Erythropoietin Therapy, Hemoglobin Targets, and Quality of Life in Healthy Hemodialysis Patients: A Randomized Trial

Robert N. Foley,* Bryan M. Curtis,† and Patrick S. Parfrey†
*
†Chronic Disease Research Group and University of Minnesota, Minneapolis, Minnesota; †Memorial University of Newfoundland, St. John’s, Newfoundland, Canada

Background and objectives: The effects of different hemoglobin targets when using erythropoiesis-stimulating agents on quality of life are somewhat controversial, and predictors of change in quality of life in endstage renal disease have not been well characterized.

Design, setting, participants, & measurements: Five hundred ninety-six incident hemodialysis patients without symptomatic cardiac disease were randomly assigned to hemoglobin targets of 9.5 to 11.5 g/dl or 13.5 to 14.5 g/dl for 96 weeks, using epoetin alfa as primary therapy. Patients and attending physicians were masked to treatment assignment. Quality of life, a secondary outcome, was prospectively recorded using the Kidney Disease Quality of Life (KDQoL) questionnaire at weeks 0, 24, 36, 48, 60, 72, 84, and 96, with prespecified outcomes being fatigue and quality of social interaction.

Results: The mean age and prior duration of dialysis therapy of the study population were 50.8 and 0.8 yr. Mortality was low, reflecting the relatively healthy group enrolled. Of 20 domains within the KDQoL only the prespecified domain of fatigue showed significant change over time between the two groups. Improvement in fatigue scores in the high-target group ranged from 3.2 to 7.9 over time (P = 0.007) compared with change in the low-target group. Higher body mass index and lower erythropoietin dose at baseline were independent predictors of improvement in multiple KDQoL domains.

Conclusions: In relatively healthy hemodialysis patients, normal hemoglobin targets may have beneficial effects on fatigue. Improvement in multiple domains of quality of life is associated with higher body mass index and lower erythropoietin requirements.


A
nemia is highly prevalent in end-stage renal disease patients, and inadequate renal erythropoietin production is a contributing cause (1,2). Although erythropoiesis-stimulating agents have been used to treat anemia in patients with chronic kidney disease (CKD) for almost two decades, optimal hemoglobin targets remain unclear, and concerns remain about the safety of normal hemoglobin levels as a target for erythropoietin therapy. In this regard, the United States Food and Drug Administration recently issued an alert to healthcare professionals about revisions to the product label for erythropoiesis-stimulating agents in patients with chronic kidney disease (3). Notable features of this label change were the recommended hemoglobin target range of 10 to 12 g/dl and the removal of all quality of life claims, with the exception of improved exercise tolerance and functional ability.

In practice, hemoglobin levels have sometimes been maintained at levels higher than 12.0 g/dl because individual patients perceive better quality of life at higher hemoglobin levels. However, randomized trials of higher hemoglobin targets have shown heterogeneous quality of life effects. Improvements were observed in prevalent hemodialysis patients with preexisting cardiac disease (4), in Scandinavian predialysis and dialysis patients (5), and in nondialysis patients enrolled in CREATE (6), but no improvement was observed in patients enrolled in CHOIR who had less severe CKD than those in CREATE (7). In addition, the validity of quality of life findings in most of these trials is uncertain because treatment assignments were not concealed from study subjects.

We enrolled 596 incident hemodialysis patients without symptomatic cardiac disease in a randomized, controlled trial that compared a normal hemoglobin target to partial correction of anemia, with epoetin alfa as the erythropoiesis-stimulating agent. Cardiac structure constituted the primary study outcome, and no difference was observed between the two groups (8). Clinically relevant secondary outcomes included quality of life, with prespecified outcomes being Energy/Fatigue scores and Quality of Social Interaction scores on the Kidney Disease Quality of Life (KDQoL) questionnaire and Vitality scores on the Short Form 36 (SF36) questionnaire. We have not previously reported the results from this trial of serial measurements using the KDQoL questionnaire. In this article, we examine the hypothesis that normal hemoglobin targets improve quality of life in comparatively “healthy” incident hemodialysis patients, and we also report the independent predictors of changes in the various quality of life domains assessed by the KDQoL.

Received September 25, 2008. Accepted January 15, 2009.

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Patrick Parfrey, Health Sciences Centre, Memorial University of Newfoundland, Street John’s, NL, Canada A1B 3V6, Phone: 709-777-7261; Fax: 709-777-6995; E-mail: pparfrey@mun.ca

Copyright © 2009 by the American Society of Nephrology

ISSN: 1555-9041/404–0726
Materials and Methods

Design

The design, methods and sample size assumptions of the study have been reported previously (8).

