated 12 CAPD patients with SC epoetin 4000 units once weekly, and found a similar efficacy to thrice-weekly epoetin at the same dose. Two studies treated ten (2) and six (4) CAPD children with once-weekly epoetin, and increases in haemoglobin concentration were seen in both studies. Lui et al (3) treated 10 CAPD patients with epoetin 100 U/kg/wk either once- or twice-weekly, and equivalent haemoglobin responses and epoetin dose requirements were seen. A similar study was conducted by the same authors in haemodialysis patients (5), and again equivalent responses were seen with once- or twice-weekly epoetin. The Austrian multicentre study in 123 pre-dialysis patients utilised a once-weekly dose of 10,000 units of epoetin subcutaneously, and found this treatment regimen effective. Other studies (some comparative) using a once-weekly treatment regimen of epoetin are summarised in Table 1.

With the recent introduction of darbepoetin alfa as a once-weekly erythropoietic therapy, either deliberately, or incidentally, there was renewed interest in the concept of once-weekly epoetin administration, particularly epoetin-beta (22, 23). The first of these studies to be published (the Swedish Study) (22) was an open-label comparison of once-weekly dosing of epoetin-beta compared with twice- or thrice-weekly dosing. The second study (from Italy) (23) was a therapeutic-equivalence study again comparing once-weekly administration of epoetin-beta with twice- or thrice-weekly administration. Both these studies reported no change in erythropoietic response or epoetin-beta dose with once-weekly administration, suggesting that this dosing regimen was an option in renal failure patients. However, both studies recruited a highly selected population of patients who were iron-replete and well-dialysed. More recently, a European multicentre study showed similar results with both once-weekly (n=54) and once-fortnightly (n=74) subcutaneous administration of epoetin-beta to peritoneal dialysis patients (24).

In a recent issue of Nephrology Dialysis Transplantation, Jones et al (25) followed up 36 unselected patients who were all receiving less than 10,000 units of epoetin subcutaneously per week. They were switched to once-weekly

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Table 1. Once-weekly erythropoietic therapy

Agent	Route of admin.	No./type of patients	Comparison with:-	Conclusion	Reference
EPO 4000 units	SC	12 CAPD	Thrice-weekly EPO	Same efficacy	Saleh et al, 1991 (1)
EPO mean 93U/kg/wk	IV or SC	10 CAPD children	None	Once-weekly therapy effective	Hisano et al, 1991 (2)
EPO 100 U/kg/wk	SC	20 CAPD	Twice-weekly EPO	Similar responses	Lui et al, 1991 (3)
EPO 150 U/kg/wk	SC	6 CAPD children	None	Once-weekly therapy effective	Goldraich et al, 1992 (4)
EPO mean 127U/kg/wk	SC	HD patients	Twice-weekly EPO	Similar responses	Lui et al, 1992 (5)
EPO 10,000 units	SC	123 pre-dialysis patients	None	Once-weekly therapy effective	Austrian multicentre study, 1992 (6)
EPO	SC	CCPD children	Thrice-weekly EPO	Same efficacy	Ongkingco et al, 1994 (7)
EPO 50 U/kg/wk	SC	25 HD patients	None	Once-weekly therapy effective	Hussain et al, 1994 (8)
EPO	SC	HD patients	Thrice-weekly EPO	Similar efficacy	Lago et al, 1996 (9)
EPO 65/U/kg/wk	SC	38 CAPD patients	Thrice-weekly EPO	Same efficacy (22% ↑ in x1/wk dose)	Frifelt et al, 1996 (10)
EPO 4000 U/wk	SC	31 pre-dialysis patients	None	Once-weekly therapy effective	Yagil et al, 1997 (11)
Epoetin-beta 102 U/kg/wk	SC	158 HD patients	Twice- or thrice-weekly epoetin-beta	Same efficacy	Weiss et al, 2000 (22)
Epoetin-beta	SC	173 HD patients	Thrice-weekly epoetin-beta	Same efficacy	Locatelli et al, 2002 (23)
Epoetin-beta	SC	190 PD patients	Twice- or thrice-weekly epoetin-beta	Same efficacy	Grzeszczak et al, 2002 (24)
Epoetin-alfa 10,000 U/wk	SC	194 CKD patients	None	Once-weekly therapy effective	Provenzano et al, 2001 (27)
Epoetin-alfa mean 85.2 + 34.6 U/kg/wk	IV and SC	203 HD patients	Twice- or thrice-weekly epoetin-alfa	Slight↓ in Hb Slight ↑ in EPO dose	Barre et al, 2002 (28)
Epoetin-alfa 40,000 U/wk	SC	36 healthy adults	Thrice-weekly epoetin-alfa	Equivalent pharmacodynamic responses	Cheung et al, 2001 (29)
Darbepoetin alfa dose-escalation	IV (in HD pts.) SC (in PD pts.)	HD and PD patients	Thrice-weekly darbepoetin alfa	Once-weekly therapy effective	Macdougall et al, 1998 (15)
Darbepoetin alfa 0.45 μg/kg/wk	SC	166 CRI patients	Twice-weekly EPO 50 U/kg SC	Similar Hb responses	Locatelli et al, 2001 (16)
Darbepoetin alfa 0.45 μg/kg/wk	IV or SC	122 dialysis patients	Thrice-weekly EPO 50 U/kg IV or SC	Similar Hb responses	Coyne et al, 2000 (17)
Darbepoetin alfa (variable dose)	IV or SC	522 HD and PD patients	Twice- or thrice-weekly EPO	Hb levels maintained	Vanrenterghem et al, 1999 (18)
Darbepoetin alfa (variable dose)	IV	507 HD patients	IV EPO thrice-weekly	Hb levels maintained	Nissenson et al, 2000 (19)
Darbepoetin alfa (variable dose)	IV or SC	703 HD and PD patients	Twice- or thrice-weekly EPO	Hb levels maintained	Graf et al, 2000 (20)
Darbepoetin alfa (variable dose)	IV	274 dialysis patients	Twice- or thrice-weekly IV EPO	IV darbepoetin alfa more effective than twice- or thrice-weekly IV EPO	Horl et al, 2002 (30)

