

Treating anemia early in renal failure patients slows the decline of renal function: A randomized controlled trial

CHARICLIA GOUVA, PETROS NIKOLOPOULOS, JOHN P.A. IOANNIDIS, and KOSTAS C. SIAMOPOULOS

Division of Nephrology, Department of Internal Medicine, and the Clinical Trials and Evidence-Based Medicine Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; and Division of Clinical Care Research, Tufts-New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts

Treating anemia early in renal failure patients slows the decline of renal function: A randomized controlled trial.

Background. Erythropoietin is known to improve outcomes in patients with anemia from chronic renal disease. However, there is uncertainty about the optimal timing of initiation of erythropoietin treatment in predialysis patients with non-severe anemia.

Methods. We conducted a randomized controlled trial of early versus deferred initiation of erythropoietin in nondiabetic predialysis patients with serum creatinine 2 to 6 mg/dL and hemoglobin 9 to 11.6 g/dL. The early treatment arm was immediately started on 50 U/kg/wk of erythropoietin alpha with appropriate titration aiming for hemoglobin of ≥ 13 g/dL. The deferred treatment arm would start erythropoietin only when hemoglobin decreased to < 9 g/dL. The primary end point was a composite of doubling of creatinine, renal replacement, or death.

Results. Eighty-eight patients were randomized (early treatment $N = 45$, deferred treatment $N = 43$) and followed for a median of 22.5 months. During follow-up, 13 versus 23 patients reached the primary end point in the two arms, respectively (log-rank $P = 0.0078$). The relative hazard for reaching an end point was 0.42 ($P = 0.012$). Adjusting for baseline serum creatinine, the adjusted relative hazard was 0.37 ($P = 0.004$), while the risk increased 2.23-fold ($P < 0.001$) per 1 mg/dL higher creatinine at baseline. The benefit was similar regardless of the baseline hemoglobin and proteinuria. No patients had any severe adverse events.

Conclusion. Early initiation of erythropoietin in predialysis patients with non-severe anemia significantly slows the progression of renal disease and delays the initiation of renal replacement therapy.

Erythropoietin (EPO) administration can correct the anemia associated with renal failure in predialysis patients [1–9]. Early concerns [10] about a potential deterioration of renal function in EPO users have been

abated by clinical evidence [4, 5, 7] showing that EPO does not deteriorate renal function. Nevertheless, the use of EPO in predialysis patients is more controversial in patients where the anemia is not so prominent. The best time to start treatment is uncertain. Usually, anemia progresses along with the deterioration of renal function, but the correlation is not perfect. Guidelines have moved the threshold for starting EPO treatment toward higher hemoglobin levels (i.e., to recommend earlier treatment), when the hemoglobin drops below 10 g/dL in the United States guidelines [11, 12], and below 11 g/dL in the European guidelines [13]. Nevertheless, surveys show that the use of EPO before dialysis is still uncommon in clinical practice [14–16], and most patients don't start EPO until the anemia is advanced. Patients without severe anemia may not benefit much symptomatically from the correction of anemia, and the cost of the treatment along with potential side effects may have to be considered more seriously. However, EPO would still be very useful in this setting if it can slow renal disease progression and delay the need for renal replacement.

In order to evaluate whether EPO can slow the progression of chronic disease in predialysis patients with non-severe anemia, we undertook a randomized trial that compared two strategies: immediate onset of treatment versus deferring EPO treatment until the hemoglobin dropped to below 9 g/dL.

METHODS

Eligibility criteria

Predialysis patients with renal impairment resulting from any cause other than diabetes mellitus with screening serum creatinine values 2.0 to 6.0 mg/dL and hemoglobin of 9.0 to 11.6 g/dL were eligible for the study. Patients with hemoglobin less than 9 g/dL were considered as candidates for immediate onset of EPO treatment and were not included in the trial. Other exclusion criteria were the presence of an easily correctable cause of anemia, such as iron deficiency (transferrin saturation

Key words: renal anemia, renal failure, erythropoietin.

Received for publication August 7, 2003
and in revised form October 22, 2003, December 4, 2003, and
February 3, 2004
Accepted for publication March 2, 2004

© 2004 by the International Society of Nephrology

<20%), transfusion dependency, the presence of systemic diseases, infections, or inflammatory conditions that might inhibit the effect of EPO, age <18 years or >85 years, uncontrollable hypertension, proteinuria >2 g per 24 hours, serum albumin <3.5 g/dL, hepatic insufficiency, active hepatitis, uncontrollable hypothyroidism, chronic alcoholism, congestive heart failure (New York Heart Association class III or IV), severe obesity (body mass index >40 kg/m²), nPNA ≤0.8 g/kg/day, history of seizures of thrombotic episodes, pregnancy, lactation, known hypersensitivity to EPO alpha, use of antilipidemic drugs, use of corticosteroids in the previous 6 months, and use of EPO in the previous 6 months. Because of concerns about induced EPO resistance at the time the study was launched [17–19], patients receiving angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) could participate if they were willing to stop these drugs, and adequate blood pressure control could be achieved with other drugs for at least 2 months before proceeding with randomization.

