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ORIGINAL ARTICLE

Association of anemia correction with health related quality of life in patients not on dialysis*

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ABSTRACT

Objective: This was an open-label study to asses the association of changes in hemoglobin with changes in health related quality of life (HRQOL) in patients treated with darbepoetin alfa.

Methods: Originally, 81 chronic kidney disease (CKD) patients not on dialysis and naïve to erythropoiesis stimulating agents (ESA) were randomly assigned into two open-label groups (3:1). As a majority of control group patients opted out of control status, this study reports on the single arm study analysis that was performed on the 48 patients who received the drug through week 16. Sixty-two patients received once-weekly darbepoetin alfa in addition to conservative management for CKD. Instruments that measured general (SF-36, FACT-anemia, FACT-fatigue, ADL and IADL) and disease specific (KDQOL) HRQOL domains were administered at baseline and after 8, 16, and 24 weeks.

Results: Compared to baseline values, mean HRQOL subscales were significantly improved in the treatment group at 16 weeks ($p < 0.05$ for SF-36 physical function; $p < 0.001$ for SF-36 vitality, FACT anemia and FACT fatigue scales). At week 16, the SF-36 mean increase for 48 treatment patients in the Vitality Subscale Score was 14.9 (SD 3.2) and the mean increase in the KDQOL Burden of Kidney Disease Subscale was 5.5 (SD 3.3). Multivariate regression analysis demonstrated a statistically significant association ($p < 0.05$) between hemoglobin levels and higher HRQOL scores on several physical function, energy and fatigue scales.

Conclusion: Improvements in hemoglobin in CKD patients not on dialysis were associated with statistically significant ($p < 0.05$), clinically meaningful (>5 points) HRQOL improvements on scales measuring physical activity, vitality and fatigue. Our study did not show an association between increased hemoglobin levels and other aspects of HRQOL, such as those relating to emotional status, sexual activity or cognition. The interpretation of our results is limited by the lack of a control arm to assess whether conservative therapy for CKD, in the absence of ESA administration, would have a comparable effect on patients' HRQOL scores. Further research needs to examine whether other aspects of HRQOL improve with anemia treatment, in the same way as those aspects of HRQOL more closely related to physical activity and fatigue.

* These data were previously presented at the American Society of Nephrology 35th Annual Meeting & Scientific Exposition, November 1–4, 2002

Introduction

Despite being a serious, debilitating complication of chronic kidney disease (CKD), anemia is often untreated in CKD patients not on dialysis. Retrospective studies have recently shown that a substantial number of early stage CKD patients suffer from anemia and associated cardio vascular disease[1–5]. A consequence of anemia is a decline in a series of physiological functions resulting in such symptoms as fatigue, weakness, lethargy, anorexia, and sleep disturbance, which impair patients' health related quality of life (HRQOL), most notably during dialysis[6–11]. Therefore, an important question in treatment of CKD is whether anemia is associated with decreased HRQOL in patients in earlier stages of CKD, before dialysis.

To quantify quality of life, HRQOL measurements utilize patient self-reports of functional health status, and include domains of role physical, cognitive and social function, psychological status, health perceptions, and general well-being. We used standard HRQOL instruments, including the Sickness Impact Profile[12], the Nottingham Health Profile[13] and the Medical Outcomes Study 36-item short-form health survey (SF-36, v1.0)[14,15]. These HRQOL instruments have been previously validated for use with patients with anemia[6–11,16,17–24]. The Kidney Disease Quality of Life (KDQOL) instrument is the only instrument that was developed specifically for and validated among patients with kidney disease[25]. The literature uses terms 'health status' and 'health related quality of life' interchangeably, so to clarify we will use HRQOL to refer to both in the remainder of this paper.

A number of studies of HRQOL in dialysis patients have provided evidence that correction of anemia increases HRQOL in end-stage renal disease (ESRD)[6,11,15,17–24]. In ESRD, anemia has been successfully treated using erythropoietic stimulating agents (ESAs), which lead to higher levels of hemoglobin[26–36]. Higher levels of hemoglobin in turn improve muscle strength and function, cardiac function, and cognitive function due to increased peripheral oxygen supply[15,36–41].

In contrast to the study of HRQOL in dialysis patients, relatively little research has focused on studying HRQOL in CKD patients not on dialysis. Although more limited in scope than in the case of ESRD, evidence also links erythropoietin therapy with anemia correction in earlier stages of CKD, before patients require dialysis[42,43]. Limited evidence also exists that the benefits of anemia correction for HRQOL extend to earlier stages of CKD[7–11,15,17–23,26–44]. However, overall the evidence supports only the fact that CKD patients with anemia are more likely to have lower HRQOL compared to CKD patients without anemia. What we do not know is if the magnitude of impact on HRQOL is great enough that therapy will produce a discernable improvement in HRQOL.

This study provides data needed to develop strategies for using darbepoetin alfa for the treatment of anemia in early-stage CKD (3 and 4) patients, including the association of hemoglobin levels and patients' self-reported quality of life. The data is useful in combination with existing efficacy data of darbepoetin alfa in increasing hemoglobin levels[45–47]. The objective of this open-label, single-arm study was to examine the association of hemoglobin levels and HRQOL in CKD patients not on dialysis.

