A comparison between once-weekly and twice- or thrice-weekly subcutaneous injection of epoetin alfa: results from a randomized controlled multicentre study

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Abstract

Background. In patients with chronic renal failure, the ability to reduce the administration frequency of subcutaneous (SC) erythropoietin (epoetin) could provide benefits and may improve compliance. The study investigated whether once-weekly SC epoetin alfa was equivalent to twice- or thrice-weekly SC administration in maintaining anaemia correction in haemodialysis patients.

Methods. Eighty-three patients were randomly assigned to either once-weekly epoetin alfa (n = 44) or their original dose twice- or thrice-weekly regimen (control, n = 39) for 12 weeks. The haemoglobin concentration was maintained within the target range of 9.0–12.0 g/dL by adjusting the dose of epoetin alfa. All patients received intravenous iron supplementation, as required.

Results. Stable haemoglobin levels were maintained without epoetin dose increases in the majority of patients in both groups (once-weekly group, 95.0%, control group, 91.4%). The mean haemoglobin levels at randomization at weeks 4, 8 and 12 were 10.7, 11.1, 11.3 and 11.0 g/dL, respectively, in the once-weekly group, and 10.5, 11.3, 11.5 and 11.3 g/dL, respectively, in the control group. The mean weekly dose of epoetin alfa at randomization at weeks 4, 8 and 12 was 142.8, 114.5, 108.6 and 104.5 IU/kg, respectively, in the once-weekly group, and 128.4, 116.0, 101.0 and 96.1 IU/kg/week, respectively, in the control group. No statistically significant between-group differences were apparent for changes in haemoglobin levels or epoetin alfa dosages at week 12.

Conclusions. This study demonstrates that once-weekly SC administration of epoetin alfa is as effective and safe as two or three times weekly administration in maintaining haemoglobin levels. Therefore, the once-weekly therapy using high dose of epoetin alfa is considered to be an efficient method in stable haemodialysis patients.

Keywords: anaemia; erythropoietin; haemodialysis

Introduction

Insufficient production of erythropoietin (EPO; epoetin) is the primary cause of anaemia in patients with chronic renal failure, and epoetin treatment is an established treatment for renal anaemia. It is also known that it is effective for the improvement of quality of life and overall sense of well-being in dialysis patients [1].

For the route of epoetin administration, subcutaneous (SC) administration is more convenient than intravenous (IV) administration in patients with peritoneal dialysis or chronic kidney disease without a fistula. The SC route improved the efficiency of therapy, resulting in a reduced dosing requirement for epoetin to maintain the target haemoglobin level [2]. The dose of epoetin required to maintain haemoglobin levels equivalent to that achieved with the IV administration is lower by 33%, when the SC route is used [3].

However, many patients with haemodialysis still continue to be treated via the IV route. The primary reason is probably discomfort with subcutaneous injections. The SC administration of two or three times weekly causes pain at every injection, once-weekly therapy using high dose of epoetin with an enlarged administration interval has been attempted since the 1990s [4]. With the recent introduction of darbepoetin alfa as a once-weekly erythropoietin therapy [5], there has been a renewed interest in the once-weekly therapy of high-dose epoetin.

This study investigated whether once-weekly SC epoetin alfa was equivalent to twice- or thrice-weekly SC administration in maintaining anaemia correction in haemodialysis patients.

Subject and method

Patients

This multicentre, open-label, randomized controlled study using two parallel groups was conducted between July 2004 and April 2005. Selected for the study were patients on
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Fig. 1. Study design. Abbreviations: Hb, haemoglobin; SC, subcutaneous.

Dosage adjustment

Patients entered a 4-week pre-study period to assess baseline haemoglobin level under stable conditions. During the pre-study period, patients received epoetin alfa (Espogen©; LG Life Science Co., Ltd., Seoul, Korea) two or three times weekly through SC injection and the weekly epoetin alfa dosage was adjusted in order to maintain the haemoglobin level at 9.0–12.0 g/dL for 4 weeks. The starting dose of epoetin alfa for the treatment period was the individual weekly dose of epoetin alfa during the pre-study period. Patients were randomly assigned to either once-weekly SC epoetin alfa or to their original two or three times weekly administration regimen (control group) for 12 weeks. The study design is presented schematically in Figure 1. SC epoetin alfa was administered after each dialysis session in the twice- or thrice-weekly group and after second dialysis session of each week in the once-weekly group. The dose of epoetin alfa used was expressed as the weekly units per body weight after dialysis (IU/kg/week).

