Testing a Single Monthly Dose of Darbepoetin Alpha to Maintain Hemoglobin Levels in Continuous Ambulatory Peritoneal Dialysis Patients

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The newly developed erythropoiesis agent darbepoetin alpha (DA) allows for once-monthly dosing in the treatment of anemia in patients on dialysis. This dosing schedule has prompted some studies to examine the efficacy of DA in patients on continuous ambulatory peritoneal dialysis (CAPD). In the present study, we assessed whether intravenous (IV) administration of DA once monthly is effective for maintaining hemoglobin levels near 10.5 g/dL in patients on CAPD.

This single-center prospective cohort study included 52 clinically stable patients (25 men, 27 women; mean age: 59 ± 10 years). All patients had been on a stable weekly or twice monthly regimen of recombinant human erythropoietin (rHuEPO) before initiation of the study. To determine the monthly dose of DA, the previously used mean weekly dose of rHuEPO was divided by 200 to determine the equivalent weekly dose of DA in micrograms; that number was then multiplied by 4 to generate the monthly dose requirement. For example, if 3000 IU rHuEPO was being administered weekly, then the monthly dose of DA was calculated to be 60 µg (3000 / 200 × 4). All patients received a monthly dose of DA the first month, and hemoglobin and other routine laboratory tests were performed monthly for 24 consecutive weeks.

In 26 patients, the calculated monthly DA dose remained stable. The monthly dose was increased by 25% in 22 patients and by 50% in 4 patients. With regard to iron stores and iron availability for erythropoiesis, no significant differences were observed in the patients on various doses of DA. Nonsignificant differences in weekly creatinine clearance as determined using the PD Adequest software (Baxter Healthcare, Tokyo, Japan) were observed between the groups. No clinically meaningful differences in other laboratory values between the groups were observed.

Once-monthly administration of DA is not always sufficient to maintain hemoglobin levels in patients on CAPD when adequate dialysis therapy is not achieved.

Key words
Recombinant human erythropoietin, darbepoetin alpha, hemoglobin, dose requirements

Introduction
Anemia is a serious problem affecting morbidity, mortality, and quality of life (1). For more than decade, recombinant human erythropoietin (rHuEPO) has been available as an effective agent to treat anemia. Although rHuEPO has proven highly effective, multiple monthly injections of rHuEPO may be inconvenient for patients and health care providers alike (2). That inconvenience cancels the advantage of continuous ambulatory peritoneal dialysis (CAPD) over hemodialysis, because one of the advantages of CAPD is a reduction in the number of patients receiving treatment in hospital (3).

The recently developed erythropoiesis agent darbepoetin alpha (DA) is widely used in treating chronic kidney disease patients, including those receiving dialysis therapy (1). Because of its longer elimination half-life and greater in vivo biological activity, this unique erythropoietic protein can be administered less frequently than rHuEPO. Several studies have confirmed this less-frequent dosing schedule for the correction and maintenance of hemoglobin levels in
people with kidney disease (1). Moreover, it has been shown that dose requirements for DA, in contrast to those for rHuEPO, are not different for intravenous (IV) and subcutaneous (SC) administration, and that blood hemoglobin levels are effectively maintained with a greater intra-dose interval of administration (1).

In the present study, the effectiveness of once-monthly IV injections of DA to maintain hemoglobin levels near 10.5 g/dL in CAPD patients was assessed, compared with the twice-monthly injections needed for rHuEPO.

**Methods**

This single-center prospective cohort study included 52 clinically stable patients (25 men, 27 women; mean age: 59 ± 10 years) on CAPD. All patients had been on a stable weekly or twice-monthly rHuEPO regimen before initiation of the study. To determine the monthly dose of DA, the previously used mean weekly dose of rHuEPO was divided by 200 to determine the equivalent weekly dose of DA in micrograms; that number was then multiplied by 4 to generate the monthly dose requirement. For example, if 3000 IU rHuEPO was being administered weekly, then the monthly dose of DA was calculated to be 60 µg (3000 / 200 × 4). All patients received a monthly dose of DA for the first month, and hemoglobin and other routine laboratory tests were performed monthly for 24 consecutive weeks.