Patients and methods

Patients

CKD patients ≥ 18 years of age were eligible for the study if they were neither receiving dialysis nor expecting to initiate dialysis within 24 weeks of enrollment into the study. To be included in the study, the patients were required to have baseline hemoglobin level ≤ 10.0 g/dL, a creatinine clearance < 40 mL/min and adequate iron stores (defined as a transferrin saturation ≥ 19.5%). All patients gave written informed consent before any study-related procedures were conducted, and this study was approved by an IRB.

Patients with uncontrolled hypertension, a hematologic disorder, and those who had received or were scheduled to receive a kidney transplant were excluded from this study. Also excluded were patients who had received erythropoietic therapy, red blood cell transfusions, or androgen therapy within the 12-week period prior to random assignment. Once in the study, patients who received iron supplementation or transfusion were not excluded from the study. This variable was included in the multivariate analysis to control for this and other potential confounders.

Study design

This was a multicenter, open-label study comprising a 1-week screening and 1-week baseline period followed by a 24-week study period. After the baseline period, eligible patients were randomly assigned (3 : 1 ratio) into a treatment group receiving darbepoetin alfa in addition to conservative management of CKD (treatment), or a control group receiving only conservative CKD management without ESAs (control). Eligible subjects were administered darbepoetin alfa SC at a starting dose of 0.45 µg/kg once-weekly for 24 weeks. During the evaluation period, the dose of darbepoetin alfa was adjusted to maintain a hemoglobin rate of rise between 1.0 and 3.0 g/dL/4 weeks until the target hemoglobin

concentration range of 12.0–13.0 g/dL was achieved, using WHO criteria.

Hemoglobin was measured at weeks 1 and 2 and then once every other week thereafter for patients in the treatment group. Hemoglobin was measured at weeks 1, 8, 12, 16, and 24 for patients in the control group. Hemoglobin was measured more often in the treatment group to guide dose titration to the target hemoglobin. Because the potential for immunogenicity exists for all therapeutic proteins, serum samples were collected from patients in the treatment group before the first dose of darbepoetin alfa and at the end of the study to detect antibody formation.

HRQOL assessments were completed at baseline and at weeks 8, 16, and 24, in all subjects, using a questionnaire that included components from the SF-36 (version 1)[14,15], KDQOL[25], Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL)[48–50], and Functional Assessment of Cancer Therapy (FACT) anemia and fatigue instruments[51].

All HRQOL assessments were self-administered questionnaires with scores ranging from 0 to 100, with higher scores indicating better HRQOL. The SF-36 (version 1) was developed from the Medical Outcomes study and is a general measure of HRQOL consisting of 36 items which contribute to eight subscales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) and two composite scores (physical composite score and mental composite score). The KDQOL is used only in kidney disease settings, and consists of nine unique scales: burden of kidney disease, social interaction, cognitive functioning, symptoms, effect of kidney disease, sexual functioning, sleep, social support, and overall health. The ADL/IADL is a self-reported measure of physical function, most commonly used in geriatric settings. The ADL consists of items assessing the ability to perform general functions (e.g., climbing stairs) while the IADL consists of items measuring the ability to perform specific activities (e.g., grocery shopping). The FACT anemia and fatigue scales were developed in cancer settings; however, the study of their validity in other disease settings is ongoing[52].

The administration of all instruments followed the validated algorithm supplied by the authors of the surveys. Surveys were carried out in a battery approach to measurement, and no ad-hoc adaptations were made in order to ensure reliability and validity of the results. All HRQOL instruments were administered in their entirety.

In addition, other medical history information was recorded including: ferritin, albumin, hospitalization, education, psychiatric drug use, antihypertension drug use, diabetes, and transfusions. These were used as controls to assess confounding.

Statistical analysis

Our statistical analysis assessed changes in HRQOL over time, and estimated the association between hemoglobin levels and changes in HRQOL. We performed the analysis on the treatment arm of this open-label study, due to the high drop-out from the control group (16 out of 19 patients, ten of whom elected to receive erythropoietic therapy). HRQOL subscales scores were calculated according to standardized algorithms specified by the respective developers[53,54]. Missing data on individual questionnaires were handled according to scoring algorithms provided by the instruments' respective authors.

Descriptive statistics are summarized for patients in the control and treatment groups. Mean HRQOL subscale scores were computed at baseline and weeks 8 and 16, allowing us to assess changes at both short and medium-length time span. The relationship between changes in self-reported HRQOL measures and changes in hemoglobin levels from the baseline to week 24 was assessed for the treatment group only as a single-arm study analysis, as explained above. The associations between treatment with darbepoetin alfa and changes from baseline in disease-specific HRQOL and self-reported physical functioning scores over a 24-week period was also assessed in the treatment group. Due to the small sample size at the end of the study, statistical inference on changes was conducted on patients up to week 16. The changes in HRQOL measures were analyzed at both 8 and 16 weeks using paired one-sided *t*-tests to assess the significance of the change from baseline for all patients in the treatment group who completed 16 weeks of study (SAS software, Version 8, SAS Institute). Trends in hemoglobin levels over time were plotted. Pooling treatment and control groups together, multivariate regression models were applied to analyze the association between hemoglobin levels and HRQOL scores in the entire study sample, focusing on the four HRQOL measures that showed statistically and/or clinically meaningful change during the study (SF-36 physical function, SF-36 vitality, FACT fatigue, and FACT anemia). The multivariate regression analysis allowed us to control for a range of factors that could potentially confound the effect of increased hemoglobin: hospitalization, education, psychiatric drug use, anti-hypertension drug use, diabetes, iron supplementation and transfusion. Because our multivariate analysis accounts for confounders, for within-unit heterogeneity, and for selection effects, the proper methodology here was to include the control group and conduct an analysis on the principle of intent-to-treat (ITT). In this multivariate analysis, the addition of control patients contributed to a more accurate inference regarding the association.

