Health-Related Quality of Life Associated With Recombinant Human Erythropoietin Therapy for Predialysis Chronic Renal Disease Patients

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● **The investigators evaluated the impact of recombinant human erythropoietin (r-HuEPO) therapy on health-related quality of life (HRQL) in predialysis chronic renal disease patients with anemia. Eighty-three patients were entered into a randomized, parallel-group, open-label clinical trial with follow-up evaluations over 48 weeks. Forty-three patients were assigned to r-HuEPO treatment, and 40 patients were assigned to an untreated control group. Hematocrit levels were measured at baseline and monthly. HRQL was assessed at baseline and at weeks 16, 32, and 48. The HRQL assessment included measures of physical function, energy, role function, health distress, cognitive function, social function, home management, sexual dysfunction, depression, and life satisfaction. Significant improvements in hematocrit levels were observed in the r-HuEPO–treated group ($P < 0.0001$), and no changes were seen in the untreated group. Correction of anemia (hematocrit ≥ 36) occurred in 79% of r-HuEPO–treated patients and 0% of control patients. Significant improvements in assessments of energy ($P < 0.05$), physical function ($P < 0.05$), home management ($P < 0.05$), social activity ($P < 0.05$), and cognitive function ($P < 0.05$) were found for the r-HuEPO–treated group. No changes were observed in the control group, except for a decrease in physical function ($P < 0.05$). Between-group differences favoring the r-HuEPO–treated group were found for energy ($P < 0.05$) and physical functioning ($P < 0.05$). In patients receiving r-HuEPO, significant improvements were seen in hematocrit levels, and these increases resulted in improvements in HRQL.**

INDEX WORDS: Health-related quality of life; recombinant human erythropoietin; anemia; predialysis chronic renal disease; randomized clinical trial.

RESEARCH INTEREST in renal disease has shifted from exclusive focus on the life-extending features of medical advances to concern about the health-related quality of life (HRQL) outcomes associated with different therapies. In addition to the clinical efficacy and the cost-effectiveness of medical therapy, there is a continued interest in determining the impact of treatment on patient functioning and well-being. A number of studies have evaluated the impact of different medical treatments for chronic renal disease and end-stage renal disease (ESRD).[1-5] Despite the clinical effectiveness of medical treatments, such as hemodialysis and kidney transplantation, their effect on HRQL may offset their life-extending benefits.[1] Understanding of the impact of treatments on patient everyday functioning is crucial for medical decision-making seeking to balance clinical benefits with HRQL outcomes.[6,7]

Treatment with recombinant human erythropoietin (r-HuEPO) is effective in alleviating anemia in patients with inadequate levels of endogenous erythropoietin. Studies have demonstrated that r-HuEPO is effective in correcting anemia associated with predialysis renal insufficiency[8-15] and ESRD.[4,16,17] Recombinant human erythropoietin therapy is also associated with improvements in the level of energy, physical, social and sexual functioning, depression, appetite, and sleeping behavior.[2,4,5,16-18] However, research assessing the HRQL effects of r-HuEPO concentrates on ESRD.[2,4,5] These studies generally note the contribution of anemia to the poor HRQL associated with renal insufficiency before dialysis, but no data are available on the impact of r-HuEPO therapy on the HRQL of predialysis renal disease patients.

Numerous symptoms associated with anemia impair physical, psychological, and social functioning. The effects of anemia, such as chronic

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Received April 28, 1994; accepted in revised form November 23, 1994.

Supported by a grant from the R.W. Johnson Pharmaceutical Research Institute and Ortho Biotech Inc, Raritan, NJ.

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0272-6386/95/2504-0004$3.00/0

fatigue, loss of appetite, cognitive and physical impairments, eating and sleeping disorders, and depression, have a profound effect on patient's daily lives.[2,4,5] No studies specifically investigated the effect of r-HuEPO therapy on HRQL for predialysis renal disease patients. Some evidence suggests that by correcting anemia, r-HuEPO improves well-being, appetite, and exercise capacity.[11,12] Reducing or correcting anemia should increase patient functioning and overall well-being.

