ELSEVIER

Impact on Health-Related Quality of Life in Kidney Transplant Recipients with Late Posttransplant Anemia Administered Darbepoetin Alfa: Results from the STRATA Study

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ABSTRACT

Posttransplant anemia (PTA) is a common, multifactorial condition that has a substantial negative impact on patients' health-related quality of life (HRQOL). Erythropoietin-stimulating agents are an effective treatment for PTA, but there is little research on HRQOL in posttransplant patients. This multicenter, prospective study enrolled adults with PTA (hemoglobin [Hb] < 11.0 g/dL). Subjects ($n = 66$) received subcutaneous darbepoetin alfa every 2 weeks for 24 weeks. Hb and patient-reported outcomes using the Short Form (SF)-36 questionnaire were assessed. Mean (standard deviation) Hb concentration increased from 9.9 (1.2) g/dL at baseline to 11.7 (1.3) g/dL during the evaluation period (14 to 24 weeks). At baseline, SF-36 scores in all the eight domains were lower (worse) compared with the general population and patients with other chronic conditions. In subjects with baseline Hb < 10 g/dL, SF-36 subscales and component summary scores were lower than in subjects with Hb ≥10 g/dL. Following treatment with darbepoetin alfa, statistically significant improvements were observed for all subjects in physical component summary (0.5 points, $P < .001$), physical functioning (11.8 points, $P = .001$), limitations due to physical health (26.5 points, $P < .001$), bodily pain (7.7 points, $P = .01$), limitations due to emotional health (15.7 points, $P = .01$), and vitality (12.8 points, $P < .001$) from baseline to week 24. Clinically significant improvements (>5 points) were observed in six subscales: physical functioning, limitations due to physical health, limitations due to emotional health, bodily pain, social functioning, and vitality. Darbepoetin alfa in kidney transplant recipients with PTA significantly increased Hb concentrations and improved HRQOL scores.

ANEMIA IS A COMMON COMPLICATION of end-stage renal disease. In many cases, anemia improves after renal transplantation, usually within the first 3 months.[1,2] However, several studies have reported a prevalence of posttransplant anemia of 30% to 40%.[3–8]

Posttransplant anemia is multifactorial in origin and involves interplay between a number of risk factors. The most common cause is graft dysfunction;[3,5,7,9,10] however, other factors have been implicated including bone marrow suppression;[5,6] systemic illnesses; acute and chronic inflammation;[11] certain medications including immunosuppressive drugs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers;[5,6] donor age;[5] hyperparathyroidism; and iron deficiency.[12] Anemia has a substantial, negative impact on patients' health-related quality of life (HRQOL). The consequences of anemia include lethargy and sleep disturbance.[13–15]

Despite the prevalence of posttransplant anemia, only 12% to 42% of patients reportedly receive treatment with erythropoiesis-stimulating agents (ESAs).[3,5,6] Darbepoetin alfa (Aranesp, Amgen Inc, Thousand Oaks, Calif USA) is an ESA with the same mechanism of action as recombinant human erythropoietin but has a longer half-life as well as

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greater biological activity.[16,17] Darbepoetin alfa is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis, and for the treatment of anemia due to the effect of concomitantly administered chemotherapy. Data from previous studies suggest that darbepoetin alfa is an effective treatment for posttransplant anemia.[18,19] Additionally, single-arm studies have reported an association of darbepoetin alfa with hemoglobin and HRQOL in nondialysis chronic kidney disease and dialysis patients.[20–22] However, little research has focused on HRQOL in posttransplant patients.

The objective of the Study of Transplant Related Anemia Treated with Aranesp (STRATA) was to assess the effect of darbepoetin alfa administered subcutaneously on hemoglobin and HRQOL.

METHODS

Design

This was a 24-week, multicenter, prospective, single-arm study carried out at 12 centers in the United States in renal transplant patients with anemia (hemoglobin $<$ 11.0 g/dL).