Patients were randomly assigned to one of the following hemoglobin targets: 9.5 to 11.5 g/dl (“low target”) and 13.5 to 14.5 g/dl (“high target”). Patients were masked to treatment assignment. Local investigators and the dialysis unit were also masked to treatment assignment. However, attending physicians had access to local clinic hemoglobin levels. The central coordinating centers provided treatment recommendations on erythropoietin dose, intravenous iron dose, and antihypertensive therapy for each patient (see below), but the local investigator was responsible for ordering treatment changes. Mean hemoglobin levels at the end of the initial 24-wk titration phase were 13.3 and 10.9 g/dl, respectively. During the maintenance phase, from weeks 24 to 96, corresponding mean hemoglobin levels were 13.1 and 10.8 g/dl.

Study Population

Inclusion criteria were as follows: age ≥ 18 yr, inception of maintenance hemodialysis within the previous 3 to 18 mo, predialysis hemoglobin between 8 and 12 g/dl, left ventricular volume index <100 ml/m², and predialysis diastolic BP < 100 mmHg. Exclusion criteria were as follows: clinical evidence or history of symptomatic cardiac failure or ischemic heart disease; daily prednisone dose ≥ 10 mg; medical conditions likely to reduce epoetin responsiveness, including uncorrected iron deficiency; concurrent malignancy; blood transfusion in the preceding month; therapy with cytotoxic agents; seizure in the preceding year; hypersensitivity to intravenous iron; and current pregnancy or breastfeeding.

Description of Study Procedures

Laboratory tests were measured centrally by Quest Diagnostics (Van Nuys, CA and Heston, UK). Hemoglobin was measured weekly for 24 wk and biweekly thereafter. With the high target, the treatment goal was increments of 0.5 to 1.0 g/dl every 2 wk, until achieving stability between 13.5 and 14.5 g/dl. Other treatment goals included predialysis diastolic BP between 70 and 90 mmHg; urea reduction ratio ≥ 67%; medical conditions likely to reduce epoetin responsiveness, including uncorrected iron deficiency; concurrent malignancy; blood transfusion in the preceding month; therapy with cytotoxic agents; seizure in the preceding year; hypersensitivity to intravenous iron; and current pregnancy or breastfeeding.

Analysis

Repeated measures ANOVA with mixed modeling was used to estimate time-integrated quality of life effects, over time, while simultaneously examining quality of life at each individual study assessment. Change from baseline in the high-target group compared with change from baseline in low-target group was calculated for each KDQoL domain. To identify factors predictive of changes in quality of life by domain the high- and low-target groups were combined. Repeated measures ANOVA with mixed modeling was used to estimate changes in quality of life over time. Multivariate models included target hemoglobin group, baseline hemoglobin, baseline epoetin dose, baseline transferrin saturation, age, sex, race, time on dialysis, body mass index, primary cause of renal disease, European or Canadian patients, type of vascular access and baseline serum albumin. Details of the reported model are included in Table 3. SAS, version 9.1 (SAS Institute Inc., Cary, NC) was used for data analysis.

Results

Five hundred ninety-six incident hemodialysis patients were enrolled in 95 treatment centers in 10 countries between February 2000 and June 2001. Table 1 compares baseline characteristics by random hemoglobin target assignment (8). Baseline characteristics were similar except for the older age of high-target subjects (52.2 versus 49.4 yr). As dictated by the study design, initial on-study epoetin doses were greater in high-target group (7009 ± 49.4 yr). Also, as dictated by the study design, only patients without symptomatic heart failure or ischemic heart disease were enrolled. Eighteen percent of participants were diabetic, and median serum albumin level was 4 mg/dl. The relatively healthy group of hemodialysis patients studied was reflected in the relatively low mortality rate: 4.7 (95% confidence interval [CI] 3.0 to 7.3) per 100 patient years in the low-target group and 3.1 (1.8 to 5.4) in the high-target group, (P = 0.25).

The proportions of study subjects with ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, and ≥ 6, and 7 quality of life assessments were 93.5%, 81.2%, 73.0%, 64.0%, 58.1% 47.2% and 29.3%, respectively. Table 2 shows the effect of the high hemoglobin target on KDQoL scores. Beneficial changes were seen in at least one of the seven assessments that followed randomization for nine scales. When all study assessments were considered, the high hemoglobin target had an overall, time-integrated effect on energy/fatigue and no effect on the other 19 dimensions assessed (Table 2). The improvement in Energy/Fatigue scores in the high-target group ranged from 3.2 to 7.9 over time (P = 0.007) compared...
with the changes in the low-target group. There was little difference in the changes of Quality of Social Interaction scores (Table 2).