This multi-center study was designed to compare changes in HRQL in r-HuEPO–treated and untreated predialysis chronic renal disease patients with anemia as part of a study to examine decline in renal function.[19] Patients were randomized to receive r-HuEPO or no r-HuEPO treatment and followed for 48 weeks. HRQL outcomes, as well as hematocrit (HCT) were measured.

METHODS

Patient Sample

A randomized, parallel-group, open-label study was conducted at 11 clinical centers in the United States. Forty-three patients were randomly assigned to receive r-HuEPO therapy, and 40 patients were assigned to serve as an untreated control group. Entry criteria included chronic renal failure patients aged 18 to 75 years with serum creatinine 3 to 8 mg/dL, HCT less than or equal to 30%, mean arterial pressure controllable below 114 mm Hg, and not currently receiving hemodialysis treatment. Patients were ineligible if they had proteinuria greater than 5 g/day, presence of iron-deficiency anemia, transfusion dependency, or presence of other systemic disease or any inflammatory condition or infection that might interfere with the effects of r-HuEPO treatment. Institutional review panels from the participating medical centers approved the research protocol, and informed consent was obtained from all patients before entry into the study.

Recombinant Human Erythropoietin Protocol

Patients were randomly assigned to either the no-treatment (n = 40) or to the r-HuEPO therapy (n = 43) regimen. The r-HuEPO used in this study was provided by Ortho Biotech Inc. (Raritan, NJ). The treatment group received 50 U/kg r-HuEPO subcutaneously, three times a week. If HCT did not increase by 2% to 3% during the first 4 weeks, the r-HuEPO dosage was increased to 75 U/kg three times weekly. Thereafter, the r-HuEPO dosage could be increased by 75 U/kg per week, to a maximum dose of 450 U/kg per week. When patients reached a HCT of 36%, the drug dosage was titrated to maintain a HCT of 35%. Maintenance doses could be given as a single weekly injection, and, at the investigator's discretion, patients could self-administer r-HuEPO doses after the first week of treatment. All patients received oral iron supplements not to exceed 200 mg elemental iron per day if their serum iron decreased below 50 μ/dL or the iron/total iron-binding capacity decreased to below 20%. Iron supplements were discontinued if the serum iron was greater than 150 μ/dL.

Treatment and study follow-up continued for 48 weeks. r-HuEPO (Procrit) was made available to both groups after the end of the study period. Patients were discontinued from the study if they required hemodialysis or received a renal transplant.

Clinical Measures

Control of phosphorus, blood glucose, blood pressure, and dietary protein intake was maintained for the duration of the study. HCT levels were measured every month. Data on the number of blood transfusions and start of hemodialysis treatment were also collected. Complete details about the clinical outcomes and adverse events of treatments in this study are reported elsewhere.[19]

Health-Related Quality of Life Measures

The HRQL assessment was administered by trained interviewers during face-to-face interviews at baseline and after 16, 32, and 48 weeks of treatment. The interview incorporated dimensions of HRQL identified to cover the expected effects of r-HuEPO therapy and anemia in predialysis chronic renal disease patients based on reviews of medical literature and discussions with nephrologists and nurses. The intent was to comprehensively measure broad areas of functioning and well-being.[6,7] Questions on age, gender, race, education, and employment status were also included in the interview.

The home management, alertness behavior, and social interaction scales from the Sickness Impact Profile[20] were selected for the interview. The Sickness Impact Profile is an established generic health status measure of disability associated with chronic illness. The home management scale measures a person's ability to perform everyday activities, such as shopping, housework, and yard maintenance. The alertness behavior scale evaluates changes in memory, judgment, and other cognitive behavior. The social interaction scale assesses social function, activities, and behavior. The SIP scales have good internal consistency and test-retest reliability[20] and have been used in previous studies of treatments for renal disease patients.[3-5] In the current study, internal consistency reliability was 0.80 for home management, 0.85 for social interaction, and 0.91 for alertness behavior. For each scale, items have assigned weights corresponding to level of disability and scores range from 0 to 100, with higher scores representing greater dysfunction.