After a 2-week screening period, there was a 2-week baseline assessment period during which baseline measurements and concomitant medication were recorded, and the Short-Form 36 (SF-36) questionnaire[23] was completed. Treatment was administered from weeks 1 to 24 (Fig 1). Darbepoetin alfa was initiated at 0.75 μg/kg subcutaneously every other week, and the dose was titrated until two consecutive hemoglobin measurements of 11.0 to 12.5 g/dL were achieved. Subjects stabilized on every-other-week dosing were converted to once-monthly dosing by doubling the every-other-week dose. Dose adjustments were used to maintain a hemoglobin concentration of 11.0 to 12.5 g/dL. Iron was administered according to study center policy until subjects were iron replete (transferrin satuation [TSAT] $>$ 19.5% and ferritin $>$100 μg/L). End-of-study assessments were carried out at week 24, or at the time of termination if a patient left the study early.

The primary endpoint was the mean hemoglobin concentration during the evaluation period (weeks 14 to 24). Other exploratory endpoints included the change from baseline in the eight SF-36 subscale scores, as well as two component summary scores (physical and mental components) at week 24. Increases from baseline in the SF-36 subscale scores indicate improvements in HRQOL. A change of 5 points or more is generally considered clinically meaningful.[24] SF-36 scores are used to estimate HRQOL-related burden of illness within this patient population and can be used to compare with general population norms and with populations with other chronic conditions. Safety endpoints included adverse events, changes in laboratory parameters, and antibody formation.

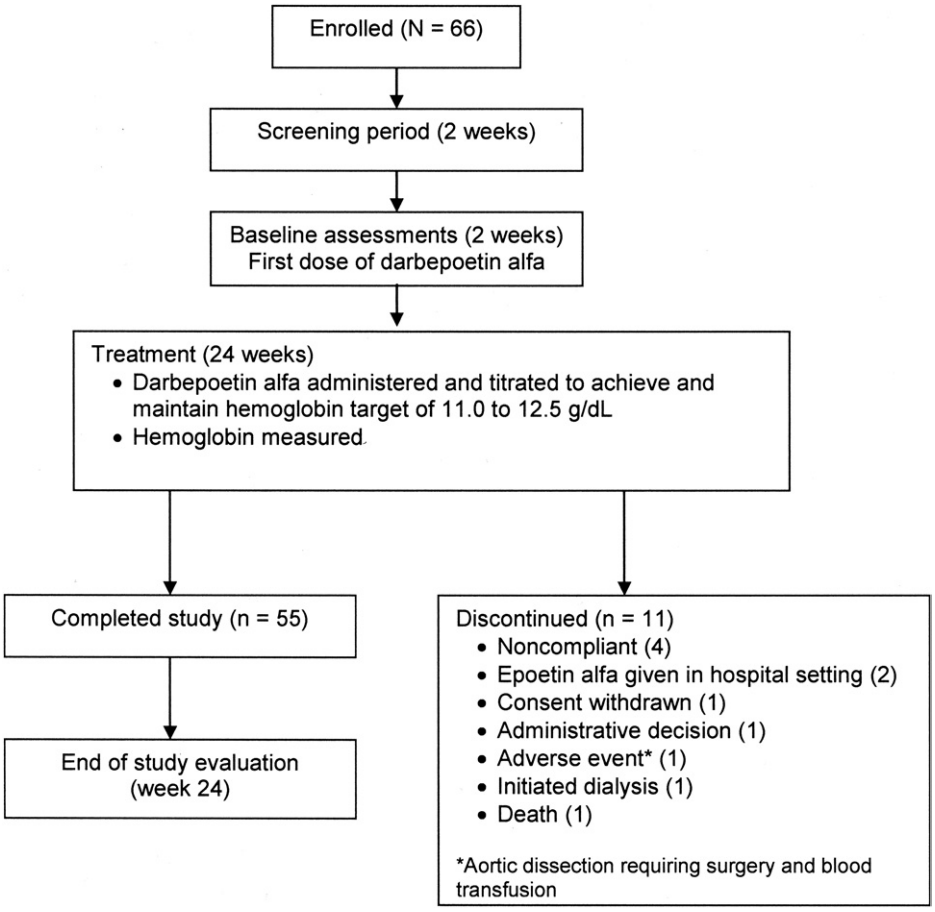

Fig 1. Study profile.