Treatment allocation

Patients were randomized to two treatment arms. In the early treatment arm patients were started immediately on subcutaneous EPO alpha (Eprex, Janssen-Cilag Pharmaceutical, Athens, Greece) 50 U per kg once per week. In the deferred treatment arm, EPO was initiated only when the hemoglobin decreased during follow-up to less than 9 g/dL (confirmed on a second measurement within less than 1 week). Dose schedules and titration of EPO was otherwise the same in the two arms. For patients receiving EPO, it was recommended that there should be no effort to further increase the hemoglobin once it had exceeded 13 g/dL. For patients exceeding this target, the dose of EPO was titrated downward to 25 U per kg once per week, or it could remain the same, according to the discretion of the clinician. For patients not reaching the target of 13 g/dL, 25 U per kg dose increments were allowed each month. Whenever the hemoglobin decreased again to below 11.6 g/dL and there was no easily identifiable cause that could be corrected, it was recommended that the dose of EPO should be titrated upwards by 25 U per kg to again reach the appropriate hemoglobin range.

All centers followed common principles for the monitoring of blood pressure, treatment of hypertension, dietary instructions, and renal failure management. Monitoring of blood pressure and treatment of hypertension was performed according to established standards, aiming for blood pressure levels <130/85 mm Hg [20] whenever possible, using restricted salt intake, and appropriate drug therapy, at the discretion of the treating clinician. For patients with higher blood pressures in the office setting, we obtained 24-hour measurements for more accurate monitoring. Hypertension was managed avoiding the

use of ACEIs and ARBs, to avoid potential EPO resistance [17–19]. Protein intake was generally restricted to less than 1 g/kg per day [21] based on appropriate dietary instructions given to the patients. No extra-low protein diets were employed in the study. Patients developing iron deficiency with documented transferrin saturation <20% were treated with oral iron supplementation. Two patients who had intolerance to oral iron received intravenous iron supplementation.

Patients were randomized using a computerized sequence kept at the coordinating center at the University of Ioannina. Once a patient had consented to be randomized, randomization was performed centrally.

End points

The study had two main end points. The first end point was progression of renal disease (defined as doubling of creatinine, a creatinine of >8 mg/dL, initiation of renal replacement) or death from any cause. The second end point was initiation of renal replacement or death from any cause, whichever occurred first. We also examined whether the level of renal failure was different in the two arms at the time of initiating renal replacement for those patients who started renal replacement.

Secondary end points included the levels of hemoglobin and hematocrit, serum creatinine, and creatinine clearance at 12 months. Creatinine clearance was determined using the Cockcroft-Gault formula.

As part of safety assessments, we recorded hospitalizations due to any reason, the occurrence of uncontrolled hypertension, severe anemia (hemoglobin <7 g/dL), and allergic local or systemic reactions. Comparisons of blood pressure at 12 months between the two arms were made adjusting for baseline measurements in analysis of variance. A nested substudy also collected information on serum lipid parameters on selected patients (data not shown).

Follow-up and measurements

Besides the screening measurements that were used for justifying eligibility, patients also had separate baseline measurements at the time of randomization. Patients were seen then on an outpatient basis at 2, 4, 6, 9, 12 months, and every 3 months thereafter. Additional visits could be made in cases of acute medical problems. At each study visit, vital signs and weight were recorded, and measurements included complete blood cell count, serum creatinine and urea, electrolytes, glucose, iron, ferritin, total iron binding capacity, urinalysis, and 24-hour urine protein, urea, and creatinine determinations.

Sample size calculations and protocol modification

The study was designed in order to have 80% power to show with alpha = 0.05, a 50% reduction in the

hazard of doubling of creatinine, creatinine >8 mg/dL, renal replacement, or death during follow-up in the early treatment arm versus the deferred treatment arm. With these estimates, we aimed for capturing 66 events during follow-up in the two arms combined. We expected that with 2.5 years of follow-up, two thirds of the patients would have an event; thus, 100 randomized patients would have to be followed for an average of 2.5 years. We expected that approximately 50 patients could be recruited rapidly, and another 50 would then be entered in the trial over a period of approximately 12 months. Thus, it was anticipated that the trial should continue until all patients had completed 2 years of follow-up.

In February 2002, case series of pure red-cell aplasia (PRCA) were reported in patients receiving mainly subcutaneous EPO alpha [22]. Although no such adverse events had been recorded in any of the enrolled patients in our study, enrollment of new patients was suspended, with 88% of the target enrollment being achieved. In November 2002, the indication of subcutaneous EPO alpha administration in chronic renal failure patients was withdrawn because PRCA had been documented in a further number of patients receiving EPO (mainly subcutaneous EPO alpha) in Europe, Australia, and Canada [23]. At this point all study patients were informed of this modification and subcutaneous EPO alpha was discontinued. Patients in both arms could then use an alternative form of EPO (e.g., subcutaneous EPO beta or darbepoetin) at the discretion of their physicians. It was felt that the potential drop-in of patients between the two arms could blur subsequent differences during prolonged follow-up because the treatment experience of the two arms would become relatively homogenized after this modification. Thus, it was elected to terminate the study and analyze the data at 1 year after the recruitment of the last patient.