The independent predictors of changes in quality of life for each domain were identified by combining both high- and low-target groups (Table 3). Among the covariates analyzed, no associations were identified for quality of social interaction, cognitive function, effects of kidney disease, dialysis staff encouragement, and patient satisfaction.

Older age was an independent predictor of deterioration in physical function only. Female sex was an independent predictor of increasing burden of kidney disease only. Nonwhite race was a strong predictor of not working.

Diabetes as a cause of renal disease had an independent and negative impact on sexual function and physical functioning, but was associated with improvement in scores for burden of kidney disease and emotional well being.

Higher body mass index (≥25.5) was independently predictive of improvement in scores for burden of kidney disease, symptoms/problems, sleep, physical functioning, role limitations-physical, general health, emotional well being, role limitations-emotional, social functioning, and energy/fatigue (Table 3).

High baseline erythropoietin dose (≥6000 IU/wk) was a significant predictor of deterioration in scores for symptoms/problems, overall health, pain, and energy/fatigue independent of other risk factors, including target hemoglobin (Table 3).

---

**Table 1. Baseline characteristics of patients enrolled in this randomized trial compared by target hemoglobin level**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Target 9.5 to 11.5 g/dl</th>
<th>Target 13.5 to 14.5 g/dl</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>300</td>
<td>296</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.0 (10.8 to 11.1)</td>
<td>11.0 (10.9 to 11.2)</td>
<td>0.54</td>
</tr>
<tr>
<td>Epoetin dose (IU per week)</td>
<td>6183 (5698 to 6667)</td>
<td>7009 (6528 to 7490)</td>
<td>0.02</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>36.8 (34.9 to 38.8)</td>
<td>35.8 (33.8, 37.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>Age</td>
<td>49.4 (47.7 to 51.2)</td>
<td>52.2 (50.4 to 53.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>39.7</td>
<td>39.5</td>
<td>0.97</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>white</td>
<td>87.7</td>
<td>91.2</td>
<td></td>
</tr>
<tr>
<td>black</td>
<td>5.7</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4.3</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>2.3</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Dialysis duration (months)</td>
<td>10.2 (9.6 to 10.8)</td>
<td>10.0 (9.4 to 10.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.3 (25.7 to 26.9)</td>
<td>26.5 (25.9 to 27.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>Country (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>3.0</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>3.3</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>32.0</td>
<td>27.7</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>3.0</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>11.0</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>2.3</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>10.7</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>22.3</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>3.0</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>9.3</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>Primary cause of renal disease</td>
<td></td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>glomerulonephritis</td>
<td>29.0</td>
<td>28.4</td>
<td></td>
</tr>
<tr>
<td>diabetes</td>
<td>16.7</td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>hypertension</td>
<td>9.3</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>polycystic kidney disease</td>
<td>7.7</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>37.3</td>
<td>35.5</td>
<td></td>
</tr>
<tr>
<td>Dialysis access (%)</td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>fistula</td>
<td>82.7</td>
<td>85.8</td>
<td></td>
</tr>
<tr>
<td>graft</td>
<td>5.0</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>catheter</td>
<td>12.3</td>
<td>8.11</td>
<td></td>
</tr>
<tr>
<td>Serum albumin (mg/dl)</td>
<td>4.0 (3.9 to 4.0)</td>
<td>4.0 (3.9 to 4.0)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Data are reported either as percent or as means (95% confidence intervals). The chi-squared test and analysis of variance were used for between-target comparisons.
Table 2. Effect of target hemoglobin on quality of life scores

<table>
<thead>
<tr>
<th>Baseline Values</th>
<th>Change from Baseline in High Target (vs. Change from Baseline in Low Target)</th>
<th>P^1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Hemoglobin g/dl</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>10.5 - 11.5</td>
<td>13.5 - 14.5</td>
<td></td>
</tr>
<tr>
<td>Burden of kidney disease</td>
<td>47.1</td>
<td>44.8</td>
</tr>
<tr>
<td>Quality of social interaction</td>
<td>66.6</td>
<td>62.8</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>69.9</td>
<td>63.3</td>
</tr>
<tr>
<td>Sleep</td>
<td>67.9</td>
<td>64.7</td>
</tr>
<tr>
<td>Social support</td>
<td>75.2</td>
<td>74.0</td>
</tr>
<tr>
<td>Work status</td>
<td>40.3</td>
<td>34.4</td>
</tr>
<tr>
<td>Dialysis staff encouragement</td>
<td>82.6</td>
<td>79.7</td>
</tr>
<tr>
<td>Patient satisfaction rating</td>
<td>75.9</td>
<td>77.3</td>
</tr>
<tr>
<td>Overall health rating</td>
<td>62.0</td>
<td>62.0</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>67.1</td>
<td>62.5</td>
</tr>
<tr>
<td>Role limitations -physical</td>
<td>48.4</td>
<td>47.7</td>
</tr>
<tr>
<td>Pain</td>
<td>72.0</td>
<td>70.7</td>
</tr>
<tr>
<td>General health</td>
<td>49.4</td>
<td>48.6</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>74.0</td>
<td>67.8</td>
</tr>
<tr>
<td>Role limitations -emotional</td>
<td>68.4</td>
<td>69.1</td>
</tr>
<tr>
<td>Social function</td>
<td>74.5</td>
<td>71.4</td>
</tr>
<tr>
<td>Energy/fatigue</td>
<td>57.9</td>
<td>53.9</td>
</tr>
</tbody>
</table>