Sensitivity and robustness analysis included estimation of hemoglobin–HRQOL association using the Heckman selection model and the random effects generalized least squares model using both treatment and control group patients (STATA software, Version 9.0, StataCorp LP). Both models maximize the panel data structure of our data; namely variation both across individuals and across different time points (baseline, week 8 and week 16) for each individual. The random effects model was used to control for heterogeneity of subjects in the pooled sample analysis. The random effects estimator (RE GLS), models unobserved intervening variables and takes into account the repeated observation structure of our panel of patients over time. With the exception of modeling heterogeneity, the model specification of the RE GLS analysis was identical to the OLS analysis, controlling for demographic variables, clinical treatment, and lab results (see note in Table 3 for the full description of the model, and the estimated variance contribution of the unobserved effect).

The Heckman selection and out-of-sample prediction of hemoglobin scores were used to assess whether the results were robust to potential self-selection due to unobserved heterogeneity of patients or due to high drop-out rate, especially in the control group. We used the different indicators of hemoglobin patterns during a patient's time of study enrollment to model the probability that they would remain or leave the study. Conditional on this probability, the standard Heckman model provides parameter estimates in the second stage (controlling for the same variables as the OLS model) that are more robust to potential selection bias than the OLS estimates.

Our final robustness analysis included using out-of-sample prediction of HRQOL scores, and then comparing the predicted scores for patients staying and for patients dropping out of the study.

Results

Patients

Baseline characteristics for the 62 patients who were randomly assigned to the treatment group to receive darbepoetin alfa are listed in Table 1. Thirteen patients who withdrew early and one patient who completed the study but did not complete the week 16 assessments were excluded from the analyses. During the study, one patient died of fungal meningitis, which the investigator did not attribute to the study drug. Analysis also revealed that there was no single systematic reason for patients in the treatment arm to drop out of the study. This is in contrast to the drop-out from the control group, which is very systematic, and is described next.

Table 1. *Baseline characteristics and patient demographics by treatment group*

Characteristics	Control group: Conservative CKD management only* *n* (%)	Treatment group: CKD management with darbepoetin alfa* *n* (%)	Treatment group: patients who completed week 16† *n* (%)
Total number of patients	19 (100)	62 (100)	48 (100)
Race			
White	7 (36.8)	29 (47)	25 (52.1)
Nonwhite	12 (63.2)	33 (53)	23 (47.9)
Sex			
Men	6 (31.6)	25 (40)	19 (39.6)
Women	13 (68.4)	37 (60)	29 (60.4)
Age (years)			
18–64	11 (57.9)	30 (48)	21 (43.8)
≥65	8 (42.1)	32 (52)	27 (56.3)
	Mean (SE)	Mean (SE)	Mean (SE)
Weight (kg)	77.8 (4.1)	77.3 (2.3)	78.4 (2.8)
Creatinine clearance (mL/min)	21.0 (2.4)	21.1 (1.1)	21.5 (1.4)
Hemoglobin (g/dL)	8.9 (0.2)	9.1 (0.1)	9.1 (0.1)
Transferrin saturation (%)	40.2 (5.3)	39.1 (5.5)	42.4 (7.1)
Serum ferritin (μg/L)	270.7 (59.0)	207.5 (20.8)	218.6 (25)

*Includes all intent-to-treat patients who had complete baseline hemoglobin and HRQOL data
†Includes all treatment group patients who had complete hemoglobin and HRQOL data at week 16

Due to the open-label design, 16 out of 19 patients in the control group withdrew from the study early. Of these, ten withdrew because they elected to receive erythropoietic therapy due to concerns regarding anemia progression. Changes in mean scores from baseline were analyzed only from the 48 patients in the treatment group who completed therapy and HRQOL assessments through week 16. This was done to ensure that changes in mean scores were not influenced by changes in sample size across time periods and across HRQOL measurements.

In the multivariate regression analysis of the association between hemoglobin and HRQOL subscale scores, we used data from both the control and treatment group, including observations even if the patients had missing values for HRQOL in some weeks but not in others (e.g. due to a drop out before week 24). For the same reason as above, we restricted our analysis to the first 16 weeks of the study. We constructed a two-dimensional (N × T) panel, where each patient in the panel is observed at 1 to 4 time periods. As a result, the total number of observations (patients × time periods) in the regression analysis ranged from 224 to 285 depending on the estimation model and the degree of missingness of specific covariates included in the model.