Statistical analyses

All analyses are based on intention-to-treat with patients analyzed in the arm where they were originally randomized. The primary end points were analyzed with Kaplan-Meier curves using the log-rank test for comparison and with proportional hazards models. Proportional hazards models were also adjusted for age, sex, and baseline hematologic parameters, serum creatinine, creatinine clearance, and proteinuria. We also assessed whether the results were different in subgroups defined by baseline parameters. For secondary continuous outcomes, we used analysis of variance (ANOVA), adjusting for baseline measurements. In the case of missing values because of death, loss to follow-up, or missed appointment, we used the last observation carried forward approach; in particular, for serum creatinine and creatinine clearance, the same approach was used to carry forward the last value of creatinine before initiation of renal replacement, for

Table 1. Baseline characteristics

	Early arm N = 45	Deferred arm N = 43	P value ^a
Female/male	20/25	18/25	0.98
Age, mean (SD), years	66.7 (10.4)	64.2 (12.2)	0.44
Weight, mean (SD), kg	72.3 (8.9)	70.4 (9.4)	0.44
Hemoglobin, mean (SD), g/dL	10.1 (0.5)	10.1 (0.6)	0.72
Hematocrit, mean (SD), %	30.8 (1.4)	31.0 (1.1)	0.58
Serum creatinine, mean (SD), mg/dL	3.27 (0.99)	3.39 (0.82)	0.27
Creatinine clearance, mean (SD), mL/min	25.7 (9.1)	22.3 (6.0)	0.14
History of hypertension, N (%)	42 (93)	36 (84)	0.19
24-hour protein, mean (SD), g	0.66 (0.39)	0.57 (0.36)	0.28

^aBased on Mann-Whitney *U* test and chi-square test with continuity correction, as appropriate.

patients who initiated renal replacement. Comparisons of discrete and continuous variables between groups at baseline were performed using the chi-square test with continuity correction and the *t* test, respectively.

Analyses were conducted with SPSS 11.0 (SPSS, Inc., Chicago, IL, USA). All *P* values are two-tailed.

Ethical issues

The study was approved by the hospital ethics board, and all patients provided informed consent. The sponsor had no role in the design of the study, in the collection, analysis, or interpretation of the data, or the drafting of the manuscript. The principal investigators had all the data collected during this trial available, and were responsible for manuscript submission.

RESULTS

Trial population

A total of 88 patients were enrolled in the study across 14 participating hospitals in Greece between November 2000 and June 2002. Forty-five were randomized in the early treatment arm and 43 were randomized in the deferred treatment arm. Patients were followed for a median of 22.5 months (interquartile range 16 to 24 months) and the total follow-up was 147.4 person-years. In the early treatment arm, 3 patients died (prostate cancer, cerebrovascular event, and car accident) and one was lost to follow-up. In the deferred treatment arm, 4 patients died (ischemic heart disease *N* = 3, cerebrovascular disease) and 2 were lost to follow-up. In the early treatment arm, patients spent a median of 17 months (interquartile range 11 to 19) in the original EPO regimen. In the deferred treatment arm, patients spent a median of 12 months (interquartile range 7 to 18) without any EPO. None of the patients in the deferred arm had their hemoglobin fall below 9 g/dL during follow-up. The two groups were well balanced in regards to

Table 2. Hematologic and renal parameters at 12 months

	Early arm	Deferred arm	P value ^a
Hemoglobin, mean (SD), g/dL	12.9 (0.4)	10.3 (1.0)	<0.001
Hematocrit, mean (SD), %	38.4 (1.5)	31.4 (2.6)	<0.001
Serum creatinine, mean (SD), mg/dL	3.81 (1.43)	5.07 (2.39)	<0.001
Creatinine clearance, mean (SD), mL/min	21.9 (9.4)	16.1 (6.3)	<0.001

^aP values are based on analysis of covariance adjusting for the baseline values. Last observation carried forward has been applied in the analyses, as described in **Methods**.