Subjects

Eligible subjects were at least 18 years old, were 6 months or more post–renal transplant, had one hemoglobin measure of < 11.0 g/dL within 3 months of screening, and had a hemoglobin concentration < 11.0 g/dL during the 2-week prestudy screening period. Patients were ineligible if they were expected to initiate renal replacement therapy (dialysis or transplantation) within 6 months of the study start; had less than 1 year life expectancy in the opinion of the study investigator; had a systematic hematologic disease, myeloma, hemolytic anemia, or malignancy; had active systemic or chronic infection, uncontrolled hypertension (defined as diastolic blood pressure > 110 mm Hg on two separate occasions during the 2 weeks prior to screening), or known hypersensitivity to darbepoetin alfa; received any ESA within the 12 weeks prior to screening; or had a red blood cell transfusion within 8 weeks prior to screening.

The study design was approved by the institutional review board at each study center, and patients' written consent was obtained before any study procedures were carried out. Clinical investigators signed an agreement to comply with the International Conference on Harmonization for Good Clinical Practice, and the FDA Code of Federal Regulations parts 50, 56, and 312.

Statistical Analysis

Descriptive statistics are provided for mean and standard deviation (SD) hemoglobin concentrations at baseline and during the evaluation period (no statistical comparisons were made), and for mean (SD) SF-36 subscale and component summary scores at baseline and week 24 using raw scores. A signed rank test was used to calculate whether the HRQOL changes from baseline to week 24 were different from 0. Regression analysis evaluated the relationship between change in HRQOL and change in hemoglobin concentration, and regression lines were plotted. A post hoc subgroup analysis was undertaken to evaluate HRQOL change stratified by subjects with hemoglobin < 10 g/dL and ≥ 10 g/dL at baseline. Data were analyzed by SAS software (version 9.1; SAS Institute, Cary, NC, USA).

Table 1. Demographics and Baseline Characteristics

	All Subjects (n = 66)
Mean (SD) age, y	51.4 (13.3)
Gender, *n* (%)	
Female	34 (51.5)
Male	32 (48.5)
Ethnicity, *n* (%)	
Caucasian	23 (34.8)
African-American	28 (42.4)
Hispanic	13 (19.7)
Asian	2 (3.0)
Mean (SD) weight, kg	87.0 (20.7)
Mean (SD) hemoglobin, g/dL	9.9 (1.2)
Mean (SD) eGFR, mL/min/1.73 m^{2}[a]	39.3 (18.4)
Creatinine, mg/dL[a]	
Mean (SD)	2.2 (1.1)
Median (range)	1.9 (0.8, 5.5)
Transplant number, *n* (%)	
First transplant	61 (92.4)
Retransplant	5 (7.6)
Time since most current transplant, (y) *n* (%)[b]	
<1	10 (15.2)
1–3 y	13 (19.7)
>3 y	41 (62.1)
Prior use of ESAs since current transplant,[c] *n* (%)	16 (24.2)
Presence of diabetes, *n* (%)	46 (69.7)

SD, standard deviation; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis stimulating agent.
[a]n = 65; [b]n = 64; [c]>12 wk prior to screening.

Table 2. Concomitant Medications

	Subjects, n (%)
Iron use	34 (52)
Oral iron	30 (45)
Intravenous iron	1 (2)
Oral and intravenous iron	3 (5)
Antihypertensive medication	62 (94)
Angiotensin-converting enzyme inhibitors	22 (33)
Angiotensin II receptor blockers	26 (39)
Immunosuppressive medication	
Steroids	63 (95)
MMF	50 (76)
Cyclosporine	32 (49)
Tacrolimus	25 (38)
Sirolimus	16 (24)
Azathioprine	3 (5)
Combinations	
Cyclosporine/steroids	5 (8)
Cyclosporine/steroids/azathioprine	1 (2)
Cyclosporine/steroids/MMF	20 (30)
Cyclosporine/MMF	2 (3)
Cyclosporine/steroids/azathioprine/MMF	1 (2)
Tacrolimus/steroids	3 (5)
Tacrolimus/steroids/azathioprine	1 (2)
Tacrolimus/steroids/MMF	19 (29)
Tacrolimus/MMF	1 (2)
Steroids/MMF	7 (11)

MMF, mycophenolate mofetil.