Repeated measures analysis of variance with mixed modeling was used to estimate changes in quality of life over time. Positive values represent improvements in quality of life. Parameter estimates are presented with standard errors in parentheses.

^P < 0.05, **P < 0.01, ***P < 0.001, ¶P < 0.0001 for the effect of target hemoglobin at week 24, 36, 48, 72, or 96.
Table 3. Multivariate analysis of changes in quality of life: Baseline associations

<table>
<thead>
<tr>
<th></th>
<th>Change from Baseline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 24</td>
<td>Week 36</td>
</tr>
<tr>
<td>Burden of kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female sex</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>(2.0)</td>
<td>(2.1)</td>
<td>(2.1)</td>
</tr>
<tr>
<td>body mass index &gt; 25.5 kg/m²</td>
<td>-1.0</td>
<td>-0.8</td>
</tr>
<tr>
<td>(2.0)</td>
<td>(2.0)</td>
<td>(2.0)</td>
</tr>
<tr>
<td>diabetic renal disease</td>
<td>1.1</td>
<td>7.5†</td>
</tr>
<tr>
<td>(2.7)</td>
<td>(2.7)</td>
<td>(2.7)</td>
</tr>
<tr>
<td>Europe</td>
<td>-2.4</td>
<td>-1.0</td>
</tr>
<tr>
<td>(2.1)</td>
<td>(2.1)</td>
<td>(2.1)</td>
</tr>
<tr>
<td>Symptoms/problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>epoetin dose &gt; 6000 IU per week</td>
<td>-1.0</td>
<td>1.6</td>
</tr>
<tr>
<td>(1.3)</td>
<td>(1.3)</td>
<td>(1.3)</td>
</tr>
<tr>
<td>body mass index &gt; 25.5 kg/m²</td>
<td>-0.1</td>
<td>-1.2</td>
</tr>
<tr>
<td>(1.2)</td>
<td>(1.3)</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Sexual function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetic renal disease</td>
<td>-2.0</td>
<td>-2.1</td>
</tr>
<tr>
<td>(4.0)</td>
<td>(4.0)</td>
<td>(4.1)</td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>body mass index &gt; 25.5 kg/m²</td>
<td>2.2</td>
<td>-1.7</td>
</tr>
<tr>
<td>(1.7)</td>
<td>(1.7)</td>
<td>(1.7)</td>
</tr>
<tr>
<td>Work status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonwhite race</td>
<td>-8.2</td>
<td>-6.2</td>
</tr>
<tr>
<td>(4.3)</td>
<td>(4.3)</td>
<td>(4.4)</td>
</tr>
<tr>
<td>Overall health rating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>epoetin dose &gt; 6000 IU per week</td>
<td>1.9</td>
<td>2.6</td>
</tr>
<tr>
<td>(1.9)</td>
<td>(1.9)</td>
<td>(2.0)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age &gt; 50.5 yr</td>
<td>-0.5</td>
<td>-2.7</td>
</tr>
<tr>
<td>(2.0)</td>
<td>(2.0)</td>
<td>(2.0)</td>
</tr>
<tr>
<td>body mass index &gt; 25.5 kg/m²</td>
<td>-0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>(2.0)</td>
<td>(2.0)</td>
<td>(2.0)</td>
</tr>
<tr>
<td>diabetic renal disease</td>
<td>0.0</td>
<td>0.4</td>
</tr>
<tr>
<td>(2.6)</td>
<td>(2.6)</td>
<td>(2.7)</td>
</tr>
<tr>
<td>Role limitations-physical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>body mass index &gt; 25.5 kg/m²</td>
<td>-2.4</td>
<td>-2.6</td>
</tr>
<tr>
<td>(4.4)</td>
<td>(4.4)</td>
<td>(4.4)</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>epoetin dose &gt; 6000 IU per week</td>
<td>-3.4</td>
<td>0.9</td>
</tr>
<tr>
<td>(2.7)</td>
<td>(2.7)</td>
<td>(2.7)</td>
</tr>
<tr>
<td>transferrin saturation ≤ 32.0%</td>
<td>-0.2</td>
<td>-3.2</td>
</tr>
<tr>
<td>(2.6)</td>
<td>(2.6)</td>
<td>(2.7)</td>
</tr>
<tr>
<td>General health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>body mass index &gt; 25.5 kg/m²</td>
<td>0.2</td>
<td>2.2</td>
</tr>
<tr>
<td>(1.7)</td>
<td>(1.7)</td>
<td>(1.7)</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dialysis duration &gt; 9.0 months</td>
<td>-3.9†</td>
<td>0.4</td>
</tr>
<tr>
<td>(1.8)</td>
<td>(1.8)</td>
<td>(1.8)</td>
</tr>
<tr>
<td>body mass index &gt; 25.5 kg/m²</td>
<td>-2.1</td>
<td>-3.7*</td>
</tr>
<tr>
<td>(1.8)</td>
<td>(1.8)</td>
<td>(1.8)</td>
</tr>
<tr>
<td>diabetic renal disease</td>
<td>3.9</td>
<td>7.1**</td>
</tr>
<tr>
<td>(2.4)</td>
<td>(2.4)</td>
<td>(2.4)</td>
</tr>
</tbody>
</table>
Table 3. Multivariate analysis of changes in quality of life: Baseline associations (continued)