Four scales from the Medical Outcome Study Short Form[21] and other Medical Outcome Study measures[22] were included in the interview form: physical function, role function, energy, and health distress. Physical function measures ability to perform everyday physical activities, such as walking up stairs or carrying groceries. The role function scale consists of two questions about health interference with work, school, or other activities. The energy scale evaluates feelings of vitality, weakness, and fatigue. The health distress measures health-related worry and frustration. All of the MOS scales have been used extensively in previous research in general

Table 1. Baseline Demographic and Clinical Characteristics

	Untreated Group (n = 40)	rHuEPO Group (n = 43)
Demographic		
Age (yrs), mean ± SE	58.4 ± 13.2	56.5 ± 11.4
Female (%)	70	65
White (%)	80	70
High school graduate (%)	75	70
Clinical		
Hematocrit (%), mean ± SE	26.8 ± 3.6	26.8 ± 4.5
Serum creatinine (mg/dL), mean ± SE	5.5 ± 1.8	5.5 ± 1.6
Glomerular filtration rate (mL/min), mean ± SE	10.0 ± 4.1	10.2 ± 4.1
Received transfusions pre-study (%)	12	7

and chronic disease populations and have demonstrated acceptable reliability and validity.[21-23] The MOS scales are standardized to a 0 to 100 scale, with higher scores indicating better health status.[21,22] Internal consistency reliability was 0.80 for the physical function scale, 0.72 for role function, 0.89 for health distress, and 0.84 for energy.

The life satisfaction scale from Campbell et al's[24] Quality of American Life survey was included. This question asks the patient to rate his or her satisfaction with life on a scale from 1 to 7, with higher scores indicating greater satisfaction. The Center for Epidemiologic Studies Depression scale[25] was used to evaluate symptoms of depression. The Center for Epidemiologic Studies Depression scale has been used extensively in epidemiologic studies of the general community and chronic disease populations. It is scored from 0 to 60, with higher scores indicating a greater number of depression symptoms. Internal consistency reliability in this sample was 0.89. The interview also included a five-item measure of sexual dysfunction constructed for this study. The sexual dysfunction scale had an internal consistency reliability of 0.72.

Data Analysis

Comparability of the two groups at baseline was assessed using the Fisher's exact test for dichotomous variables and the *t*-test for continuous variables. Data analyses used all available HRQL data and an intent-to-treat analysis. Paired *t*-tests were used to assess changes within treatment groups between baseline and follow-up scores at week 48, and *t*-tests for independent samples were used to assess differences in changes in HRQL scores between the groups at week 48. Ordinary least squares regression analysis was used to examine treatment group differences in changes in HRQL scores after adjusting for baseline HRQL scores. No adjustment was made for multiple comparisons. *P* values are based on two-tailed tests of significance.

RESULTS

Baseline Characteristics

The groups were comparable at baseline, although there were slightly more women and whites in the untreated group (Table 1). Baseline hematocrit, glomerular filtration rate and serum creatinine were almost identical. Twelve percent of the untreated group and 7% of the r-HuEPO group received transfusions during the 3 months before the study. The r-HuEPO and untreated groups were comparable on HRQL scores at baseline (Table 2).

Withdrawals From Study

Twenty of the 43 r-HuEPO–treated patients (47%) completed the clinical trial, and 15 of the 40 untreated patients (38%) completed the trial. The rate of study discontinuation attributable to the start of hemodialysis treatment was comparable in both groups, 16 of 43 (37%) in the r-HuEPO group and 13 of 40 (33%) in the control group. Three patients in the untreated control group and one in the r-HuEPO group dropped out of the study because of adverse events. None of these events was related to r-HuEPO treatment or study participation. Details about the study dropouts are described by Roth et al.[19] There were no statistically significant differences in demographic and clinical characteristics or most of the HRQL scores between the completed r-HuEPO group patients and dropouts and between completed control group patients and dropouts. Role function scores were significantly worse at baseline for patients completing the study compared with dropouts ($P = 0.0256$).