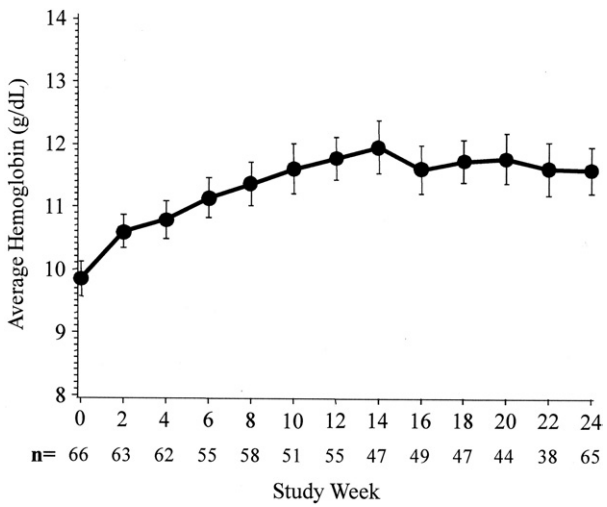

Fig 2. Mean hemoglobin (g/dL) concentration over time with 95% confidence intervals.

Table 3. HRQOL Scores

SF-36 domain	Norms for General US Population[51] (SD)	Score at Baseline, mean (SD), $n = 66$	Score at wk 24, mean (SD), $n = 55$	Change from Baseline, mean (SD), $n = 55$	*P* Value vs Baseline
Physical component summary	—	−1.5 (1.1)[a]	−0.8 (1.1)[c]	0.5 (0.8)[f]	<.0001
Mental component summary	—	−0.4 (1.1)[a]	−0.1 (1.2)[c]	0.3 (1.0)	.0748
Physical functioning	84.2 (38.8)	49.5 (30.5)	62.5 (26.67)	11.8 (25.8)	.0013
Role limitations due to physical health	81.0 (23.3)	32.9 (40.1)[b]	60.8 (41.5)[d]	26.5 (41.7)[c]	<.0001
Bodily pain	75.2 (34.0)	59.4 (27.5)	69.3 (27.5)	7.7 (22.6)	.0143
General health	72.0 (23.7)	45.8 (19.8)	47.8 (20.83)[d]	1.7 (14.6)[d]	.3965
Role limitations due to emotional health	81.3 (33.0)	57.7 (43.3)[b]	72.8 (39.4)[e]	15.7 (41.8)[c]	.01
Vitality	60.9 (21.0)	38.6 (21.1)	51.8 (21.9)	12.8 (18.6)	<.0001
Social functioning	83.3 (22.7)	63.6 (26.2)	73.4 (25.85)	7.5 (29.8)	.0675
Mental health	74.7 (18.1)	66.6 (19.9)	72.8 (20.5)	4.1 (16.3)	.0697

HRQOL, health-related quality of life; SF-36, Short-Form-36; SD, standard deviation
[a]$n = 62$; [b]$n = 63$; [c]$n = 51$; [d]$n = 53$; [e]$n = 54$; [f]$n = 48$.

RESULTS

A total of 66 patients were recruited, and 55 patients (83.3%) completed the study. Eleven (16.7%) patients discontinued the study (Fig 1). The reasons for patient withdrawal are given in Fig 1. The most common reason was noncompliance ($n = 4$; 6.1%). One patient died from respiratory arrest, which was determined to be unrelated to the study medication.

The mean (SD) age of the subjects who received darbepoetin alfa was 51.4 (13.3) years; 13 patients (19.7%) were aged 65 years or older, and the oldest patient was 76 years. Supplemental iron was given to 34 patients (52%). Demographics and baseline characteristics are provided in Table 1 and concomitant medications in Table 2. The proportion of females enrolled in the study (51.5%) was higher than in the general renal transplant population, but is consistent with the higher prevalence of anemia among females in transplant patients.[25]

All patients received immunosuppressive medications as indicated in Table 2, and all patients received mycophenolic mofetil, azathioprine, or sirolimus. Mean (SD) creatinine levels and estimated glomerular filtration rate levels (calculated using Modified Modification of Diet in Renal Disease [MDRD] Formula) remained stable between baseline and follow-up (2.2 [1.1] vs 2.4 [1.4] mg/dL and 39.3 [18.4] vs 37.3 [19.8] mL/min/1.73 m^2).