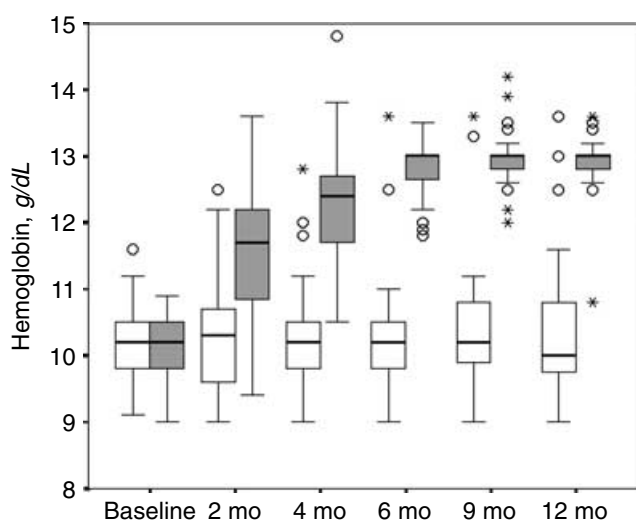


Fig. 1. Hemoglobin levels at baseline and during follow-up (at 2, 4, 6, 9, and 12 months) in the deferred (white boxes) and early (gray boxes) treatment groups. The box plots show the median (horizontal line), interquartile range (box), and range (whiskers), unless there are also outliers and/or extreme values with 1.5 to 3 and >3 box lengths, respectively, away from the edge of the box, in which case these are shown by circles and asterisks.

all baseline characteristics (Table 1). The majority of patients had a history of hypertension, while 10 patients had biopsy-documented glomerulonephritis (6 and 4 in the two arms, respectively), 3 patients had polycystic disease (1 and 2 in the two arms, respectively), and 3 had obstructive nephropathy caused by nephrolithiasis (1 and 2 in the two arms, respectively). The majority of patients (30 and 35 patients in the early and deferred EPO arms, respectively) had stage 4 chronic kidney disease, while a few patients had stage 5 chronic kidney disease (5 and 3 in the two arms, respectively), or stage 3 disease (10 and 5 in the two arms, respectively).

Hematologic and renal function parameters at 12 months

At 12 months, the two groups clearly differed in levels of hemoglobin and hematocrit (Table 2, Fig. 1). With one exception, patients in the early treatment arm consistently managed to reach hemoglobin levels of 12.5 mg/dL

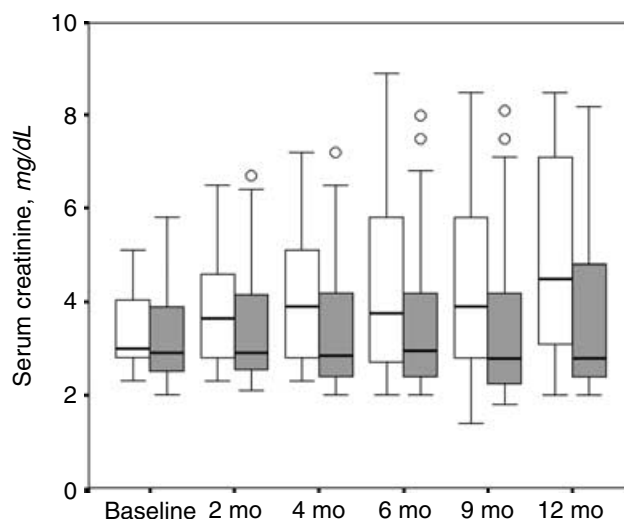


Fig. 2. Serum creatinine levels at baseline and during follow-up (at 2, 4, 6, 9, and 12 months) in the deferred (white boxes) and early (gray boxes) treatment groups. The box plots show the median (horizontal line), interquartile range (box), and range (whiskers), unless there are also outliers and/or extreme values with 1.5 to 3 and >3 box lengths, respectively, away from the edge of the box, in which case these are shown by circles and asterisks. Not shown are two creatinine values above 10 mg/dL.

or higher, while most patients on the deferred treatment arm who had started EPO in the interim had also reached similar hemoglobin levels. Serum creatinine and creatinine clearance were also significantly better in the early treatment group than in the deferred treatment group (Table 2, Fig. 2).

Primary end points for long-term follow-up

During follow-up, 13 versus 23 patients reached the end point of doubling of creatinine, renal replacement, or death in the early versus deferred treatment arms, respectively. For renal replacement or death, there were 13 versus 22 patients with an event in the two arms, respectively. In the early treatment arm, 3 patients died and 10 patients started renal replacement (6 of whom had doubled their serum creatinine or had reached values >8 mg/dL by the time of starting renal replacement). In the deferred treatment arm, 4 patients died, 18 started renal replacement (11 of whom had doubled their serum creatinine or had reached values >8 mg/dL by the time of starting renal replacement), and 1 had a doubling of serum creatinine without starting renal replacement. Thus, the difference between the two arms was largely caused by initiation of renal replacement. In Kaplan-Meier analyses (Fig. 3), the difference was formally statistically significant for both end points (log-rank $P = 0.0078$ and $P = 0.011$, respectively). The mean (SD) creatinine clearance in the early versus deferred EPO arm at the time of initiation of renal replacement was 11.1 (1.5) mL/min versus 11.0 (1.8)