During the study treatment period, the haemoglobin level of each patient was maintained within the target range of 9.0–12.0 g/dL by adjusting the dose of epoetin alfa. During the treatment period, a 25% increase in epoetin alfa dose was allowed if there was a decrease in haemoglobin >1 g/dL from the previous level. The epoetin alfa dose was reduced by 25% after an increase in haemoglobin ≥1 g/dL compared with the previous value. The epoetin alfa dose was increased by 25% if the haemoglobin level was <9 g/dL, and reduced by 50% if a haemoglobin level of >12 g/dL was recorded. During the treatment period, intravenous iron preparation was supplemented if necessary (transferrin saturation is <20% or ferritin level <100 ng/mL).

Assessments of efficacy and safety

The following variables were recorded in all subjects: haemoglobin and haematocrit were measured every two weeks; serum iron, ferritin, transferrin saturation, serum electrolyte, liver transaminase and C-reactive protein were recorded every 4 weeks; serum parathyroid hormone level, chest X-ray and electrocardiogram were also recorded.

The primary efficacy variable was the mean haemoglobin level at week 12. Secondary outcome variables were the mean epoetin alfa dose at week 10 and the proportion of patients who maintained a stable haemoglobin level (≥9.0 g/dL) without requiring an increase in total weekly...
dose. Safety variables assessed were the patient’s compliance to epoetin alfa, blood pressure and adverse events.

**Statistical analysis**

It was estimated that a sample size of 27 patients per treatment group would enable 80% power to detect a decrease of 0.75 g/dL in the haemoglobin level [6]. Assuming a dropout rate of 20%, a total of 34 patients per treatment group had to be enrolled. A two-sample t-test was used to compare differences in the haemoglobin, haematocrit and weekly epoetin alfa dose. Comparisons between treatment groups were carried out using the χ²-test to assess whether there was any significant difference between groups in the number of patients who maintained stable haemoglobin levels without increase in the epoetin dose. The main conclusions are based on the results for the intention-to-treat (ITT) population, although results for the per-protocol population are also given. Measured values of the results were expressed in average ± standard deviation. Interval estimates of differences between treatments are given as 95% confidence levels. A significant level of 5% was considered statistically significant. Data were recorded using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) and all calculations were carried out using the SAS System version 6.10 (SAS institute, Cary, NC, USA).

**Results**

A total of 146 patients were included in the pre-study period. As 63 patients discontinued the study during screening, 83 patients completed the pre-study period. Eighty-three patients were randomly assigned to either once-weekly group (n = 44) or control group (n = 39), who continued with their previous dose of epoetin alfa twice or thrice weekly. Of the 44 patients randomized to once-weekly administration, 27 had received epoetin alfa twice weekly in the pre-study period and 17 had received the drug three times weekly. In the control group, 27 and 12 patients received epoetin alfa two or three times weekly, respectively. The causes of renal failure in the randomized population were diabetes mellitus (41 patients), hypertensive renal disease (29), chronic glomerulonephritis (11) and uraemia of unknown origin (2). Patient demographics and baseline characteristics are listed in Table 1. There were no significant differences in sex, age, body weight, duration of dialysis, haemoglobin, haematocrit, ferritin and transferrin saturation between the two groups. Mean Kt/V values were 1.47 ± 0.28 in the once-weekly group compared with 1.43 ± 0.27 in controls.

Of the 44 patients randomized to once-weekly administration, 27 had received epoetin alfa twice weekly in the pre-study period and 17 had received the drug three times weekly. In the control group, 27 and 12 patients received epoetin alfa two or three times weekly, respectively. The causes of renal failure in the randomized population were diabetes mellitus (41 patients), hypertensive renal disease (29), chronic glomerulonephritis (11) and uraemia of unknown origin (2). Patient demographics and baseline characteristics are listed in Table 1. There were no significant differences in sex, age, body weight, duration of dialysis, haemoglobin, haematocrit, ferritin and transferrin saturation between the two groups. Mean Kt/V values were 1.47 ± 0.28 in the once-weekly group compared with 1.43 ± 0.27 in controls.