Clinical Outcomes Evaluation

In an intent-to-treat analysis, the r-HuEPO–treated group showed a significant increase in HCT from baseline to last available value (*P*

Table 2. Changes From Baseline to Week 48 in Health-Related Quality of Life Scores

Scale*†	Baseline Scores (Mean ± SE) rHuEPO	Baseline Scores (Mean ± SE) Untreated	Week 48 Evaluation‡ (Mean ± SE change from baseline score) rHuEPO	Week 48 Evaluation‡ (Mean ± SE change from baseline score) Untreated	Intent to Treat§ Between-Group Comparison *P*	Complete Data‖ Between-Group Comparison *P*
Energy (+)	36.8 ± 3.1	34.5 ± 3.7	+5.8 ± 3.6*	−3.1 ± 2.0	0.036	0.010
Physical function (+)	44.3 ± 4.4	49.1 ± 4.8	+7.8 ± 3.8*	−4.8 ± 2.1*	0.006	0.030
Role function (+)	40.7 ± 6.4	46.8 ± 6.8	+1.7 ± 6.9	−0.0 ± 4.0	0.944	0.049
Health distress	34.9 ± 4.4	33.9 ± 3.9	−3.4 ± 3.8	+2.4 ± 2.2	0.192	0.098
Home management (−)	37.7 ± 4.1	40.2 ± 4.5	−6.1 ± 3.6*	+0.1 ± 3.8	0.240	0.021
Alterness behavior (−)	25.1 ± 5.2	18.4 ± 4.3	−8.8 ± 3.5*	−0.1 ± 3.1	0.065	0.050
Social interaction (−)	24.4 ± 3.3	21.8 ± 2.7	−4.4 ± 2.9*	+2.6 ± 2.7	0.086	0.014
Life satisfaction (+)	4.9 ± 0.2	4.8 ± 0.2	+0.1 ± 0.2	+0.0 ± 0.01	0.935	0.679
Sexual dysfunction (−)	13.9 ± 0.6	13.7 ± 0.7	−0.6 ± 0.4	−0.1 ± 0.3	0.230	0.264
Depression (−)	14.2 ± 1.5	13.0 ± 1.7	−0.6 ± 1.2	+1.5 ± 1.2	0.229	0.095

* Higher scores on these scales indicate better health status. Scores range from 0 to 100, except Life Satisfaction, which ranges from 1 to 7.

† Higher scores on these measures indicate worse health status. Scores range from 0 to 100, except for Depression, which ranges from 0 to 60, and Sexual Dysfunction, which ranges from 0 to 20.

‡ Values with asterisks (*) represent significant within-group changes based on intent to treat and paired *t*-tests, $P < 0.05$.

§ Intent to treat analysis, two-tailed *t*-test for independent groups.

‖ Data for 20 rHuEPO-treated and 15 untreated, control patients completing 48 weeks in study, two-tailed *t*-test for independent groups.

< 0.0001). No changes in HCT were observed in the control group. Mean change in HCT was significantly higher in the r-HuEPO–treated group compared with the untreated group ($P < 0.0001$). Mean HCT increased 4.7 percentage points in the r-HuEPO group compared with a decrease of 1.0 percentage points in the untreated group.

Correction of anemia, defined as reaching a HCT level of 36%, over the course of the trial was achieved by 34 of 43 (79%) r-HuEPO–treated patients compared with 0 of 40 (0%) control group patients ($P < 0.0001$). Nine of 40 (23%) untreated patients needed at least one blood transfusion, whereas only 4 of 43 (9%) r-HuEPO–treated patients required transfusions during the study ($P = 0.33$).

Health-Related Quality of Life Evaluation

Within-group comparisons. Table 2 summarizes the changes in HRQL scores for untreated and r-HuEPO group patients who completed 48 weeks of follow-up. The intent-to-treat analysis showed that after 48 weeks of follow-up, the control group showed no significant changes in HRQL scores except for a significant decrease in physical function ($P = 0.03$). The r-HuEPO group showed significant increases in energy ($P = 0.045$) and physical function ($P = 0.046$) and reduced impairment in cognitive function ($P = 0.015$).

The within-group analyses were also performed using data for patients with complete data over the first 16 weeks and entire duration of the study. No changes in HRQL scores were observed in the untreated group after 16 or 48 weeks of follow-up. Between baseline and 16 weeks, the r-HuEPO–treated group showed statistically significant improvements in energy ($P < 0.04$), cognitive function ($P = 0.038$), physical function ($P = 0.045$), and sexual function ($P < 0.04$). Between baseline and 48 weeks, the r-HuEPO–treated group showed statistically significant improvements in energy ($P = 0.016$), cognitive function ($P = 0.031$), role function ($P = 0.012$), social activities ($P = 0.023$), and home management ($P < 0.002$).