The mean (SD) hemoglobin concentration increased from 9.9 (1.2) g/dL at baseline to 11.7 (1.3) g/dL during the evaluation period (Fig 2). The mean (SD) change in hemoglobin concentration was 1.8 (1.4) g/dL.

The results of the HRQOL outcomes are summarized in Table 3. At baseline, all eight subscales of SF-36 were below the US general population norms, indicating decreased physical functioning, limitations due to physical health, bodily pain, general health, limitations due to emotional health, vitality, social functioning, and mental health. Nu-

Table 4. Hemoglobin Concentrations and HRQOL Scores by Baseline Hemoglobin < 10 g/dL and ≥ 10 g/dL

	Hemoglobin < 10 g/dL				Hemoglobin ≥ 10 g/dL			
SF-36 Domain	Score at Baseline, Mean (SD)	Score at wk 24, Mean (SD)	Change from Baseline Mean (SD)	*P* Value	Score at Baseline, Mean (SD)	Score at wk 24, Mean (SD)	Change from Baseline Mean (SD)	*P* Value
Hemoglobin	8.9 (0.9)[a]	11.2 (1.4)[d]	2.3 (1.4)[d]	<.0001	10.7 (0.6)[j]	11.9 (1.2)[k]	1.2 (1.9)[k]	<.0001
PCS	−1.6 (1.1)[b]	−1.1 (1.2)[e]	0.5 (0.8)[l]	.011	− 1.4 (1.1)[a]	−0.8 (1.0)[f]	0.6 (0.9)[g]	.002
MCS	−0.7 (1.1)[b]	−0.2 (1.4)[e]	0.4 (1.1)[i]	.136	−0.2 (1.0)[a]	0.0 (1.0)[f]	0.2 (0.9)[g]	.336
Physical functioning	45.1 (30.9)[a]	56.5 (29.3)[f]	8.7 (20.2)[f]	.035	53.7 (29.9)[h]	68.4 (22.8)[d]	14.8 (31.3)[d]	.015
Limitations due to physical health	26.6 (37.0)[f]	55.0 (42.1)[g]	26.0 (41.8)[g]	.005	39.1 (42.6)[a]	66.1 (41.0)[d]	26.9 (42.4)[h]	.003
Bodily pain	56.4 (28.5)[a]	64.7 (26.1)[f]	6.1 (26.7)[f]	.242	62.2 (26.7)[f]	73.7 (28.6)[d]	9.2 (18.2)[d]	.012
General health	42.3 (21.6)[a]	45.2 (22.7)[h]	3.5 (16.2)[h]	.280	49.1 (17.6)[f]	50.2 (19.0)[f]	0.0 (12.9)[f]	.997
Limitations due to emotional health	46.2 (42.8)[c]	67.9 (42.7)[h]	17.3 (51.0)[g]	.102	68.8 (41.4)[a]	77.4 (36.4)[d]	14.1 (31.5)[h]	.031
Vitality	32.6 (20.0)[a]	46.9 (22.6)[d]	14.4 (22.3)[f]	.002	44.3 (20.7)[f]	56.6 (20.5)[d]	11.3 (14.4)[d]	<.001
Social functioning	59.4 (28.3)[a]	68.1 (27.4)	5.1 (33.8)[f]	.441	67.6 (23.1)	78.6 (23.5)[d]	9.8 (25.8)[h]	.054
Mental health	64.2 (21.7)[a]	70.6 (23.2)[f]	5.7 (16.0)[f]	.076	68.9 (17.9)[f]	75.0 (17.8)[d]	2.5 (16.8)[h]	.432

PCS, physical component summary; MCS, mental component summary.
[a]$n = 32$; [b]$n = 30$; [c]$n = 31$; [d]$n = 28$; [e]$n = 24$; [f]$n = 27$; [g]$n = 25$; [h]$n = 26$; [i]$n = 31$; [j]$n = 34$; [k]$n = 29$.

merically lower scores of all eight subscales and both component summary scores were observed in subjects with a hemoglobin concentration < 10 g/dL compared with ≥ 10 g/dL at baseline (Table 4).