Association of physical functioning and HRQOL scores with hemoglobin

To ascertain the relationship between hemoglobin and HRQOL scores, we first examined whether changes in subscale scores were associated with changes in hemoglobin levels. Hemoglobin concentration measurements were collected from 62 patients at baseline and from 48 patients at week 16. The mean hemoglobin concentration increased from 9.1 g/dL at baseline to 11.3 g/dL at week 8, and 12.6 g/dL at week 16 (Figure 1). By analyzing data at baseline, week 8 and week 16, we were able to capture more detailed trends in both hemoglobin levels and HRQOL subscale scores, allowing us to better understand shorter-term and medium-term changes. Relative to baseline, of the 48 patients that completed 16 weeks of the study, improvements were demonstrated in several HRQOL subscales by week 8, and 12 of 21 HRQOL subscales by week 16 ($p < 0.05$) (Table 2).

HRQOL improvements at 16 weeks were statistically significant ($p < 0.05$) for the SF-36 physical function, general health, role physical, social functioning, vitality/energy, and mental health scales and were considered to be clinically relevant because the improvements were greater than 5 points per scale[15].

Improvements were also detected in the KDQOL symptoms, effects of kidney disease, sleep, and global health scales and the FACT anemia and fatigue scales ($p < 0.05$). Improvements in the ADL/IADL scales were not statistically significant ($p > 0.05$) (Table 2).

Sensitivity analysis indicated that patients in the treatment group who dropped out were not expected to have significantly different HRQOL subscale scores ($p > 0.05$), excluding the danger of bias due to the patients' self-selection out of the sample (see sensitivity analysis below for more details).

Multivariate regression analysis of the association between HRQOL scores and hemoglobin

Multivariate regression results showed a statistically significant association ($p < 0.05$) between hemoglobin

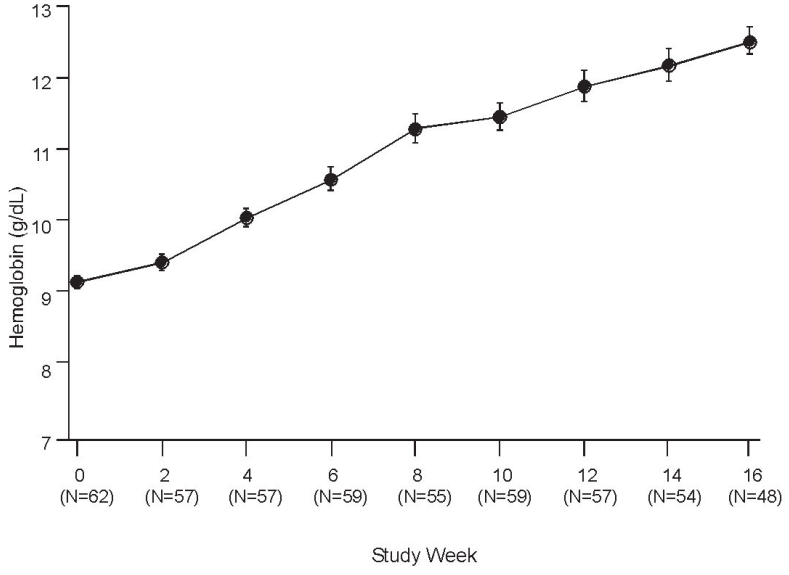

Figure 1. *Hemoglobin concentrations over the course of the study, numbers are reported as mean (± SE)*

Table 2. *Mean (SE) scores at baseline and change from baseline by time point*

HRQOL scales	Treatment group: CKD management with darbepoetin alfa (n = 48)		
	Baseline Mean (SE)	Change: baseline to week 8 Mean (SE)	Change: baseline to week 16 Mean (SE)
SF-36			
Physical function	40.9 (4.0)	+7.4 (2.9)*	+9.5 (2.9)*
Pain	62.8 (3.9)	+6.1 (3.7)	+4.8 (3.4)
General health	40.4 (2.6)	+6.4 (1.9)**	+8.2 (2.2)**
Role physical	25.5 (5.4)	+14.4 (4.1)**	+18.1 (5.5)**
Social functioning	61.5 (4.3)	+11.2 (4.7)*	+16.1 (4.6)**
Vitality/energy	38.4 (3.0)	+13.4 (2.8)**	+14.9 (3.2)**
Mental health	69.8 (2.2)	+2.3 (1.8)	+5.3 (2.3)*
Role emotional	54.9 (6.1)	+1.4 (4.5)	+6.9 (6.7)
KDQOL			
Burden of kidney disease	52.4 (2.9)	+9.8 (3.2)*	+5.5 (3.3)
Social interaction	75.3 (2.2)	+1.9 (2.9)	+3.3 (2.9)
Cognitive functioning	80.4 (2.2)	–0.3 (2.5)	+2.3 (2.4)
Symptom	73.5 (1.9)	+4.2 (1.6)*	+7.8 (1.9)**
Effects of kidney disease	75.1 (2.8)	+3.6 (2.5)	+4.6 (2.1)*
Sexual functioning	80.8 (7.9)	+6.9 (6.3)	+5.8 (5.4)
Sleep	64.6 (3.1)	+0.6 (2.7)	+3.2 (1.9)*
Social support	77.8 (3.5)	+4.6 (3.3)	–3.8 (4.2)
Overall health	58.5 (2.6)	+9.8 (3.3)*	+4.3 (2.1)*
ADL/IADL			
Scale	89.0 (1.9)	+1.6 (1.3)	+1.2 (1.5)
Subscale	82.8 (2.6)	+2.6 (1.9)	+3.5 (2.3)
FACT			
Anemia	68.3 (2.1)	+6.6 (1.6)**	+7.1 (1.8)**
Fatigue	42.4 (1.6)	+5.8 (1.3)**	+6.0 (1.4)**