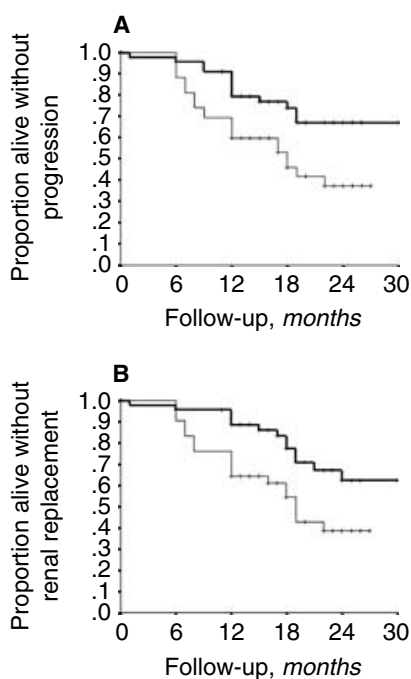


Fig. 3. Kaplan-Meier plots for doubling of creatinine, renal replacement, or death (A), and renal replacement or death (B) in the early (thick line) versus deferred (thin line) treatment arms.

mL/min. There was no statistically significant difference ($P = 0.98$). The respective mean (SD) serum creatinine values were 6.69 (0.76) mg/dL and 6.95 (0.85) mg/dL in the two arms ($P = 0.43$).

The relative hazard (RH) of doubling of creatinine, renal replacement, or death was 0.42 (95% CI, 0.21–0.83, $P = 0.012$) in patients where EPO was started early than deferred. Adjusting for baseline serum creatinine, the adjusted RH was 0.37 (95% CI 0.18–0.73, $P = 0.004$), while the risk increased 2.23-fold (95% CI 1.56–3.18, $P < 0.001$) per 1 mg/dL higher serum creatinine at baseline. The unadjusted RH for death or renal replacement similarly was 0.43 (95% CI 0.22–0.85). Considering both treatment allocation and initial serum creatinine, the RH was 0.38 (95% CI 0.19–0.76, $P = 0.006$), while the risk of an event increased 2.25-fold (95% CI 1.57–3.23, $P < 0.001$) per 1 mg/dL higher creatinine at baseline. Sex, age, weight, 24-hour protein, creatinine clearance, and the hematologic condition at baseline did not provide any additional independent information once these two parameters had been considered for either outcome.

Interaction terms between baseline serum creatinine and treatment arm were not significant, suggesting a similar benefit in patients with high and low baseline creatinine. For doubling of creatinine, renal replacement, or death, the RH was 0.33 ($P = 0.033$) in subgroup of patients with baseline serum creatinine >4 mg/dL ($N = 22$) and 0.43 ($P = 0.077$) for the subgroup of patients with baseline serum creatinine ≤ 4 mg/dL ($N = 66$). The ben-

efit was also similar in subgroups with different baseline hemoglobin levels [RH 0.38, $P = 0.036$ for hemoglobin ≥ 10 g/dL ($N = 59$) vs. RH 0.44, $P = 0.12$ for hemoglobin < 10 g/dL ($N = 29$)], and different levels of baseline proteinuria [RH 0.48, $P = 0.13$ for proteinuria ≤ 500 mg per 24 hours ($N = 44$) vs. RH 0.38, $P = 0.054$ for proteinuria > 500 mg per 24 hours ($N = 44$)].

Adverse events

Ten patients were hospitalized, 4 in the early treatment arm (cardiac disease, pneumonia, urinary tract infections $N = 2$) and 6 in the deferred treatment arm (prostate cancer, pneumonia, cardiac disease, viral infections $N = 2$, breast cancer). Hypertension was well controlled in all study subjects. After adjusting for baseline values, the office measurements of systolic and diastolic, as well as the mean blood pressure at 12 months were nonsignificantly higher in the early treatment arm by 1.1 mm Hg ($P = 0.31$), 0.3 mm Hg ($P = 0.81$), and 0.6 mm Hg ($P = 0.59$), respectively, and for those patients who had 24-hour determinations the mean blood pressure was nonsignificantly higher by 0.3 mm Hg ($P = 0.87$) in the early EPO arm. One patient in each arm had a mean blood pressure exceeding 105 mm Hg at baseline in the office and verified by 24-hour measurements, and 1 other patient in each arm had a similarly elevated mean blood pressure at 12 months. Six patients had systolic blood pressure above 140 mm Hg or diastolic blood pressure above 90 mm Hg at baseline, but none had such levels at 12 months. No patients developed severe anemia and no patients had severe allergic reactions to EPO.

DISCUSSION

This randomized controlled trial shows that the initiation of EPO in predialysis patients with non-severe anemia results in a 60% reduction in the risk of initiation of renal replacement or death. We observed a similar benefit in patients with different degrees of baseline renal impairment, hemoglobin level, and degree of proteinuria. These data strongly suggest that early initiation of EPO in predialysis patients with mild anemia is likely to be highly beneficial.