Treatment with darbepoetin alfa was associated with a significant improvement in physical component summary (PCS), physical functioning, limitations due to physical health, bodily pain, limitations due to emotion health, and vitality scores (Table 3). Clinically meaningful improvements (>5 points) were observed in six subscales; physical functioning, limitations due to physical health, limitations due to emotional health, bodily pain, social functioning, and vitality.

HRQOL outcomes in all subscales were consistently lower in the hemoglobin concentration < 10 g/dL group compared with the ≥ 10 g/dL group at baseline and at week 24. Consistent with all subjects at follow-up, significant improvements from baseline were found in PCS and five subscales, namely, physical functioning, vitality, bodily pain, limitations due to physical health, and emotional health in subjects with a hemoglobin concentration ≥ 10 g/dL at baseline. In subjects with a baseline hemoglobin concentration < 10 g/dL, statistically significant increases from baseline to the end of the study were observed in PCS, physical functioning, vitality, and limitations due to physical health (Table 4). Clinically meaningful improvements (>5 points) were observed in all eight subscales in the subjects with a baseline hemoglobin < 10 g/dL and in six subscales in subjects with hemoglobin concentration ≥ 10 g/dL at baseline. The two subscales not reporting clinically meaningful improvements in this group were general health and mental health.

The relationship between the change in SF-36 subscales for vitality and physical functioning and physical component summary scores and change in hemoglobin concentration is shown in Fig 3 and in subjects with a hemoglobin concentration < 10 g/dL and ≥ 10 g/dL at baseline in Fig 4 (data for PCS only shown).

Safety

All 66 of the recruited subjects received at least one dose of darbepoetin alfa and were included in the safety analysis. Thirteen subjects (20%) experienced at least one serious adverse event (SAE). The most common SAEs were urinary tract infection ($n = 3, 5\%$), pyrexia ($n = 3, 5\%$), acute renal failure ($n = 3, 5\%$), and nausea ($n = 2, 3\%$), and were representative of the general posttransplant population. One patient died during the study of respiratory failure/arrest. None of the SAEs was considered to be related to darbepoetin alfa. Two patients received at least one red blood cell transfusion during the study. No clinically significant changes were observed in laboratory parameters, and all patients tested negative for neutralizing antibodies to darbepoetin alfa.