*Significance at $p < 0.05$; ** significance at $p < 0.001$

levels and the four HRQOL subscale scores selected as manifesting most statistically and clinically important changes over time. After controlling for demographic variables, clinical treatment, major comorbidities, and lab results (see note in Table 3 for the full description of the model), higher hemoglobin levels were associated with significantly higher SF-36 Physical Function score ($p < 0.05$), SF-36 Vitality score ($p < 0.001$), FACT fatigue score ($p < 0.001$), and the FACT anemia score ($p < 0.001$). The estimated relationship held even when the model controlled for time period effects and the patients' baseline hemoglobin levels, as reported in Table 3. The OLS regression showed good fit based on R^2 values (SF-36 physical function: 0.68; SF-36 vitality: 0.54; FACT fatigue: 0.65; FACT anemia: 0.67). The F-statistic indicated joint significance of the model variables (SF-36 physical function: 57.2; SF-36 vitality: 16.2; FACT fatigue: 25.7; FACT anemia: 27.8).

To illustrate the marginal contribution of increasing hemoglobin levels on these QOL subscales, Figure 2 uses OLS parameter estimates to plot the relationship between hemoglobin and the four different HRQOL subscale scores once all other covariates in the model have been controlled for. All other covariates held constant, increasing hemoglobin level was associated with up to a 20-point increase in HRQOL, depending on the scale and the range of hemoglobin change (Figure 2). Using the same OLS fitted HRQOL subscale scores to compare patients below and above the clinically relevant hemoglobin value of 11 g/dL, as suggested by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines, illustrates that a hemoglobin increase to the

Table 3. *Multivariate regression analysis of the association between hemoglobin levels and two SF-36 HRQOL scores, using OLS, random effects GLS, and the Heckman selection model*

	OLS	RE GLS	Heckit	OLS	RE GLS	Heckit
	SF-36 physical function			SF-36 vitality		
Hemoglobin level	1.92* (0.80)	1.92* (0.80)	1.79* (0.80)	3.35** (0.80)	3.40** (0.77)	3.30** (0.75)
Base Hb level	–1.60 (2.04)	–1.92 (1.79)	–1.58 (1.46)	–1.79 (1.48)	–1.88 (1.54)	–1.62 (1.39)
Base HRQOL score	0.78** (0.039)	0.78** (0.053)	0.77** (0.042)	0.60** (0.058)	0.60** (0.060)	0.60**(0.054)
Creatinine clearance	0.039 (0.10)	0.079 (0.133)	0.056 (0.115)	0.16 (0.11)	0.17 (0.12)	0.16* (0.11)
N	225	225	257	228	228	285
	FACT fatigue			FACT anemia		
Hemoglobin level	1.18** (0.32)	1.20** (0.32)	1.12** (0.31)	1.35** (0.42)	1.35** (0.39)	1.26** (0.38)
Base Hb level	–1.33* (0.60)	–1.32* (0.67)	–1.35* (0.60)	–1.66* (0.73)	–1.63* (0.83)	–1.69* (0.73)
Base HRQOL score	0.67** (0.050)	0.67** (0.049)	0.67** (0.044)	0.69** (0.049)	0.70** (0.046)	0.69**(0.040)
Creatinine clearance	0.10 (0.053)	0.11* (0.050)	0.11* (0.045)	0.088 (0.061)	0.093 (0.062)	0.099 (0.055)
N	227	227	285	224	224	285

*Significance at $p < 0.05$; **significance at $p < 0.001$. Standard errors in parentheses. The control covariates included in the model are: demographics (age, sex, race, and education), time effect (ordinal scale for baseline, week 8, week 16, and end of study), lab values (mean ferritin level and mean albumin level), and indicator variables for hospitalization, psychiatric drug use, anti-hypertension drug use, diabetes, iron supplementation and transfusion. All models include an intercept. OLS is the pooled ordinary least squares estimator. RE GLS is the random effects generalized least squares panel estimator. The estimated faction of variance due to the unobserved effect for the four models is 0.18 (SF-36 pf), 0.067 (SF-36 vitality), 0.072 (FACT fatigue), 0.099 (FACT anemia). The Heckit is the Heckman selection model, where the selection equation includes a patients' baseline hemoglobin, the last measurement of hemoglobin available for the time period, minimum level of hemoglobin during the study, and the maximum level of hemoglobin during the study. The second stage regression equation for the Heckit model is identical to OLS and RE GLS