Previous randomized trials have clearly documented the beneficial effect of EPO in predialysis patients toward correcting the anemia of chronic renal failure [1–9]. Various other benefits of raising the hemoglobin to normal or near normal concentration in the setting of renal failure, such as improved cognitive function, exercise performance, amelioration of left ventricular performance, and quality of life have also been reported [9, 24–29]. Some of the randomized studies have already shown that renal function (as determined by serum creatinine or creatinine clearance and glomerular filtration rate) is not

deteriorating in the short-term [3, 4], and is probably actually comparatively better during longer-term follow-up [5, 7] in patients given EPO versus those not given EPO treatment. With one exception [7], these studies have not focused particularly on hard clinical end points. Kyriyama et al [7] described a significant decrease in the requirement for renal replacement in patients treated with intravenous EPO in a randomized trial of 73 predialysis patients. That study recruited patients with more severe anemia than patients in our study, with a mean hematocrit of 27.3%, and with all patients having hematocrit less than 30%. That study also recruited mostly patients with severe proteinuria (mean 4 g per 24 hours), had a preponderance of diabetics, and aimed for less strict blood pressure control (<160/95 mm Hg) than what is the current goal. Our study is the first, to our knowledge, to document a clear clinical benefit for predialysis patients with mild anemia and strict blood pressure control.

The beneficial effect of predialysis initiation of EPO in terms of hard clinical outcomes is also supported by observational data from the Health Care Financing Administration [30]. Out of 4866 patients, only 1107 had started EPO before dialysis. However, these patients had decreased risk for mortality during follow-up (RH 0.80), and the benefit was even larger when EPO has resulted in higher hematocrit (RH 0.67). Recent surveys have shown that only 11% to 26% of patients initiate EPO before dialysis and more than two thirds of patients start renal replacement with a hemoglobin <11 mg/dL [14–16]. According to our findings, these surveys reflect inappropriate underuse of a beneficial treatment.

In this trial we aimed for hemoglobin levels that are slightly higher than those recommended by the most recent guidelines [12]. However, the difference is subtle. The optimal target level for hemoglobin cannot be determined based on our data. The beneficial clinical effect of EPO could be due to a variety of pathophysiologic mechanisms. Correcting anemia increases oxygen delivery to tissues and reduces hypoxia. Hypoxia of tubular cells may be the main link between interstitial fibrosis and tubular damage [31]. Chronic reduction in nephron number is linked with increased oxygen consumption by the remaining nephrons and increased production of reactive oxygen species [32]. Oxidative stress may enhance both tubular damage and interstitial fibrosis. Apoptosis also plays a role in the progressive loss of tubular cells in chronic kidney disease [33, 34]. In vitro EPO protects endothelial and vascular smooth muscle cells against apoptosis [35, 36]. In theory, other cells that express the EPO receptor, such as the proximal tubular and medullary collecting duct cells of the kidney [37], could also be protected against apoptosis.

EPO should be added to the limited list of measures known to delay end-stage renal disease, including protein restriction and optimal control of blood pressure [38].

Our study pertains to a nondiabetic population. In diabetics, the use of ACEIs is strongly indicated [39] and recent evidence suggests [40] that ACEIs may offer an additional benefit beyond that conferred by blood pressure reduction, especially in the presence of considerable proteinuria, even in nondiabetic patients. This was not as clear when our study was designed, thus we opted to avoid angiotensin inhibition because data suggested a potential interference with response to EPO [17–19], although this issue is currently controversial [41]. It is possible that if patients had been treated with ACEIs, the rate of decline in kidney function might have been somewhat slower in both groups. Only 3 patients in our study discontinued angiotensin inhibition therapy in order to be enrolled. Moreover, the additional benefit of angiotensin inhibition seems absent among patients with <500 mg daily urine protein [40]. Our study cohort had generally low levels of proteinuria, and half of our patients had levels below 500 mg per 24 hours. Reassuringly, the observed benefit did not depend on the degree of proteinuria. Nevertheless, our current clinical policy is to use both EPO and angiotensin inhibition concurrently in patients with chronic renal disease.

A limitation of the study was the inability to continue the original design for the anticipated 2 years, although this did not affect the ability of the trial to show differences between the compared arms. The form of subcutaneous EPO alpha that was used in the trial has currently been withdrawn because of concerns about PRCA. However, there is no reason to believe that the other available forms of EPO would be less beneficial in slowing renal disease progression. Moreover, it is currently speculated that the increased incidence of PRCA with the European preparation of subcutaneous EPO alpha compared with other preparations of subcutaneous EPO is probably not caused by the drug, but by the replacement of human serum albumin by polysorbate 80 and glycine in the preparation. These substances may increase EPO aggregation and enhance antibody formation, and antigenicity may also be increased by the presence of silicone in pre-filled syringes [23]. With different preparations of EPO the rate of PRCA should be too low to be of concern.

We should caution that initiation of renal replacement therapy may be influenced somehow by physician decision-making in a nonblinded study. Theoretically, physicians may have attempted to start renal replacement at a more advanced stage of renal failure when patients had not been randomized to the early EPO arm. Additionally, if EPO improved overall well being, renal replacement may have been delayed among EPO recipients, even in the face of very poor renal function. However, we documented that the renal function at the time of initiation of renal replacement was very similar in the two arms. It is also reassuring that the course of serum creatinine and creatinine clearance values over time showed a

clear, statistically significant superiority of the early EPO arm. Therefore, it is more likely that the delay in initiation of renal replacement reflects mostly a genuine beneficial effect of renal disease progression rather than subjective biases.