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A total of 75 patients (40 in the once-weekly group and 35 in the control group) completed a 12-week study and were evaluated for efficacy. Four patients (9.1%) in the once-weekly group and four controls (11.4%) were withdrawn from the evaluation prior to week 12 for the following reasons: protocol violation in four patients (dose change in the study period, two patients; haemoglobin level >12.0 g/dL at randomization, one patient and once-weekly therapy at randomization, one patient); adverse events unrelated to epoetin alfa treatment in three patients (cerebral haemorrhage, two patients; coronary artery disease, one patient); withdrawn owing to transplantation in one patient. Patient deposition is summarized in Figure 2. There was no statistically significant difference between groups in the number of patients who maintained stable haemoglobin levels (≥9.0 g/dL) without an epoetin alfa dose increase (P = 0.75). In the majority of patients (once-weekly group, 95.0%, control group, 91.4%), stable haemoglobin levels were maintained without increase in the epoetin dose. The epoetin alfa dose was reduced in 23 out of 40 (57.5%) patients in the once-weekly group and 21 out of 35 (60.0%) patients in the control group.

At randomization, the mean haemoglobin level in once-weekly group was 10.7 ± 0.8 g/dL compared with 10.5 ± 0.7 g/dL among controls. At the initiation of treatment, the haemoglobin levels at weeks 4, 8 and 12 were 11.1 ± 1.1, 11.3 ± 1.3 and 11.0 ± 1.1 g/dL, respectively, in the once-weekly group and 11.3 ± 0.9, 11.5 ± 1.4 and 11.3 ± 1.5 g/dL, respectively, in the control group.
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Fig. 2. Patient deposition.

Fig. 3. Mean haemoglobin (A) and haematocrit (B) in both groups remained stable throughout the study (mean ± SD).

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Epoetin dose (IU/kg/week)</th>
<th>Haemoglobin (g/dL)</th>
<th>Epoetin dose (IU/kg/week)</th>
<th>Haemoglobin (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>142.8 ± 64.8</td>
<td>10.7 ± 0.8</td>
<td>128.4 ± 50.4</td>
<td>10.5 ± 0.7</td>
</tr>
<tr>
<td>Week 4</td>
<td>114.5 ± 65.8</td>
<td>11.1 ± 1.1</td>
<td>116.0 ± 55.3</td>
<td>11.3 ± 0.9</td>
</tr>
<tr>
<td>Week 8</td>
<td>108.6 ± 69.9</td>
<td>11.3 ± 1.3</td>
<td>101.0 ± 49.0</td>
<td>11.5 ± 1.4</td>
</tr>
<tr>
<td>Week 12</td>
<td>104.5 ± 69.6</td>
<td>11.0 ± 1.1</td>
<td>96.1 ± 52.8</td>
<td>11.3 ± 1.5</td>
</tr>
</tbody>
</table>

Table 2. Epoetin alfa dose and haemoglobin concentration at baseline and weeks 4, 8, 12 (mean ± SD)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>One-weekly group (n = 44)</th>
<th>Control group (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change (90% CI)</td>
<td>Mean Change (90% CI)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>10.66 0.32 10.61 0.79</td>
<td>11.40 0.38 1.20</td>
</tr>
<tr>
<td>Baseline</td>
<td>Week 12</td>
<td>Baseline</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>31.90 1.10 31.41 2.34</td>
<td>33.00 2.00 33.75 1.20</td>
</tr>
<tr>
<td>Baseline</td>
<td>Week 12</td>
<td>Baseline</td>
</tr>
<tr>
<td>Epoetin dose (IU/kg/week)</td>
<td>140.88 −27.34 126.47 −25.72</td>
<td>113.54 −40.39 100.75 −35.39</td>
</tr>
<tr>
<td>Baseline</td>
<td>Week 12</td>
<td>Baseline</td>
</tr>
</tbody>
</table>

Table 3. Mean haemoglobin concentration, haematocrit and epoetin alfa dose for the protocol population (n = 75)