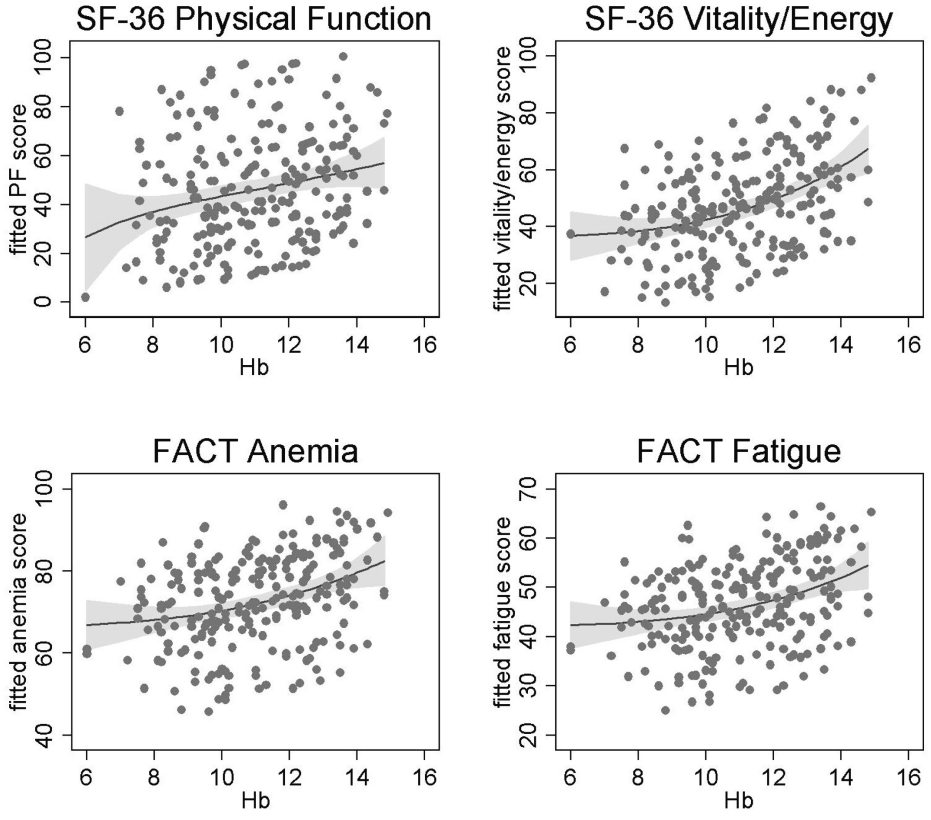

Figure 2. *The relationship between hemoglobin levels and fitted values for four HRQOL scores. Fitted values are based on the OLS estimates presented in Table 3, therefore the illustrated relationship between hemoglobin levels and HRQOL scores is after controlling for all other variables in the model. The fitted line is a fractional polynomial regression with 95% confidence intervals*

target range was associated with a 7.9 point increase on the SF-36 physical function score, a 11.2 point increase on the SF-36 vitality score, a 4.8 point increase on the FACT fatigue score, and a 6.2 point increase on the FACT anemia score (Figure 3).

Sensitivity and robustness analysis

Our sensitivity analyses addressed the extent to which our results were robust to any potential bias due to unobserved heterogeneity of patients or due to non-negligible dropout rates, especially in the control group. The parameter estimates of the contribution of hemoglobin to HRQOL subscale scores remain almost identical to our pooled OLS analysis. (Table 3)

Second, Table 3 also includes the two-stage Heckman model, in which we controlled for potential selection bias. The Heckman model estimates for hemoglobin association with HRQOL were only marginally lower than OLS estimates, and were still statistically significant.

In our final robustness analysis using out-of-sample prediction of HRQOL subscale scores, the comparison of the two populations of patients, did not detect any systematic difference in the distribution of the four HRQOL domains which were predicted. Finally, we could not distinguish statistically between the mean predicted HRQOL subscale scores for patients staying in the study and patients dropping out, using a *t*-test comparison of means in each of the four HRQOL domains. Focusing this analysis exclusively on the treatment group also showed no statistical evidence for the difference in predicted HRQOL scores for patients staying in the study versus patients dropping out of the study.

Discussion

Of the 62 subjects treated with weekly injections of darbepoetin alfa, 48 patients completed 16 weeks of therapy. HRQOL domains were significantly ($p < 0.05$) improved after 16 weeks of therapy, often with improvement noted within 8 weeks after initiating darbepoetin alfa therapy. This improvement was associated with increased hemoglobin levels. While HRQOL domains were improved by 8 weeks, a time when hemoglobin levels were on average 11.3 g/dL, these domains showed strong statistically and clinically significant improvements by week 16.