<table>
<thead>
<tr>
<th></th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 24</td>
</tr>
<tr>
<td>Role limitations-emotional</td>
<td></td>
</tr>
<tr>
<td>body mass index &gt; 25.5 kg/m²</td>
<td>-4.5</td>
</tr>
<tr>
<td></td>
<td>(4.4)</td>
</tr>
<tr>
<td>Social function</td>
<td></td>
</tr>
<tr>
<td>body mass index &gt; 25.5 kg/m²</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>(2.4)</td>
</tr>
<tr>
<td>Energy/fatigue</td>
<td></td>
</tr>
<tr>
<td>target hemoglobin 13.5 to 14.5</td>
<td>6.2*</td>
</tr>
<tr>
<td>g/dl</td>
<td>(1.9)</td>
</tr>
<tr>
<td>epoetin &gt; 6000 IU per week</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>(1.9)</td>
</tr>
<tr>
<td>body mass index &gt; 25.5 kg/m²</td>
<td>-1.9</td>
</tr>
<tr>
<td></td>
<td>(1.9)</td>
</tr>
</tbody>
</table>

Repeated measures analysis of variance with mixed modeling was used to estimate changes in quality of life over time. Increasing values represent better quality of life. Parameter estimates are presented with standard errors in parentheses. Adjustment was made for target hemoglobin, hemoglobin, epoetin dose, transferrin saturation, age, sex, race, dialysis duration, body mass index, primary cause of renal disease, European or Canadian patient, vascular access for dialysis and serum albumin. The following reference groups were used: target hemoglobin 10.5 to 11.5 g/dl, hemoglobin > 11.1 g/dl, epoetin dose ≤ 6000 units per week, transferrin saturation > 32.0%, age ≤ 51.5 up years, male sex, white race, dialysis duration ≤ 9.0 months, body mass index ≤ 25.5 kg/m², renal disease not due to diabetes, Canada, fistula or graft for dialysis access, serum albumin > 4.0 g/dl. No associations were identified for quality of social interaction, cognitive function, effects of kidney disease, dialysis staff encouragement, and patient satisfaction.

*P < 0.05, **P < 0.01, ***P < 0.001, ¶P < 0.0001 for week 24, 36, 48, 72 or 96.

Discussion

Randomized controlled trials comparing a normal hemoglobin target to partial corrections of anemia with epoetin have varied in the stage of CKD disease of patients enrolled, primary outcomes assessed, statistical power to compare major clinical outcomes, and research methodology. Nonetheless, signals have emerged to suggest that higher hemoglobin targets may be harmful. Clinical events related to higher hemoglobin targets in some trials have included higher vascular access thrombosis (4), higher BP or greater requirements for antihypertensives (7,8,12), cardiovascular events (4,7), earlier need for renal replacement therapy (6), and higher mortality (4,7). Adverse events for the current study were reported in the original paper, and a significantly higher number of cerebrovascular events occurred in the high hemoglobin group (n = 12) compared with the low hemoglobin group (n = 4) (8). These adverse outcomes have not been seen uniformly across studies, and several outcomes have had marginal statistical significance and wide confidence intervals for effect estimates. However higher vascular access thrombosis and hypertension have been observed in the early studies comparing no treatment of anemia with partial correction using epoetin (13).

