Once-weekly erythropoietic therapy: is there a difference between the available preparations?

Iain C. Macdougall

Department of Renal Medicine, King’s College Hospital, London, UK

Keywords: darbepoetin alfa; epoetin; epoetin-beta; erythropoietic therapy

Introduction

Epoetin administration once weekly to renal failure patients is not new, and indeed a series of publications examining this frequency of administration appeared in the early 1990s [1–11]. During the last decade, however, nephrologists largely settled on twice- or thrice-weekly administration for most of their patients, and the small number who end up on once-weekly dosing are generally those who are responding well to epoetin therapy in the maintenance phase of treatment. It is certainly less common to start such patients on once-weekly administration, although a large Austrian multicentre study in pre-dialysis patients did utilize a treatment regimen of 10 000 U of epoetin once weekly [6].

There is little doubt that the introduction of darbepoetin alfa around the middle of last year once again focused our minds on the concept of once-weekly dosing [12]. This product was specifically developed to be a longer-acting erythropoietic agent, 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 h compared with 8.5 h 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.

### Once-weekly administration of epoetin

Beginning in the early 1990s, 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 s.c. epoetin 4000 U once weekly, and found a similar efficacy to thrice-weekly epoetin at the same dose. Two studies treated 10 [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/week 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 utilized a once-weekly dose of 10 000 U of epoetin s.c. and found this treatment regimen effective. Other studies (some comparative) using a once-weekly treatment regimen of epoetin are summarized 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) s.c. 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 <10 000 U of epoetin s.c. per week. They were switched to once-weekly administration, as in 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 have also recently been reported, one at the American Society of Nephrology meeting last year [27], and one at the recent European Renal Association meeting in Copenhagen [28]. Both studies were uncontrolled, but both suggested that once-weekly administration of epoetin-alfa was possible in some renal failure patients. A randomized 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 last year [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 randomized dose-escalation studies examining the efficacy of i.v. therapy in haemodialysis patients and s.c. therapy in peritoneal dialysis patients. Both protocols involved randomization 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/week 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 i.v. darbepoetin alfa administered once weekly was more efficacious than twice- or thrice-weekly i.v. epoetin in a population of haemodialysis patients.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Admin. route</th>
<th>No. of patients</th>
<th>Type of patients</th>
<th>Comparison with</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epo, 4000 U s.c.</td>
<td>Thrice-weekly Epo</td>
<td>12 CAPD patients</td>
<td>Thrice-weekly Epo</td>
<td>None</td>
<td>Same efficacy</td>
<td>Saleh et al., 1991 [1]</td>
</tr>
<tr>
<td>Epo, 10 000 U</td>
<td>Thrice-weekly Epo</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Similar responses</td>
<td>Austrian multicentre study, 1992 [2]</td>
</tr>
<tr>
<td>Epo, mean dose 93 U/kg/week</td>
<td>Thrice-weekly Epo</td>
<td>10 CAPD children</td>
<td>None</td>
<td>None</td>
<td>Once-weekly therapy effective</td>
<td>Hisano et al., 1991 [3]</td>
</tr>
<tr>
<td>Epo, 150 U/kg/week s.c.</td>
<td>Thrice-weekly Epo</td>
<td>20 HD patients</td>
<td>Twice-weekly Epo</td>
<td>None</td>
<td>Similar responses</td>
<td>Lui et al., 1991 [4]</td>
</tr>
<tr>
<td>Epo, mean dose 127 U/kg/week s.c.</td>
<td>Thrice-weekly Epo</td>
<td>158 HD patients</td>
<td>Twice- or thrice-weekly epoetin-beta</td>
<td>Same efficacy</td>
<td>Same efficacy</td>
<td>Weiss et al., 2000 [5]</td>
</tr>
<tr>
<td>Epoetin-alfa, 10 000 U s.c.</td>
<td>Thrice-weekly Epo</td>
<td>194 CKD patients</td>
<td>Twice- or thrice-weekly Epo</td>
<td>None</td>
<td>Similar responses</td>
<td>Locatelli et al., 2001 [6]</td>
</tr>
<tr>
<td>Epoetin-alfa, mean dose 85.2 ± 34.6 U/kg/week</td>
<td>Thrice-weekly Epo</td>
<td>203 HD patients</td>
<td>Twice- or thrice-weekly Epo</td>
<td>None</td>
<td>Similar Hb responses</td>
<td>Macdougall et al., 1998 [7]</td>
</tr>
<tr>
<td>Darbepoetin alfa, Variable dose</td>
<td>Thrice-weekly Epo</td>
<td>36 healthy adults</td>
<td>None</td>
<td>None</td>
<td>Superior efficacy</td>
<td>Nissen et al., 2000 [8]</td>
</tr>
<tr>
<td>Darbepoetin alfa, Variable dose</td>
<td>Thrice-weekly Epo</td>
<td>122 dialysis patients</td>
<td>None</td>
<td>None</td>
<td>Similar Hb responses</td>
<td>Coyne et al., 2000 [9]</td>
</tr>
<tr>
<td>Darbepoetin alfa, Variable dose</td>
<td>Thrice-weekly Epo</td>
<td>507 HD patients</td>
<td>None</td>
<td>None</td>
<td>Similar Hb responses</td>
<td>Grit et al., 2002 [10]</td>
</tr>
<tr>
<td>Darbepoetin alfa, Variable dose</td>
<td>Thrice-weekly Epo</td>
<td>703 HD patients</td>
<td>None</td>
<td>None</td>
<td>Superior efficacy</td>
<td>Hörl et al., 2002 [11]</td>
</tr>
</tbody>
</table>
Comparison of once-weekly epoetin with once-weekly darbepoetin alfa

What we are lacking now 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 appropriate for intravenous epoetin.

In a further uncontrolled study, Simon Roger (personal communication) switched patients from epoetin-alfa to darbepoetin alfa with a conversion factor of 200 U of epoetin to 1 µg of darbepoetin alfa. By month 3, the equivalent dosing to maintain the haemoglobin concentration was 232 U of epoetin to 1 µg of darbepoetin alfa, and by month 4 the conversion factor was 238:1.

Conclusions

Once-weekly administration of both epoetin and darbepoetin alfa is possible provided the drug is given s.c. It is possible that higher doses of epoetin may have to be used to obtain the same biological response, and this is of course also dependent on what conversion factor is used to compare epoetin with darbepoetin alfa. The SPC for darbepoetin alfa suggests a conversion factor of 200 U of epoetin to 1 µg of darbepoetin alfa, but this ratio may alter, particularly at higher dosage levels. With i.v. administration, once-weekly dosing is really only feasible for darbepoetin alfa, with its longer elimination half-life.

References

24. Grzeszczak W, Sulowicz W, Rutkowski B et al. on behalf of the European Collaborative Group. Once weekly and once fortnightly (every 2 weeks) subcutaneous epoetin beta is effective in


**Editor’s note**

This Editorial Comment should have been published together with the Letter by Dr Jones and the Reply by Dr Weiss (Volume 17 Number 10 page 1855).