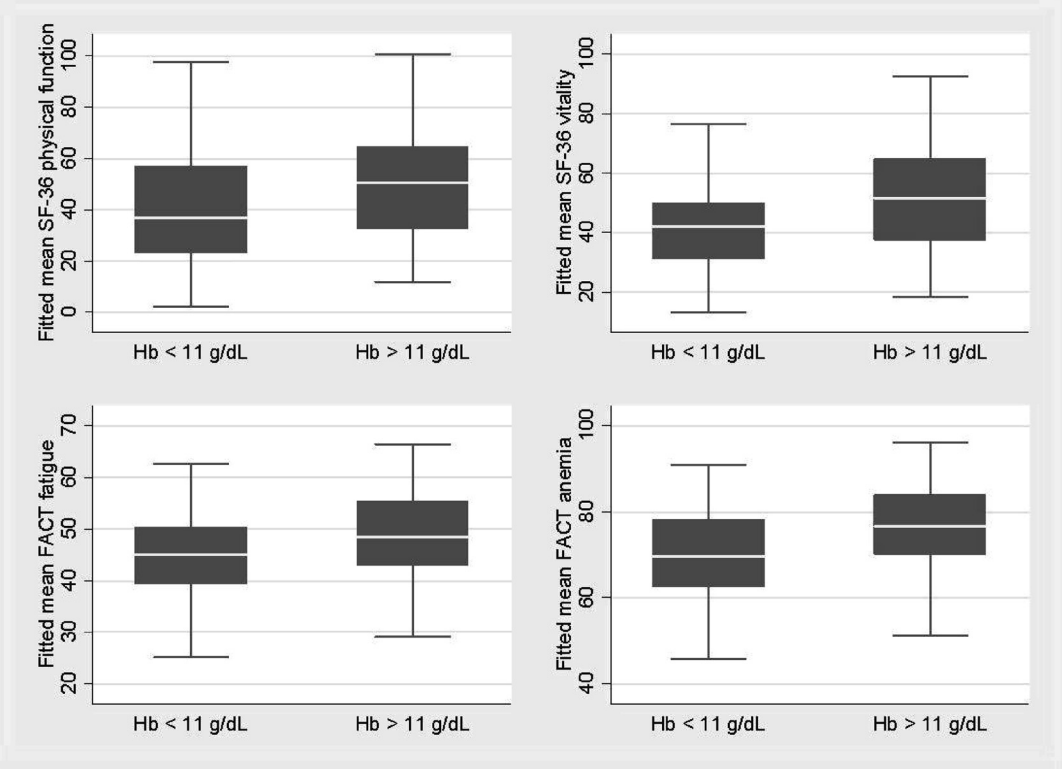

Figure 3. *Mean fitted HRQOL scores by clinically-relevant hemoglobin ranges. Fitted values are based on the OLS estimates presented in Table 3, therefore the illustrated relationship between hemoglobin levels and HRQOL scores is after controlling for all other variables in the model. The clinically-relevant hemoglobin levels follow KDOQI guidelines for focusing on the mean for all patients below and above the critical hemoglobin value of 11 g/dL. The upper edge of the box is the 75th percentile, while the lower edge is the 25th percentile; the line represents the median; and the whiskers extend to the lower and higher adjacent value (effectively min and max)*

When HRQOL scores showed a clinically and statistically significant change, multivariate regression demonstrated a statistically significant association between higher hemoglobin levels and higher quality of life measures. This relationship proved robust even after controlling for potential confounding factors, unobserved patient variation, and selection bias. The marginal contribution for improved hemoglobin levels in CKD patients was estimated to lead to clinically significant improvements in HRQOL scores.

The SF-36, KDQOL, and ADL/IADL questionnaires have been evaluated previously for the general population and for patients with kidney disease. Though the FACT anemia and fatigue questionnaires were designed specifically to evaluate anemia self-reported HRQOL in patients with cancer, the application of these questionnaires to the chronic kidney disease setting has been limited. In the present study, the improvements in HRQOL with improvements in hemoglobin as measured by the FACT anemia and fatigue questionnaires were consistent with the improvements observed in the SF-36 and KDQOL.

Anemia has been shown to be associated with fatigue, insomnia, and depression[55] and erythropoietin therapy has been shown to increase muscle strength and function, cardiac function, and cognitive ability associated with greater peripheral oxygen supply. In a recent study in 634 patients with CKD by Perlman *et al*. hemoglobin concentration correlated positively with Medical Outcomes Study SF-36 subscale scores and was a statistically significant predictor for individual mental and physical component scores[56]. In another study of Epoetin alfa use in CKD patients with anemia, increases in KDQOL scores were associated with an increase of 1 g/dL or more in hemoglobin[57]. Therefore we had expected the most notable changes in HRQOL associated with increased hemoglobin to occur in the physical, vitality, lethargy, role and social functioning domains. In the SF-36 scale, these domains are measured as physical function, role physical, social functioning, and vitality/energy. In the KDQOL scale, these domains correspond to burden of kidney disease, social interaction, effects of kidney disease, and overall health. The FACT scale is specific to anemia and we expected an improvement in both FACT anemia and fatigue scores.

The largest increases in HRQOL scores were observed on the SF-36 role physical, social functioning and vitality/energy scores. On the KDQOL scale, we observed statistically significant improvements ($p < 0.05$) in the burden of kidney disease, symptom and overall health scores. Both indexes on the FACT scale, anemia and fatigue, were significantly ($p < 0.001$) improved after 8 and 16 weeks and associated with increases in HRQOL. The improvements on the FACT scale also were well above the threshold for clinical significance (> 5 points)[58]. This evidence is consistent with findings in dialysis patients. Increases in hemoglobin following treatment with epoetin alfa were associated with patient reported reductions in fatigue and depression, increased working capacity and exercise tolerance, and better relationships with others[8,10,25,59–61].