Controversy exists concerning target hemoglobin levels for erythropoiesis-stimulating agent therapy in CKD. The European Medicines Agency stipulated a uniform target hemoglobin range for all patients with CKD of 10 to 12 g/dl, with a warning not to exceed a concentration of 12 g/dl (14). It noted that trials with high target hemoglobin concentrations “have not shown significant benefits attributable to the administration of epoetins to increase hemoglobin concentrations beyond the level necessary to control symptoms of anemia and to avoid blood transfusion.” However, the current study of “healthy” patients starting hemodialysis, with a sample size similar to CREATE (6), clearly demonstrates that higher hemoglobin targets reduce the need for blood transfusions (11) and produce an improvement in symptoms of fatigue. The latter is consistent with the significant improvements in vitality scores, measured by the SF36, reported in an earlier paper (8).

Although only one of 20 domains in the KDQoL and one in the SF36 showed significant improvements, these occurred in two of the three prespecified quality of life outcomes identified before starting the trial, on the basis of previous studies and biologic plausibility. Energy/fatigue scores were significantly higher in the high hemoglobin group compared with the low hemoglobin group, and the differences were of clinical significance (10,13). We compared our results to those obtained from one of the initial erythropoietin randomized controlled trials (RCTs) reported in 1990 (13). Change in baseline fatigue score at 6 mo in the group whose hemoglobin level increased from 69 to 102 g/dl (n = 32) versus that of controls (n = 34) was 8, whereas in the current study the comparable change in the group whose hemoglobin level increased from 11.0 to 13.3 versus the control group was 6. Of interest, the baseline fatigue seen in the 1990 study in the intervention group was 41, and in our study it was 54, reflecting the healthier patients enrolled in the current study.
It is likely that the cost of the higher hemoglobin needed to obtain this quality of life benefit will be high (15). The improvement in quality of life observed is consistent with results in hemodialysis patients with overt cardiovascular disease (4), in Scandinavian predialysis and dialysis patients (5), and in non-dialysis-dependent CKD patients enrolled in CREATE, but is divergent from the CHOIR trial, in subjects with non–dialysis-dependent CKD (7). It should be noted however, the improvement in quality of life observed in the Besarab et al. study (4) was for improved Physical Function score in relation to achieved hematocrit.

Meta-analysis of reported RCTs concludes that normalization of hemoglobin with erythropoietin is harmful (16). We await the results of TREAT, a global RCT of 4000 predialysis diabetic patients with chronic kidney disease, planned to stop after the occurrence of 1800 cardiovascular events, to provide further evidence on the potential benefit and safety of hemoglobin targets above those currently recommended (<12 g/dl) (17). Quality adjusted costs of higher targets are extremely expensive (15). Although current international guidelines for erythropoietin therapy are justified (3,14) nonetheless, in a patient centered paradigm of care, individuals who need to avoid blood transfusions, or those at low risk of adverse outcomes who value improved energy and vitality, should not be disadvantaged by strict adherence to guidelines.

Some of the limitations of this study are worth considering. Attending physicians were masked as to assigned target hemoglobin group, but they had access to local clinic results for patient care, making it possible to unmask the assigned group. Unmasking patients to treatment assignment could influence their perceptions of quality of life. However, patients were masked, a design feature that tends to lessen the possibility that patient-related biases could explain the findings. By design, we studied hemodialysis patients without overt cardiac disease, and the generalizability of our findings to other populations with chronic kidney disease is not certain. Our results are applicable to approximately 50% of the dialysis population (18). The high dropout rate was anticipated because patients such as those in our study are usually referred for and then wait for renal transplantation. This was taken into account in the sample size estimate.

Combining both the intervention and control groups from whom serial measurements of quality of life were obtained provided a valuable resource to examine changes in quality of life in an incident cohort of hemodialysis patients. Multivariate modeling suggested that higher body mass index and lower erythropoietin dose at baseline were independent predictors of better quality of life across several domains. These predictions were independent of age, sex, diabetes mellitus, and serum albumin, and were identified in a group without symptomatic cardiac disease. Further investigation of the role of inflammation and cardiac biomarkers on quality of life is underway in this cohort, particularly because it is possible that both lower body mass index and higher erythropoietin requirements are markers for subclinical inflammation or even subclinical cardiac disease.