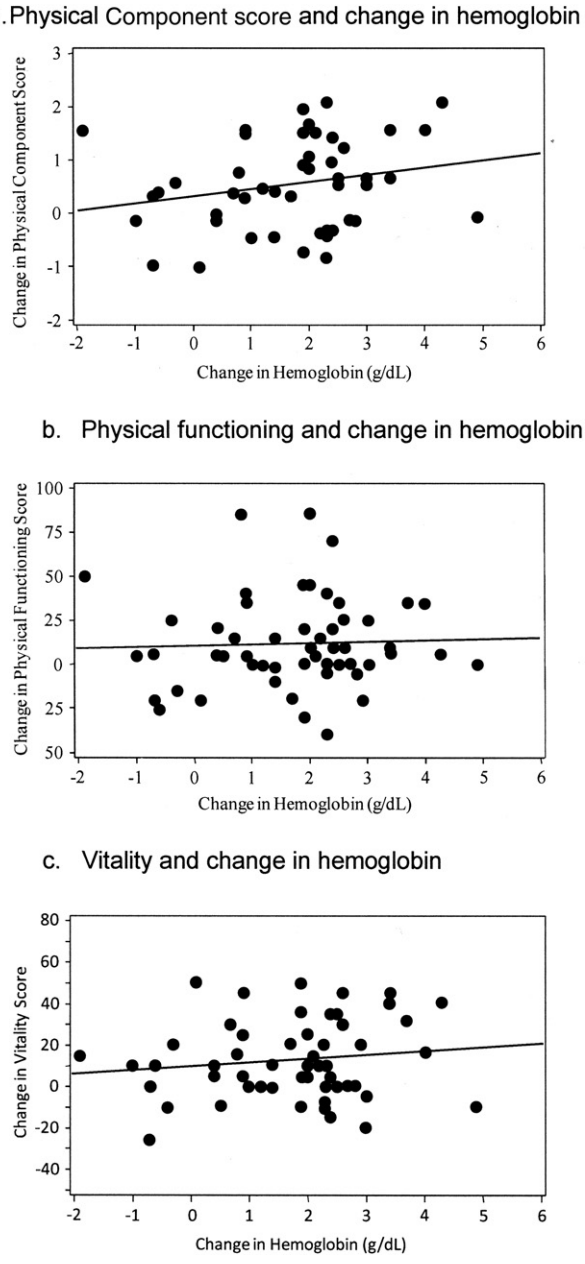

Fig 3a-c. Change in Short Form-36 domain scores and change in hemoglobin concentration following treatment with darbepoetin alfa. **(a)** Physical component score and change in hemoglobin. **(b)** Physical functioning and change in hemoglobin. **(c)** Vitality and change in hemoglobin.

DISCUSSION

This exploratory multicenter study showed that treatment with darbepoetin alfa effectively increased hemoglobin concentrations and was associated with a significant improvement in HRQOL scores as assessed by SF-36 in kidney transplant recipients with posttransplant anemia and was well tolerated.

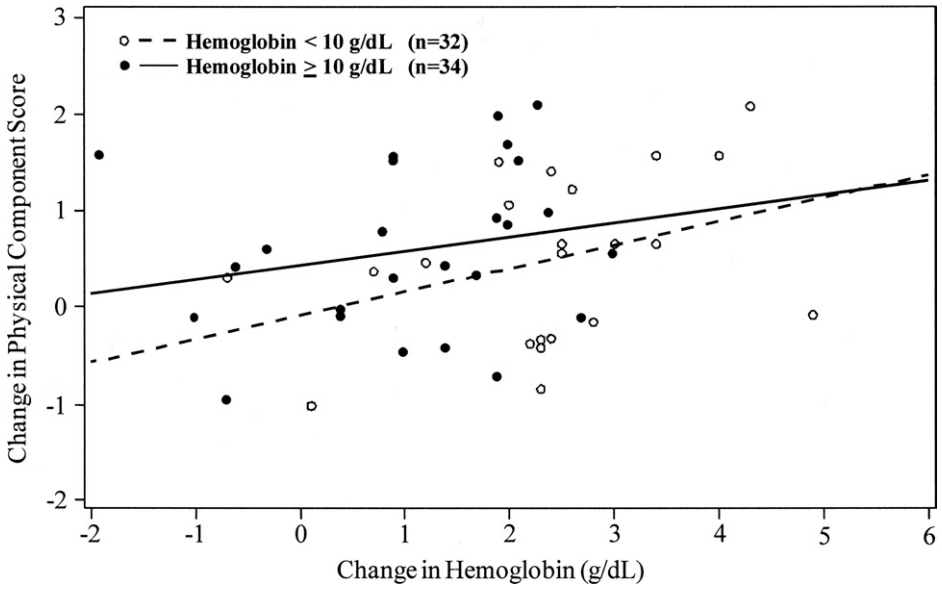

Fig 4. Change in physical component score and change in hemoglobin in subjects with hemoglobin < 10 g/dL and ≥ 10 g/dL following treatment with darbepoetin alfa.

Statistically significant improvements in SF-36 scores were observed for PCS score as well as 5 individual subscales: physical functioning, limitations due to physical health, limitations due to emotional health, bodily pain, and vitality. Clinically meaningful improvements in SF-36 scores of 5 points or more were also observed in a range of HRQOL subscales including physical functioning, limitations due to physical health, and vitality.