(Figure 3A). There were no statistically differences in mean haemoglobin levels between groups. The haemoglobin level in the once-weekly group was significantly higher at weeks 4 and 8 than the baseline (P < 0.01) and that in the control group was higher at weeks 4, 8 and 12 than the baseline (P < 0.01). At randomization, the mean haematocrit level in once-weekly group was 32.0 ± 2.4% compared with 31.2 ± 2.4% among controls. At the initiation of treatment, the haematocrit levels at weeks 4, 8 and 12 were 32.9 ± 3.3, 33.2 ± 3.7 and 32.9 ± 3.4%, respectively, in the once-weekly group and 33.0 ± 3.1, 33.7 ± 4.4 and 33.5 ± 4.4%, respectively, in the control group (Figure 3B). There were no statistically differences in mean haematocrit levels between groups.

The mean weekly epoetin alfa doses are shown for the two groups in Table 2. In the once-weekly group, the mean weekly dose of epoetin alfa was 104.5 ± 69.6 IU/kg at the end point of the study compared with 142.8 ± 64.8 IU/kg at baseline, a change of 26.8%. In the control group, the mean weekly dose of epoetin alfa was 96.1 ± 52.8 IU/kg at the end point of the study compared with 128.4 ± 50.4 IU/kg at baseline, a change of 25.2%. The mean dose of epoetin alfa was slightly higher in the once-weekly group compared with controls. But, the changes in the mean dose of epoetin alfa between two groups for weeks 0–12 were not statistically significant.

In the protocol population, the mean changes in the haemoglobin concentration from baseline to week 12 (0.32 and 0.79 g/dL in the once-weekly and the control group, respectively) and 90% CI of these changes (0.04–0.60 and 0.38–1.20, respectively) were within the specified equivalence range in both groups (±0.75 g/dL) (Table 3). From baseline to week 12, a mean change of weekly epoetin alfa doses of −27.34 IU/kg/week was observed in the once-weekly group and −25.72 IU/kg/week in the control group.

At randomization, the mean serum ferritin level in once-weekly group was 338.3 ± 424.4 ng/mL compared with 305.7 ± 323.5 ng/mL among controls. The ferritin level at weeks 4, 8 and 12 was 349.5 ± 440.9, 360.6 ± 413.0 and 395.5 ± 461.5 ng/mL, respectively, in the once-weekly group and 274.8 ± 329.0, 263.5 ± 329.0 and 279.5 ± 330.5 ng/mL, respectively, in the control group. Though
the once-weekly group showed a slightly higher level, no significant difference was observed. Also, the transferrin saturation at randomization was 29.8 ± 12.8% in the once-weekly group and 35.4 ± 16.4% in controls. Mean transferrin saturation values at weeks 4, 8 and 12 were 30.0 ± 12.4, 30.4 ± 15.7 and 31.3 ± 15.9%, respectively, in the once-weekly group and 36.4 ± 19.6, 36.5 ± 18.8 and 33.0 ± 17.4%, respectively, in the control group. The mean transferrin saturation values were slightly lower in the once-weekly group compared with controls. But, the changes in mean transferrin saturation values between two groups for weeks 0–12 were not statistically significant.

While systolic blood pressure before the clinical trial was higher in the once-weekly group than the control group (P = 0.03), there was no significant difference between groups in both systolic and diastolic blood pressure during the trial (Figure 4). Epoetin alfa given once weekly was well tolerated, and there was no requirement for an increase in antihypertensive treatment compared with controls. In the biochemical test, including serum electrolyte, liver transaminase and C-reactive protein, no significant change was observed throughout the study period. No remarkable change was noted in chest X-ray and electrocardiogram before and after the administration of epoetin alfa.

There were no clinically significant differences in the numbers and types of adverse events observed in the once-weekly group and control group. Table 4 lists adverse events that occurred in more than 5% of patients. Most adverse events were considered by the investigators to be unrelated to epoetin alfa and disappeared in time without any treatment. Serious adverse events were reported in more patients in the control group than once-weekly group (25.6% versus 20.5% of patients, respectively). These adverse events in the once-weekly group included inflammation at the injection site was reported in four patients; cardiovascular disease in three patients, gastric ulcer in one patient and diabetes mellitus in one patient. In the control group, inflammation at the injection site was reported in four patients; cardiovascular disease, nervous system disorder, hypoglycemia, musculoskeletal disorder, infection and urinary disease were reported in one patient each. Cerebral haemorrhage occurred in one patient in the once-weekly group and one patient in controls, and sepsis was reported in one patient in the control group; these were not considered to be related to the study medication.