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administration, as per the Weiss study (22), and there was a significant fall in the mean haemoglobin over the subsequent 16 weeks despite a significant increase in epoetin dose. The authors concluded that caution must be exercised in extrapolating data from a carefully conducted study in a selected patient population to an "everyday life" largely unselected population. Further data to support this latter conclusion were generated from a study of reduced dosing frequency of epoetin in 26 haemodialysis patients at Inverclyde Royal Hospital in Scotland. Again, a significantly lower mean haemoglobin was found after conversion to once-weekly epoetin (P=0.002) along with a trend towards higher weekly epoetin doses (26).

Two multicentre studies with once-weekly epoetin-alfa were also recently reported, one at the American Society of Nephrology meeting in 2001 (27), and one at last year's European Renal Association meeting in Copenhagen (28). Both studies were uncontrolled, but both suggested that once-weekly administration of epoetin-alfa was possible in renal failure patients. A randomised controlled trial comparing the pharmacokinetics and pharmacodynamics of epoetin alfa administered subcutaneously once weekly and three times weekly to 36 healthy adults was also reported recently (29), with similar pharmacodynamic responses seen in both groups despite differences in total erythropoietin exposure.

Once-weekly administration of darbepoetin alfa

The first treatment studies with darbepoetin alfa were randomised dose-escalation studies examining the efficacy of IV therapy in haemodialysis patients and SC therapy in peritoneal dialysis patients. Both protocols involved randomisation of patients to either once-weekly or thrice-weekly darbepoetin alfa administration, using four sequential dosing regimens. There was a dose-dependent increase in haemoglobin in both studies with no apparent difference between once and three times weekly dosing with darbepoetin alfa (15). Two further studies examined the correction of anaemia with once-weekly darbepoetin alfa 0.45 μg/kg/wk in 166 patients with chronic renal insufficiency (16) and 121 dialysis patients (17). Again, similar haemoglobin responses were seen with an equivalent dose of epoetin given two or three times weekly. Two studies have also examined the effect of switching patients from epoetin to a less frequent dose of darbepoetin alfa (18, 19). Patients on twice- or thrice-weekly epoetin were converted to once-weekly darbepoetin alfa, and patients on once-weekly epoetin were converted to darbepoetin alfa once every other week (18). The mean haemoglobin remained stable from baseline to the evaluation period for both treatment groups. Similar results were found in the North American study (19) and in an open-label study of 703 dialysis patients from Europe and Australia (20). Recently, Horl et al (30) concluded that IV darbepoetin alfa administered once weekly was more efficacious than twice- or thrice-weekly epoetin in a population of haemodialysis patients.

Comparison of once-weekly epoetin with once-weekly darbepoetin alfa

What we are lacking at the present time is a head-to-head study comparing once-weekly epoetin with darbepoetin alfa. No such study has yet been published, and in the climate of evidence-based medicine, purists might legitimately suggest that such a study is required to confirm or refute the hypothesis that once-weekly darbepoetin alfa is more effective than once-weekly epoetin treatment, due to its longer biological half-life. In the meantime, there are reasonably robust scientific data to support once-weekly darbepoetin alfa administration to haemodialysis patients intravenously (30), whereas this dosing frequency is not really appropriate for intravenous epoetin.

In a further uncontrolled study, Roger et al (Simon Roger, personal communication) switched patients from epoetin-alfa to darbepoetin alfa with a conversion factor of 200 units of epoetin to 1 μg of darbepoetin alfa. By month 3, the equivalent dosing to maintain the haemoglobin concentration was 238 units of epoetin to 1 μg of darbepoetin alfa.

Conclusions

Once-weekly administration of both epoetin and darbepoetin alfa is possible provided the drug is given subcutaneously. It is, however, likely that higher doses of epoetin would have to be used to obtain the same biological response. The SPC for darbepoetin alfa suggests a conversion factor of 200 units of epoetin to 1 μg of darbepoetin alfa, but this ratio may alter, particularly at higher dosage levels. With intravenous administration, once-weekly dosing is really only feasible for darbepoetin alfa with its longer elimination half-life. Thus, in summary, although direct comparisons between epoetin and darbepoetin alfa are lacking, the body of evidence suggests that the latter drug is more likely to be successful with once-weekly administration in a greater number of patients.

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