The study indicated that every area of HRQOL is affected in this patient population, with subjects having all eight subscales of the SF-36 lower (worse) than the US general population at baseline. Hemoglobin concentration was shown to affect HRQOL, with subjects with a baseline hemoglobin concentration < 10 g/dL having lower SF-36 scores in all areas of HRQOL than those subjects with a hemoglobin concentration ≥ 10 g/dL. Moreover, treatment to raise hemoglobin concentrations increased HRQOL; however, the posttreatment scores remained below general population levels, suggesting that the cause of lower HRQOL scores is multifactorial.

The baseline scores were below those observed across other chronic conditions, including end-stage renal disease, myocardial infarction, diabetes mellitus, and chronic heart failure.[26, 27]

Darbepoetin alfa increased hemoglobin concentrations in this study. Moreover, subjects with a hemoglobin concentration < 10 g/dL experienced greater HRQOL improvements with raising hemoglobin compared to the group with ≥10 g/dL at baseline.

Previous studies have reported an association between treatment with ESAs and improvement in HRQOL in various populations with different underlying causes of anemia and anemia caused by chemotherapy or HIV, and in patients with chronic kidney disease (CKD) (dialysis and nondialysis).[28–31] A number of studies, including randomized controlled trials, have reported quality-of-life changes in renal failure patients treated with ESAs.[32–44] A meta-analysis of these studies reported significant improvements in quality of life from baseline after ESA treatment ($P < .001$), including improvements in physical and fatigue scores. The magnitude of change is not directly comparable to our study as these studies did not use the SF-36 to assess quality of life, but used other validated measures (Karnofsky Performance Scale, the Kidney Diseases Questionnaire, and the Sickness Impact Profile). A number of studies in CKD patients have assessed HRQOL using the SF-36. In randomized controlled trial in nondialysis CKD patients with treated and untreated groups, the mean change in vitality scores (measured by SF-36) from baseline to follow-up was 5.8 for the treatment group and –3.1 for the untreated group.[43] In an open-label randomized controlled trial (CHOIR) with low versus high hemoglobin targets, vitality score from baseline to follow-up improved by 10 in the high hemoglobin target group compared with 8.2 in the low hemoglobin target group.[45] Two single-arm, open-label studies reported similar results to our study, with mean change in vitality scores from baseline to follow-up ranging from 14.1 to 14.9.[13, 21] However, single-arm studies do not allow evaluation of a potential placebo effect.

This is one of the few studies to assess the HRQOL effects of an ESA in posttransplant patients. A recent study by Kawada et al[46] highlighted that posttransplant anemia has a negative impact on HRQOL and reported that significant HRQOL improvements were associated with ESA use in patients with a hemoglobin concentration over 13.3 g/dL. This was in contrast to a previous study, which reported no improvement in HRQOL in posttransplant anemia patients treated with ESAs to a target of 11.0 to 12.0 g/dL.[47] The authors suggested that a higher target concentration of hemoglobin was key for HRQOL improvement in

posttransplant patients.[46] However, our study reported HRQOL benefits with a hemoglobin target of 11.0 to 12.5 g/dL. Important differences between these two earlier studies and this study include patient cohorts; in the earlier studies, patients were Japanese and therefore demographically dissimilar to our patients, and also they had better preservation of kidney function at baseline and fewer comorbidities. Additionally, these studies and our study did not have comparator groups, and as mentioned above, cannot allow for a placebo effect.

Patients with posttransplant anemia following successful renal transplantation are underdiagnosed, and consequently potentially undertreated.[3,5,6] It has been suggested that this may be due to safety and efficacy concerns or to patient perception that ESAs are associated with poor graft function.[48] The results of this study suggests that darbepoetin alfa effectively increases hemoglobin in this patient population.

Several limitations should be considered when interpreting the results of the study, the most important of which is that this study was a single-arm study, which prevents the evaluation of a potential placebo effect. SF-36 has not been validated in the posttransplant anemia population, but has been validated in the general population and for patients with ESRD.[49] The study was not designed to assess whether clinical outcomes were associated with changes in HRQOL parameters, although others have suggested that a 5-point change in HRQOL parameters is clinically meaningful.[50]

In conclusion, patients with posttransplant anemia have lower HRQOL than the general population. Treatment with darbepoetin alfa was associated with an increase in hemoglobin concentrations and improvements in HRQOL in these patients.

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