The patients were followed once monthly on an outpatient basis. During the study, if hemoglobin levels decreased by more than 1.0 g/dL over a period of 4 weeks, the total monthly DA dose was increased by 25% over the previous dose. If hemoglobin levels decreased by more than 1.5 g/dL over a period of 4 weeks, the total monthly DA dose was increased by 50% over the previous dose. The primary efficacy endpoint of the study was the change in hemoglobin level from baseline and then monthly during the study period. The secondary endpoints included the changes in the required dose of DA.

To maintain adequate control of uremia, weekly creatinine clearance calculated by the PD Adequest software (Baxter Healthcare, Tokyo, Japan) was evaluated every 3 months.

**Statistical analysis**

Results are expressed as mean ± standard error of the mean. The statistical analyses used the Student t-test for unpaired samples and the Mann–Whitney test for comparisons of means. The analyses of the effects of DA on longitudinal change in hemoglobin levels were performed by repeated-measures analysis of covariance, followed by a Newman–Keuls test for evaluation of significance. A simple regression analysis for corrections among the variables was performed to identify the contributors to fluctuations in hemoglobin level. Statistical significance was set at \( p < 0.05 \). All calculations were performed using the StatView statistical software package (version 5.0: SAS Institute, Cary, NC, U.S.A.).

**Results**

**Patient demographics**

The study enrolled 52 CAPD patients receiving rHuEPO twice month, who then received DA once monthly. Using the protocol described earlier, 26 patients (50%, group I) remained on a stable monthly DA dose. The monthly dose was increased by 25% in 22 patients (42%, group II), and by 50% in 4 patients (8%, group III). Table I summarizes the demographic and baseline characteristics of the groups. Overall, the mean age of the patients was 59 ± 10 years, and the duration of CAPD therapy was 5.3 ± 2.7 years. One half the patients had diabetic nephropathy. The mean level of hemoglobin was 10.5 ± 0.9 g/dL. Transferrin saturation was 32.6% ± 4.2%. No significant differences were noted between the groups, including weekly creatinine clearance calculated using the PD Adequest software. Also, no clinically meaningful differences in laboratory values were observed between the groups (data not shown).

**Hemoglobin values throughout the study**

Figure 1 shows a retrospective analysis of the serial changes in hemoglobin level during the study period. In group I, hemoglobin levels were maintained near 10.7 g/dL throughout the study. Hemoglobin levels in groups II and III declined at 2 months after the start of DA and fell below 9.5 g/dL at 3 months after the start of DA. Hemoglobin levels at 3 and 4 months in groups II and III were significantly lower than baseline levels (\( p < 0.05 \)). Three months after the start of DA, doses were increased by 25% and 50% in the patients of groups II and III respectively. Two months after the doses of DA were increased, hemoglobin levels in groups II and III increased and were maintained to the end of the study.
Monthly Darbepoetin Alpha to Maintain Hemoglobin

TABLE 1  Demographics and baseline characteristics of the study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>26</td>
<td>22</td>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>12/14</td>
<td>12/10</td>
<td>1/3</td>
<td>25/27</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62±7</td>
<td>51±13</td>
<td>57±7</td>
<td>59±10</td>
</tr>
<tr>
<td>Duration of PD (months)</td>
<td>5.3±2.7</td>
<td>5.1±2.9</td>
<td>5.2±2.4</td>
<td>5.3±2.7</td>
</tr>
<tr>
<td>Diabetes (with/without)</td>
<td>13/13</td>
<td>8/14</td>
<td>1/3</td>
<td>22/30</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.7±0.8</td>
<td>10.3±1.0</td>
<td>10.2±0.6</td>
<td>10.5±0.9</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>32.6±4.3</td>
<td>33.3±4.2</td>
<td>29.5±3.6</td>
<td>32.6±4.2</td>
</tr>
<tr>
<td>Weekly CCr (L)</td>
<td>59.6±4.3</td>
<td>61.4±4.2</td>
<td>60.3±15.1</td>
<td>60.4±5.8</td>
</tr>
</tbody>
</table>

TSAT = transferrin saturation; CCr = clearance of creatinine.