Between-groups comparison. Differences between treatment groups in changes in HRQL scores over the 48-week study were evaluated using an intent-to-treat and all data from completed patients. In the intent-to-treat analysis, statistically

significant differences between the two groups were demonstrated for energy ($P = 0.038$) and physical function ($P = 0.005$). Differences between the r-HuEPO and untreated group were not statistically significant for social activities ($P = 0.086$) and cognitive function ($P = 0.065$).

When the analysis was done using only data from patients completing the study, the r-HuEPO group showed significant improvements in 5 of 10 HRQL measures compared with the untreated group. Between-group differences in changes in health status scores were detected for energy ($P = 0.0096$), physical function ($P = 0.03$), role function ($P = 0.049$), home management ($P = 0.02$), and social activities ($P = 0.014$). The difference in changes in cognitive behavior approached statistical significance ($P = 0.057$).

Previous research has suggested that a five-point change in Sickness Impact Profile scale scores is clinically important.[26] We therefore determined the proportion of patients in each treatment group with improvements that exceeded five points in Sickness Impact Profile home management, alertness behavior, and social activity scale scores over the 48-week study. More r-HuEPO–treated patients showed improvements in home management scores compared with control patients ($P = 0.042$; 46% versus 25%). Ten percent of untreated patients and 28% of r-HuEPO patients had improvements in alertness behavior scores ($P = 0.039$), and 15% of control patients and 35% of r-HuEPO patients showed improvements in social activity scores ($P = 0.037$).

Regression analyses, adjusting for baseline HRQL scores, indicated that there were significant differences between the treatment groups on changes in measures of energy ($P = 0.019$) and physical function ($P = 0.008$) in an intent-to-treat approach. The r-HuEPO–treated group improved in energy scores and ability to perform physical activities, whereas control group patients remained unchanged. When the analysis was performed using data for those subjects who completed the study, significant treatment group differences were observed for energy ($P = 0.013$), physical function ($P = 0.006$), and home management ($P = 0.023$).

Correlation Between Changes in HCT and HRQL Scores

After 16 weeks of treatment, significant correlations were found between change in HCT and changes in energy scores ($r = 0.35$, $P < 0.007$) and physical function ($r = 0.37$, $P < 0.004$). After 48 weeks of treatment, correlations were found between HCT and energy scores ($r = 0.37$, $P < 0.02$), physical function ($r = 0.35$, $P < 0.03$), sexual dysfunction ($r = -0.45$, $P < 0.02$), and social activities ($r = 0.39$, $P < 0.02$). These correlations suggest that changes in HCT are related to changes in patient reports of energy and fatigue, increases in physical activities and functioning, improved sexual function, and increases in social activities and behavior.

DISCUSSION

This is the first study demonstrating the impact of r-HuEPO treatment on HRQL in predialysis renal disease patients over a 48-week period. The findings indicate that r-HuEPO enhances the HRQL of predialysis renal disease patients. Patients reported improved energy and increased physical functioning. The r-HuEPO–treated group had improvements in their ability to perform activities around their homes, improved social activity, and increased levels of cognitive function. The untreated patients reported significantly reduced physical functioning and no change in other areas of functioning and well-being. No significant changes were observed for the measures of psychological distress or life satisfaction in either group. However, there were consistent increases in most of the HRQL scores in the r-HuEPO–treated group and decreases in most of these same scores in the untreated group during the study. These improvements in HRQL are similar to those observed in studies of ESRD patients.[4,5]

As in previous studies of r-HuEPO therapy,[8-15,19] significant improvements in HCT were seen. Almost 80% of r-HuEPO patients achieved a HCT greater than 36%. Fewer r-HuEPO–treated patients (9%) required a blood transfusion compared with 23% of untreated patients. In the untreated control group, HCT remained unchanged during the study. No apparent effect was observed in terms of progression of renal disease.[19]