We conclude that in incident, relatively healthy, hemodialysis patients without symptomatic cardiac disease, normal hemoglobin targets improve energy scores. Higher body mass index and lower erythropoietin dose at baseline were independent predictors of change in several domains of quality of life.

**Acknowledgments**

The Canadian-European Normalization Of Hemoglobin With Erythropoietin Trial was funded by Johnson and Johnson Pharmaceutical Research and Development. The study sponsor identified the participating centers, monitored the data collection, and entered the data in a central database.

We are grateful to Janet Morgan in Canada and to Aileen Foley in England for coordinating patient enrollment and management. We are also grateful to Barbara Wittreich, Daniel Sullivan, Martin Zagari, and Dieter Frei from Ortho Biotech who made the RCT possible, and to Lou Marra from Janssen Ortho who facilitated the data transfer to the authors for the analysis in the current report.

Members of the Canadian European Study Group

EPO-INT-68 Independent Data Monitoring Committee Members: L.J. Wei, Boston, MA; M.-M. Samama, Paris, France; P. Ivanovich, Chicago, IL; M.A. Pfeffer, Boston, MA
Principal Investigator/ Site: W. Hoezel, Wien, Austria; H.-K. Stummvoll, Linz, Austria; G. Mayer, Innsbruck, Austria; H. Graf, Wien, Austria; H. Holzer, Graz, Austria; Y. Yanrenzeghem, Leuven, Belgium; M. Jadoul, Belguim; P. Parfrey, St. John’s, Canada; P. Barre, Montreál, Canada; A. Levin, Vancouver, Canada; P. Cartier, Montréal, Canada; N. Muïhead, London, Canada; A. Fine, Winnipeg, Canada; B. Murphy, Calgary, Canada; S. Hanka, St. John’s, Canada; P. Campbell, Edmon-ton, Canada; V. Pichette, Montréal, Canada; S. Tobe, Toronto, Canada; C. Lok, Toronto, Canada; D. Kates, Kelowna, Canada; D. Holland, Kingston, Canada; G. Karr, Penticton, Canada; G. Pyłchuk, Saskatoon, Canada; G. Wu, Mississauga, Canada; M. Vasilevsky, Montréal, Canada; E. Carlsile, Hamilton, Canada; E.R. Gagne, Fleurimont, Canada; W. Callaghan, Windsor, Canada; G. Soltys, Greenfield Park, Canada; P. Tam, Scarborough, Canada; R. Turcot, Trois-Rivieres, Canada; M. Ber rall, Toronto, Canada; J. Zacharias, Winnipeg, Canada; S. Donnelly, Toronto, Canada; G. London, Fleury-Merogis, France; A. London, Aulnay sous Bois, France; F.P. Wambergue, Lille, France; H. Geiger, Frankfurt, Germany; V. Kliem, Hann Muenden, Germany; R. Winkler, Rostock, Germany; B. Kraemer, Regensburg, Germany; H. Schiffi, Munich, Germany; R. Brunkhorst, Hanover, Germany; D. Seybold, Bayreuth, Germany; M. Hilfenhaus, Langenhagen, Germany; D. Schau man, Hameln, Germany; R. Goetz, Bad Windsheim, Germany; P. Roch, Regensburg, Germany; H.-P. Brasche, Ludwigsafen, Germany; V. Wizemann, Giessen, Germany; K. Bittner, Ansbach, Germany; K. Appen, Hamburg, Germany; B. Schroeder, Bad Toelz, Germany; W. Schropp, Munich, Germany; D. O’Donoghue, Salford, England; I. Mac Dougall, London, England; G. Warwick Leicester, England; M. Raftery, London, England; K. Harting, Stevenage, England; J. Kwan, Carshal ton, England; P. Conlon, Dublin, Ireland; G. Mellotte, Dublin, Ireland; K. Siamopoulos, Ioannina, Greece; N. Tsaparas, Crete, Greece; D. Tsa kiris, Veria, Greece; V. Vargemezis, Alexandroupolis, Greece; S. Fer enenci, Gyor, Hungary; S. Goroh, Kisvárda, Hungary; I. Kulszar, Szombataly, Hungary; L. Lacey, Debrecen, Hungary; K. Akcösi, Veszprem, Hungary; I. Solt, Székesfehérvár, Hungary; O. Arkossy, Budapest, Hungary; E. Kiss, Szeged, Hungary; J. Manitus, Bydgoszcz, Poland; B. Ruthowski, Gdansk, Poland; A. Wiecek, Katowice, Poland; W. Sutowicz, Krakow, Poland; A. Ksiazek, Lublin, Poland; S. Czekalski, Poznan, Poland; M. Klinger, Wroclaw, Poland; M. Mysliwiec, Białystok, Poland; H. Augustyniak-Bartosik, Mińcz, Poland; M. Mi iela, Warszawa-Miedzylisie, Poland; A. Sydor, Tarnow, Poland; R. Rudka,
References