CONCLUSION

With these caveats, we conclude that early treatment of non-severe anemia may be a useful intervention for deterring the need for renal replacement in patients with chronic renal failure. A formal cost-effectiveness analysis could also be performed to evaluate the exact cost-benefit ratio for the early administration of EPO in such patients.

APPENDIX

The following investigators participated in this multicenter study in Greece: University Hospital, Ioannina: K. Siamopoulos; Hatzikosta General Hospital of Ioannina: M. Pappas; Hippocrates Hospital, Thessalonica: D. Memmos; Evangelismos Hospital, Athens: N. Nikolopoulou; Laikon General Hospital, Athens: C. Stathakis; General Hospital, Kavala: K. Kalaitzidis; Thriaseion Hospital, Athens: J. Papadakis; General Hospital, Larissa: I. Stefanidis; Papageorgiou Hospital, Thessalonica: G. Sakellariou; General Hospital, Volos: C. Sirganis; General Hospital, Veria: D. Tsakiris; General Hospital, Edessa: N. Zoumbaridis; Papanikolaou Hospital, Thessalonica: K. Sombolos; General Hospital, Kalamata: G. Bristogiannis.

ACKNOWLEDGMENTS

The authors wish to thank Mrs. Aleka Papageorgiou for the skilled secretarial assistance.

Reprint requests to Kostas C. Siamopoulos, MSc, M.D., FRSH, Professor of Medicine/Nephrology, Department of Internal Medicine, Medical School, University of Ioannina, GR451 10 Ioannina, Greece.
E-mail:ksiamop@cc.uoi.gr

REFERENCES

- STONE WJ, GRABER SE, KRANTZ SB, *et al*: Treatment of the anemia of predialysis patients with recombinant human erythropoietin: A randomized, placebo-controlled trial. *Am J Med Sci* 296:171-179, 1988
- SILVERBERG DS, BLUM M, AGBARIA Z, *et al*: The effect of intravenous iron alone or in combination with low-dose erythropoietin in the rapid correction of anemia of chronic renal failure in the predialysis period. *Clin Nephrol* 55:212-219, 2001
- THE US RECOMBINANT HUMAN ERYTHROPOIETIN STUDY GROUP: Double blind, placebo-controlled study of the therapeutic use of recombinant human erythropoietin for anemia associated with chronic renal failure in pre-dialysis patients. *Am J Kidney Dis* 18:50-59, 1991
- ROTH D, SMITH RD, SCHULMAN G, *et al*: Effects of recombinant human erythropoietin on renal function in chronic renal failure predialysis patients. *Am J Kidney Dis* 24:777-784, 1994
- TEPLAN V, SCHUCK O, KNOTEK A, *et al*: Enhanced metabolic effect of erythropoietin and keto acids in CRF patients on low-protein diet: Czech multicenter study. *Am J Kidney Dis* 41(Suppl 3):S26-S30, 2003
- KLEINMAN KS, SCHWEITZER SU, PERDUE ST, *et al*: Anemia in predialysis patients and its effect on renal function double-blind, placebo-controlled trial. *Am J Kidney Dis* 14:486-495, 1989
- KURIYAMA S, TOMONARI H, YOSHIDA H, *et al*: Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in non-diabetic patients. *Nephron* 77:177-185, 1997
- BENNETT WM: A multicenter clinical trial of epoetin beta for anemia of end-stage renal disease. *J Am Soc Nephrol* 1:990-998, 1991
- CLYNE N, JOGESTRAND T: Effect of erythropoietin treatment on physical exercise capacity and on renal function in predialytic uremic patients. *Nephron* 60:390-396, 1992
- GARCIA DL, ANDERSON S, RENKE HG, BRENNER BM: Anemia lessens and its prevention with recombinant human erythropoietin worsens glomerular injury and hypertension in rats with reduced renal mass. *Proc Natl Acad Sci USA* 85:6142-6146, 1988
- NATIONAL KIDNEY FOUNDATION: Kidney Dialysis Outcomes Quality Initiative clinical practice guidelines for the treatment of anemia of chronic renal failure. *Am J Kidney Dis* 30(Suppl 3):S192-S240, 1997
- NATIONAL KIDNEY FOUNDATION: NKF-K/DOQI clinical practice guidelines for anemia of chronic kidney disease. *Am J Kidney Dis* 37(Suppl 1):S182-S238, 2001
- WORKING PARTY FOR EUROPEAN BEST PRACTICE GUIDELINES for the management of anemia in patients with chronic renal failure. *Nephrol Dial Transplant* 14(Suppl 5):S1-S50, 1999
- VALDERRABANO F, HORL WH, JACOBS C, *et al*: European survey on anaemia management (ESAM). *Nephrol Dial Transplant* 15(Suppl 4):S1-S76, 2000
- VALDERRABANO F, HORL WH, MACDOUGALL IC, *et al*: Pre-dialysis survey on anaemia management. *Nephrol Dial Transplant* 18:89-100, 2003
- HORL WH, MACDOUGALL IC, ROSSERT J, *et al*: Predialysis survey on anaemia management: Patient referral. *Am J Kidney Dis* 41:49-61, 2003
- MATSUMURA M, NOMURA H, KONI I, MABUCHI H: Angiotensin-converting enzyme inhibitors are associated with the need for increased recombinant human erythropoietin maintenance doses in hemodialysis patients. *Nephron* 77:164-168, 1997
- ALBITAR S, GENIN R, FEN-CHONG M, *et al*: High dose enalapril impairs the response to erythropoietin treatment in haemodialysis patients. *Nephrol Dial Transplant* 13:1206-1210, 1998
- MACDOUGALL IC: The role of ACE inhibitors and angiotensin II receptor blockers in the response to epoetin. *Nephrol Dial Transplant* 14:1836-1841, 1999
- The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 24:2413-2446, 1997
- MARONI BJ: Protein restriction in the pre-end-stage renal disease (ESRD) patient: Who, when, how, and the effect on subsequent ESRD outcome. *J Am Soc Nephrol* 9(Suppl 12):S100-S106, 1998
- CASADEVALL N, NATAF J, VIRON B, *et al*: Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 346:469-475, 2002
- ECKARDT KU, CASADEVALL N: Pure red-cell aplasia due to antierythropoietin antibodies. *Nephrol Dial Transplant* 18:865-869, 2003
- PICKETT JL, THEBERGE DC, BROWN WS, *et al*: Normalizing hematocrit in dialysis patients improves brain function. *Am J Kidney Dis* 33:1122-1130, 1999
- METRY G, WIKSTROM B, VALIND S, *et al*: Effect of normalization of hematocrit on brain circulation and metabolism in hemodialysis patients. *J Am Soc Nephrol* 10:854-863, 1999
- McMAHON LP, McKENNA MJ, SANGKABUTRA T, *et al*: Physical performance and associated electrolyte changes after haemoglobin normalization: A comparative study in haemodialysis patients. *Nephrol Dial Transplant* 14:1182-1187, 1999
- MORENO F, SANZ-GUAJARDO D, LOPEZ-GOMEZ JM, *et al*: Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology. *J Am Soc Nephrol* 11:335-342, 2000
- HAYASHI T, SUZUKI A, SHOJI T, *et al*: Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. *Am J Kidney Dis* 35:250-256, 2000
- PORTOLES J, TORRALBO A, MARTIN P, *et al*: Cardiovascular effects of recombinant human erythropoietin in predialysis patients. *Am J Kidney Dis* 29:541-548, 1997
- FINK J, BLAHUT S, REDDY M, LIGHT P: Use of erythropoietin before