Serial changes in hemoglobin level

Figure 1 shows the changes in hemoglobin level for groups I (open circles), II (filled triangles), and III (filled squares). In group I (no increase in the dose of darbepoetin alpha), Hb levels were maintained throughout the study. In groups II (25% increase in the dose of darbepoetin alpha) and III (50% increase in the dose of darbepoetin alpha), Hb levels at 3 and 4 months declined significantly compared with baseline values. These decreased Hb levels increased toward the end of the study. *p < 0.05.

Serial changes in weekly creatinine clearance

Figure 2 shows a retrospective analysis of changes in weekly creatinine clearance during the study period. Weekly creatinine clearance in group I was maintained at a similar level throughout the study. In groups II and III, gradual declines were observed toward the end of the study; however, those declines were nonsignificant with respect to group I.

Correlations between hemoglobin levels and weekly creatinine clearance

Figure 3 shows correlations between hemoglobin levels and weekly creatinine clearance at baseline and at 3 months. These values showed a significant correlation (p < 0.05). In general, no adverse events
attributable to DA were observed, and no clinically meaningful changes in laboratory values were evident during the study period.

**Discussion**

The goal of the present study was to determine if the DA dosing interval could be further extended and still maintain Hb levels above a therapeutic target of 10.5 g/dL in CAPD patients previously stabilized on DA administered once monthly. Mean hemoglobin levels above 10.5 g/dL were maintained in 26 of 52 evaluable patients. Of those 26 patients, 22 required a 25% increase and 4, a 50% increase above the starting dose.

This exploratory study in patients on CAPD demonstrated that DA administered once monthly maintained hemoglobin levels effectively and safely in 26 of 52 patients previously stabilized by dosing once every 2 weeks. Previously, Theodoridis et al. (3) studied 11 stable CAPD patients who had received rHuEPO once weekly and who were assigned to receive the equivalent weekly DA dose once monthly for 24 weeks. They were able to maintain a constant monthly dose of DA during the evaluation period in all but 2 patients. Also, several other studies (4,5,6) involving relatively small numbers of CAPD patients reported that treatment with DA maintained target hemoglobin levels with less frequent dosing than was required with rHuEPO. Compared with those other studies, our study showed that treatment with DA once monthly maintained half our CAPD patients; increased doses were required for the other half.

Renal anemia is a result of several factors, such as underlying inflammation, circulating uremic inhibitors of erythropoietin action, and iron deficiency, among others. In addition, iron deficiency is well-known factor in erythropoietin resistance. In the present study, we observed no differences in transferrin saturation, removing it as the cause of iron deficiency in the patients of groups II and III.

In the present study, we observed a mild decline in weekly creatinine clearance in the patients of groups II and III, indicating that uremic factors might produce erythropoietin resistance. Indeed, a significant correlation was observed between hemoglobin level and weekly creatinine clearance at baseline and at 3 months after the start of DA therapy. Thus, assessments of weekly creatinine clearance are recommended monthly in CAPD patients who receive DA.

**Conclusions**

Once-monthly administration of DA is not always sufficient to maintain hemoglobin levels in patients on CAPD when adequate dialysis therapy is not achieved.

**Disclosures**

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**References**

4. Macdougall IC, Matcham J, Gray SJ on behalf of the NESP 960245/246 Study Group. Correction of anaemia with darbepoetin alfa in patients with chronic


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