Disclosures

P.S.P. has received research support and has been an academic advisor to companies that make erythropoietin products: Ortho Biotech, Amgen, and Roche. R.N.F. has received research support and honoraria from Ortho Biotech and honoraria from Atyfax, Amgen, Ortho Biotech, and Roche. B.M.C. has received research support and honoraria from Ortho Biotech and Roche. R.N.F. has received research support and honoraria from Amygen, Amgen, and Roche. B.M.C. has received research support and honoraria from Ortho Biotech, and Roche. P.S.P. declares that he had full access to all of the data in the study and had final responsibility for the decision to submit for publication.
ANEMIA TREATMENT IMPROVES HEART STRUCTURE AND QUALITY OF LIFE IN KIDNEY DISEASE PATIENTS

However, Different Levels of Erythropoietin Therapy Are Needed to Achieve These Effects

Washington, DC (Friday, March 27, 2009) — In chronic kidney disease patients, different levels of anemia treatment have a beneficial effect on the heart and improve quality of life, according to a pair of studies appearing in the April 2009 issue of the Clinical Journal of the American Society Nephrology (CJASN). The findings indicate that different levels of treatment may be warranted for different patients.

Patients with chronic kidney disease often have low levels of erythropoietin (a hormone that stimulates the formation of red blood cells) and develop anemia. Anemia can cause enlargement of the heart, predisposing individuals to heart failure and death. Synthetic erythropoietin partially corrects anemia, and doctors prescribe it to try to increase patients’ hemoglobin levels to 10-12 g/dl (hemoglobin is the predominant protein in red blood cells). Prescribing higher levels of erythropoietin may result in normal hemoglobin levels (greater than 13 g/dl), but recent clinical trials suggest that this may cause serious adverse effects, including death.

Two recent studies by Patrick Parfrey, MD (Memorial University of Newfoundland), and colleagues examined the effects of different levels of anemia treatment on heart structure and quality of life in chronic kidney disease patients.

The first study was a systematic review of published data on the effects of anemia on the heart. By analyzing 15 available studies involving 1,731 patients with kidney disease, the investigators found that partial correction of severe anemia with erythropoietin improved heart structure, but fully correcting anemia provided no additional benefit.

The second study assessed whether normalization of hemoglobin improves quality of life in kidney disease patients. The study was conducted because anemia-induced fatigue is a prominent symptom in patients with kidney disease. In a randomized trial performed in Canada and Europe, Dr. Parfrey and his team enrolled 596 relatively healthy patients starting dialysis. The researchers found that patients...
experienced less fatigue when they were treated with erythropoietin to reach a normal hemoglobin level compared with patients who were treated to achieve only partial correction of anemia.

Erythropoietin therapy can provide some benefits (such as reduced fatigue), but investigators concluded that the recommended hemoglobin target range is 10-12 g/dl. Treating patients to reach a normal hemoglobin level (>13 g/dl) does not improve heart structure and can cause significant harm to patients.

“It is possible that patients at low risk of an adverse side effect from erythropoietin therapy would value the improvement in quality of life provided by the higher hemoglobin level,” said Dr. Parfrey. “However the cost of this improvement in quality of life will be high, because erythropoietin is expensive,” he added.

The authors noted that a large clinical trial (TREAT) of 4,000 diabetic patients with chronic kidney disease will end this year and should provide additional information on the benefits and harms of prescribing erythropoietin to achieve a normal hemoglobin level.

The authors reported no financial disclosures.

The articles, entitled “Erythropoietin Therapy and Left Ventricular Mass Index in CKD and ESRD Patients: A Meta-Analysis” (doi 10.2215/CJN.02730608) and “Erythropoietin Therapy, Hemoglobin Targets, and Quality of Life in Healthy Hemodialysis Patients: A Randomized Trial,” (doi 10.2215/CJN.04950908) will appear online at http://cjasn.asnjournals.org/ on April 1, 2009.

More than 11,000 physicians and scientists committed to preventing kidney disease and making life better for patients work together as members of the American Society of Nephrology (ASN). Whether providing expert care to patients, performing cutting-edge medical research, or training the next generation of kidney experts, these nephrologists change lives. Through advocacy, ASN informs policymakers about issues of importance to kidney doctors and their patients. ASN also funds research, convenes world-renowned meetings, and generates educational tools that enable nephrologists to be most effective. Building on a 40-year history, ASN brings rigor, integrity, and ingenuity to all its work.

# # #