Our findings are consistent with several other studies in non-dialysis CKD patients with anemia. In a previous 48-week study, 43 patients with anemia of chronic kidney disease treated with a t.i.w. dose of epoetin alfa experienced an increase in hematocrit from a mean of 26.8% to a mean of 31.5% (4.7% change). Relative to baseline, by week 48 the mean scores for physical function increased from 44.3 to 52.1 (7.8-point change) and the mean vitality/energy scores increased from 36.8 to 42.6 (5.8-point change). In the present 16-week segment of the study, 48 patients with anemia of chronic kidney disease received 16 weeks of q.w. darbepoetin alfa treatment, which increased mean hemoglobin from 9.1 to 12.6 g/dL (3.5 g/dL change). The mean HRQOL scores increased from 40.9 to 50.4 (9.5-point change) for physical function and from 38.4 to 53.3 (14.9-point change) for vitality/energy. Similarly, in a 52-week, multicenter, single-arm study in which darbepoetin alfa was administered every other week for the treatment of anemia in non-dialysis CKD patients, SF-12 component scores (physical and mental) and KDQOL subscale scores (kidney burden, kidney effects, and kidney symptom scores) improved significantly between baseline and week 12 ($p < 0.0001$), and these improvements were maintained through week 52[62]. Data from a 603-patient trial of patients with anemia and CKD, randomized to two different target levels of hemoglobin (13.0–15.0 g/dL, and 10.5–11.5 g/dL), demonstrated increases in HRQOL in the group treated to the higher hemoglobin level, which were sustained at the 2-year follow-up[63]. However, one study of 1432 patients randomized to higher (13.5) and lower (11.3) hemoglobin targets did not demonstrate any difference in quality between those subjects treated to the lower hemoglobin target and those treated to the higher hemoglobin target[64]. In addition to improving quality of life, recombinant human erythropoietin alfa (rHuEPO) treatment of anemia in CKD patients has been shown to help reduce left ventricular hypertrophy (LVH)[65–68], reduce angina incidence in patients with coronary heart disease after anemia treatment[69], and improve cognitive and brain electrophysiologic function[7,24,40,70]. Observational data from registries has suggested that rHuEPO treatment may generally decrease the risk of death due to CVD[71,72], but prospective randomized trials have yet to provide evidence on long-term benefits on mortality due to CVD.

Our study has several limitations. The current study was an open-label study which was conducted at the time that darbepoetin alfa first became available for the treatment of anemia in patients not on dialysis. There was a large drop-out rate (84%) in the control group, with the majority of those who dropped out choosing to initiate treatment for their anemia with an ESA. Due to this drop out, a comparison of changes in HRQOL was not feasible between the treatment and control groups. We conducted a number of sensitivity analyses to determine whether or not the results were robust to the potential impact of this drop-out rate. The results of the sensitivity analyses confirm that the drop-out rates do not impact the reported association of changes of hemoglobin with changes in HRQOL in the treatment arm. More specifically, we decided to conduct a single arm analysis of HRQOL change over time, focusing on the behavior of the treatment group in terms of improvement in HRQOL associated with improvements in anemia, secondary to therapy. However, to put our findings to a more stringent test, we included the small group of control patients available in our multivariate analysis to assess if the model used to describe the effects on the single treatment arm was robust to the inclusion of drop-outs. This sensitivity analysis confirmed our main findings of the positive association of higher hemoglobin levels with improvements in certain aspects of HRQOL.

While our analysis indicates absence of statistical bias, the limitation of our study that remains is that we are not able to draw comparisons in HRQOL changes between patients who are receiving ESAs and patients who are receiving conservative therapy (including a low-sodium diet and regular hypertension monitoring) for early CKD. More research is needed to understand how both primary care physicians and nephrologists treat patients in the early stages of CKD, and what effect this has on patients' HRQOL.

In addition, while ESAs were administered in order to change the patients' hemoglobin levels, a major limitation of this analysis is that it is not a double-blind, controlled randomized clinical trial. As such, evidence presented here does not allow us to draw strong inferences on the effectiveness of ESA therapy. Given this limitation, we can only attribute changes in HRQOL levels to the observed evidence regarding hemoglobin levels and not drug administration directly.

Finally, the consistency of our results across instruments (i.e. showing evidence that physical activity-related HRQOL shows improvement) and the consistency of our results with the still-limited number of QOL studies in pre-dialysis CKD, offers indirect support for further application of the existing instruments in future CKD research. However, the evaluation of validity and reliability of the instruments used in this study is beyond the scope of this paper, especially given space constraints and the additional analyses and additional patient recruitment that would be needed for a full validation study.

Conclusion

In this study, CKD patients not on dialysis were treated with darbepoetin alfa and demonstrated an improvement in anemia. Anemia correction was associated with statistically significant improvements in a number of aspects of HRQOL, including physical functioning and fatigue. (While there is no single criterion for assessing clinical relevance across all scales, > 5 points is taken as a conservative rule of thumb, validated in surveys such as FACT to correspond to clinical change.)

Our results contribute to a better understanding of and treatment options for CKD patients not on dialysis with anemia. A recent study has estimated the prevalence of anemia at the earlier stages of CKD at between 1% and 2%, rising to 5% in stage 3 CKD patients (GFR, 30–59 mL/min/1.73 m^2) and up to 50% in stage 4 CKD patients (GFR, 15–29 mL/min/1.73 m^2)[5].These results suggest a more general message that treating anemia at early stages of CKD could be important for improving the physical quality of life in this patient population. At the same time, more longer-term studies are needed to evaluate the full health benefits of treating early CKD patients for anemia.

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