These changes in HCT were correlated with changes in HRQL scores. Energy, physical function and activities, and social activities were most strongly related to changes in HCT. For example, for every 1-unit increase in HCT, energy scores increase 1.34 points and physical function scores

increase 1.53 points. This means that an increase on 6% in HCT results in an 8-point increase in energy scores and a 9-point increase in physical function scores. A study of r-HuEPO therapy in ESRD patients also found that measures of energy level and physical function were most strongly correlated with changes in hemoglobin.[4]

The changes in HRQL are clinically significant. More of the r-HuEPO group showed practically significant improvements in Sickness Impact Profile home management, alertness behavior, and social activity scores compared with controls. A change of 5 to 10 points in Medical Outcome Study scale scores is considered clinically significant.[22,27] Using the more conservative 10-point criterion, 40% of r-HuEPO patients and 15% of controls had improvements in energy scores ($P = 0.026$). Fifty-seven percent of r-HuEPO patients compared with 15% of controls showed clinically significant improvements in physical function scores ($P = 0.0007$). r-HuEPO–treated patients clearly demonstrated clinically significant increases in energy, ability to perform everyday physical activities, cognitive function, and social activities.

Several issues must be considered when interpreting the results of this study. First, the statistical comparisons were performed on small sample sizes resulting in a conservative bias. This factor reduces the statistical power to detect differences where differences may in fact be present. The consistent pattern of improvements in HRQL scores in the r-HuEPO group and the pattern of decreases in functioning in the untreated group support the benefits of the active treatment. Adjustment for multiple statistical comparisons would reduce the number of statistically significant findings, but the two primary end points, energy and physical functioning, still remain statistically significant. These results are comparable to those on r-HuEPO therapy in ESRD patients.[4,5] Recent research indicates that the Medical Outcome Study physical function scale discriminates best between different levels of medical severity.[27]

Second, a large proportion of subjects did not remain in the study for the entire 48 weeks; 53% of the r-HuEPO–treated group and 62% of the control group discontinued. Most of these patients dropped out of the study because of the start of hemodialysis (29 of 48 dropouts; 60%) or intercurrent illness or death (7 of 48; 14.6%). Therefore, almost 75% of the dropouts left the study because of renal disease or other medical conditions unrelated to treatment. However, there were no differences between study completers and dropouts on baseline clinical, demographic, or most HRQL measures. Completers reported worse role functioning than dropouts at baseline. The similarity between dropouts and completers suggests that no serious bias was operating in the analysis of HRQL scores. It is very likely that patients who discontinued had more advanced renal disease, as demonstrated by need for dialysis, and that this may have influenced the HRQL scores. However, dropout because of progression to ESRD was similar in the two treatment groups, and both groups demonstrated similar decrements in renal function,[19] so that any impact on change in HRQL scores would impact both groups.

Finally, there is a concern that the absence of double-blinding and the subjective nature of HRQL measures may have resulted in perceived improvements among r-HuEPO–treated patients. This may be a problem, but the strong association between changes in HCT and physical function and energy scores suggest that r-HuEPO's impact on HCT translated into improvements in functioning and well-being in treated patients. Other studies have documented an association between change in HCT and HRQL outcomes.[4,28] The dramatic impact on HRQL demonstrated over the course of the 48-week study would be difficult to maintain based entirely on placebo response.

In summary, these findings support the benefit of r-HuEPO therapy in terms of both clinical outcomes and impact on HRQL. Consistent findings supporting improvements in level of energy and lack of fatigue and increased physical functioning paralleled the improvement in HCT levels. Changes in social activity levels, abilities to perform everyday activities around the house and yard, and in improved memory, concentration, and thinking also occurred. These improvements in HRQL occurred despite apparent decreases in renal function. These findings provide additional support using comprehensive measures of health status and well-being that r-HuEPO treatment is not only effective in increasing HCT, it also increases HRQL in predialysis renal disease patients.

ACKNOWLEDGMENT

The authors thank William Furlong and Marie Townsend, McMaster University, for their assistance in developing measures for this study. They also thank Joe Reblando at Batelle and Marina Adler, PhD, now at the University of Maryland, Baltimore County, for their assistance with the statistical analyses.

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