- the initiation of dialysis and its impact on mortality. *Am J Kidney Dis* 37:348–355, 2001
31. FINE LG, BANDYOPADHAY D, NORMAN JT: Is there a common mechanism for the progression of different types of renal diseases other than proteinuria? Towards the unifying theme of chronic hypoxia. *Kidney Int* 57(Suppl 75):S22–S26, 2000
 32. SCHRIER RW, SHAPIRO JI, CHAN L, HARRIS DC: Increased nephron oxygen consumption: Potential role in progression of chronic renal disease. *Am J Kidney Dis* 23:176–182, 1994
 33. KAGEDAL K, JOHANSSON U, OLLINGER K: The lysosomal protease cathepsin D mediates apoptosis induced by oxidative stress. *FASEB J* 15:1592–1594, 2001
 34. YANG B, JOHNSON TS, THOMAS GL, et al: Apoptosis and caspase-3 in experimental anti-glomerular basement membrane nephritis. *J Am Soc Nephrol* 12:485–495, 2001
 35. CARLINI RG, ALONZO EJ, DOMINGUEZ J, et al: Effect of recombinant human erythropoietin on endothelial cell apoptosis. *Kidney Int* 55:546–553, 1999
 36. AKIMOTO T, KUSANO E, INABA T, et al: Erythropoietin regulates vascular smooth muscle cell apoptosis by a phosphatidylinositol 3 kinase-dependent pathway. *Kidney Int* 58:269–282, 2000
 37. WESTENFELDER C, BIDDLE DL, BARANOWSKI RL: Human, rat, and mouse kidney cells express functional erythropoietin receptors. *Kidney Int* 55:808–820, 1999
 38. HEBERT LA, WILMER WA, FALKENHAIN ME, et al: Renoprotection: One or many therapies? *Kidney Int* 59:1211–1226, 2001
 39. BRENNER BM, COOPER ME, ZEEUW D, et al: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001
 40. JAFAR TH, SCHMID CH, LANDA M, et al: Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 135:73–87, 2001
 41. ABU-ALFA AK, CRUZ D, PERAZELLA MA, et al: ACE inhibitors do not induce recombinant human erythropoietin resistance in hemodialysis patients. *Am J Kidney Dis* 35:1076–1082, 2000