Table 4. Adverse events occurring in >5% of patients

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Once-weekly group (n = 44)</th>
<th>Control group (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>8 (18.2%)</td>
<td>7 (17.9%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (6.8%)</td>
<td>7 (17.9%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2 (4.5%)</td>
<td>4 (10.3%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (9.1%)</td>
<td>3 (7.7%)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>4 (9.1%)</td>
<td>9 (23.1%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (9.1%)</td>
<td>5 (12.8%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (9.1%)</td>
<td>3 (7.7%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8 (18.2%)</td>
<td>5 (12.8%)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>1 (2.3%)</td>
<td>4 (10.3%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8 (18.2%)</td>
<td>3 (7.7%)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (11.4%)</td>
<td>5 (12.8%)</td>
</tr>
<tr>
<td>URI</td>
<td>21 (47.7%)</td>
<td>17 (43.6%)</td>
</tr>
<tr>
<td>Injection site inflammation</td>
<td>4 (9.1%)</td>
<td>2 (5.1%)</td>
</tr>
</tbody>
</table>

Discussion

These results show that once-weekly SC administration of epoetin alfa is as effective and safe as two or three times weekly administration in maintaining a stable haemoglobin level. Although it might be expected that a reduction in dosage frequency would lead to a reduction in haemoglobin levels in the once-weekly group, there was no statistically significant difference in average weekly dose of epoetin alfa between two groups. On week 12, the average weekly dose of epoetin alfa in the once-weekly group was 104.5 ± 69.6 IU/kg and 96.1 ± 52.8 IU/kg in the control group. From baseline to week 12, a mean change of weekly epoetin alfa doses of −38.3 IU/kg/week (−26.8%) was observed in the once-weekly group and −32.3 IU/kg/week (−25.2%) in the control group.

With the recent introduction of darbepoetin alfa as a once-weekly erythropoietin therapy, various reports of once-weekly treatment of high-dose epoetin appeared, particularly epoetin beta. Two large-scale, randomized trials of epoetin beta treatment in stable haemodialysis patients demonstrated no change in erythropoietic response or epoetin beta dose with once-weekly administration [7,8]. The first of these studies was an open-label comparison of once-weekly dosing of epoetin beta compared with twice- or thrice-weekly dosing [7]. The second study was a therapeutic-equivalence study again comparing once-weekly treatment of epoetin beta with twice- or thrice-weekly administration [8]. However, in other studies on dialysis patients, the required dose tended to be increased when the administration frequency of epoetin beta was decreased from three times weekly to once weekly [9].

Until recently, only clinical studies with limited numbers of patients had reported on the once-weekly epoetin alfa regimen [10–12]. Two multicentre studies with once-weekly epoetin alfa have also recently been reported. A prospective, open-label study by Provenzano et al. [13] evaluated the efficacy of 16 weeks of treatment with once-weekly SC epoetin alfa in patients with chronic kidney disease not on dialysis. This study was uncontrolled, but suggested that once-weekly epoetin alfa therapy was possible in some patients with chronic kidney disease. A crossover, intraindividual comparison study was reported.
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Limitations of our study were that the study period was short and the sample size was relatively small. As the quantitative assessment of erythropoiesis during epoetin treatment reveals a gradually increased haemoglobin level to reach a plateau within 6–12 weeks [17], the patients in our study were evaluated for 12 weeks.

In conclusion, the study demonstrated that the efficacy and safety of high dose of epoetin alfa, when administered once weekly, were comparable to 2–3 times weekly therapy. Also, once-weekly therapy using high-dose epoetin alfa is beneficial for costs of nursing time and healthcare. Therefore, once-weekly therapy using high dose of epoetin alfa is considered to be an efficient method in stable haemodialysis patients.

Conflict of interest statement. None declared.

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