Clinical Nephrology, Vol. 44 No. 3 – 1995 (201–208)

The use of epoetin beta in anemic predialysis patients with chronic renal failure

K. M. KOCH[1], R. A. P. KOENE[2], D. MESSINGER[3], O. QUARDER[3] and P. SCIGALLA[3]

[1]Medizinische Hochschule Hannover, Hannover, Germany, [2]Academisch Ziekenhuis Nijmegen, Nijmegen, Netherlands, [3]Boehringer Mannheim GmbH, Mannheim, Germany

Abstract. Two clinical studies were conducted to investigate the efficacy and safety of epoetin beta in 26 anemic predialysis patients. Epoetin beta was administered subcutaneously either daily or thrice weekly. Mean duration of treatment was 211 days (interquartile range: 105 to 350 days). Results: Renal anemia could be corrected and the regular transfusion need could be eliminated in all patients. There was no difference in the dose requirement per week between daily and thrice weekly administration of epoetin beta. Regarding the entire study population, there was no acceleration of the progression of renal failure during epoetin beta treatment nor were there any notable changes in laboratory values other than retention values. Epoetin beta was safe and well tolerated; the most important adverse event was the development or aggravation of hypertension.

Key words: erythropoietin – predialysis – anemia

Introduction

Since the mid-eighties, recombinant human erythropoietin (rhEPO) has been used successfully to correct renal anemia and to eliminate the chronic need for transfusions in patients with end-stage renal failure (ESRF) [Bommer et al. 1988, Eschbach et al. 1991, Samtleben et al. 1991, Scigalla et al. 1990, Canadian Erythropoietin Study Group 1988 and 1990]. As renal anemia is frequently very pronounced even in the compensated stage of chronic renal failure, attempts were made to use rhEPO to correct renal anemia in predialysis patients [Frenken et al. 1989, Lim et al. 1990, Eschbach et al. 1989]. Irrespective of uremia, an increase in packed cell volume, and thus blood viscosity, will cause a greater rise of efferent than of afferent vascular resistance in the glomerulus, because the efferent arterioles are smaller in caliber and have a greater length than the afferent arterioles. The result is a rise in glomerular intracapillary pressure, independnt of the patient's systemic blood pressure. This is reflected in the clinical findings that glomerular filtration fraction rises when polycythemia is induced and decreases after phlebotomy [Koene and Frenken 1992]. There were concerns that the rise in glomerular transmembrane pressure would result in destruction of renal structure, glomerulosclerosis and ultimately in the acceleration of chronic renal failure. The initial data from animal experiments appeared to confirm this hypothesis [Myers et al. 1975, Gretz et al. 1987].

In these studies however, a possible influence of systemic blood pressure could not be excluded as the blood pressure of the animals treated with rhEPO was distinctly higher than in the controls [Garcia et al. 1988]. These animal experiments were therefore repeated with monitoring of blood pressure. This study showed that antihypertensive treatment prevented an acceleration of the progression of renal failure in the animals treated with rhEPO [Ruedin et al. 1991].

The results of the pilot clinical studies in predialysis patients with normal blood pressure (with or without antihypertensive therapy) showed that an increase in PCV to values around 38% did not result in a significant change in kidney function [Lim et al. 1990, Eschbach et al. 1989; Koene and Frenken 1990].

Two multicenter studies were conducted with similar designs except for the frequency of administration of epoetin beta (a recombinant human erythropoietin). The aims of both studies were:

- to estimate the epoetin beta dose required to reach and to maintain the target PCV,
- to investigate the effect of daily or thrice weekly, s.c. administration of epoetin beta on renal anemia in terms of changes in PCV, red blood cell count, transfusion need and iron metablism parameters,
- to evaluate the effect of epoetin beta on the progression of renal failure, and
- to determine the clinical tolerability of epoetin beta in uremic predialysis patients with anemia.

Received May 19, 1995; in revised form June 29, 1995

Correspondence to O. Quarder, Abt. VA-MKP, Sandhofer Straße 116, D-68305 Mannheim, Germany

Methods

Patients and study design

Since the efficacy of s.c. rhEPO in uremic dialysis patients had already been demonstrated, double-blind, placebo-controlled studies were not considered ethically justifiable. Therefore both studies were conducted without a control group.

Inclusion criteria

Adult predialysis patients with renal anemia (PCV < 30 vol %) and stable chronic renal failure. A prerequisite for the enrollment of the patients in the study was the availability of 8 to 10 serum creatinine values in the patients' medical records over the last 1 to 4 years.

Primary exclusion criteria

Epilepsy, thrombocytosis, poorly controlled hypertension, iron, vitamin B_{12} or folic acid deficiency, malignant tumor, acute or chronic infections.

Dose regimen

The patients in one study received epoetin beta daily at first and the patients in the other study received epoetin beta three times a week. The reason for the daily administration in the first trial was the observation from a pilot study by Granolleras et al. [1991] that the dose could be reduced by daily rhEPO administration. However, this hypothesis was not confirmed [Bommer et al. 1991], and therefore an amendment was made to the study protocol, allowing the investigators to choose administration three times per week.

The initial dosage of epoetin beta s.c. was set as follows:

≤ 75 kg body weight: 3 × 1000 IU per week or 7 × 500 IU per week

> 75 kg body weight: 3 × 2000 IU per week or 7 × 1000 IU per week

During the correction phase, the patients reported to the investigators every two weeks.

If the PCV increase was < 3% after 6 weeks, the dose was to be increased by 500 IU epoetin beta in patients with daily administration and by 1000 IU epoetin beta in patients with administration three times a week. This was to be repeated in 4-week intervals until the target PCV of 33–37% was attained. The individual target PCV was reached if the individual increase of PCV, compared to the mean value of the three PCV values in the run-in phase, was at least 7% and if no blood transfusions were given in the preceding 4 weeks.

On achieving the target PCV (end of correction phase), the last required epoetin beta dose was reduced by 500 IU in patients with daily administration and by 1000 IU in patients receiving epoetin beta three times a week. In patients who reached the target PCV with 500 or 1000 IU, the epoetin beta dose was halved to 250 or 500 IU. During the maintenance phase the individual epoetin beta doses were adjusted according to the course of PCV. The patients reported to the investigators every 4 weeks.

Determined variables

During the studies, the following variables were determined: body weight, blood pressure, hemoglobin, PCV, erythrocytes, reticulocytes, platelets, leucocytes and differential blood count; creatinine, urea, potassium, sodium, phosphate, calcium, alkaline phosphatase, transaminases, total protein, albumin, prothrombin time, PTT, iron, ferritin, transferrin, EPO serum levels and anti-EPO antibodies.

Statistical analysis

The two studies were analyzed together, because the study design and the study variables were identical. For primary variables, study analysis was stratified by administration frequency.

The PCV increase per week for the first six weeks of the correction phase (without a dose increase) and for the total correction phase (primary variable) were calculated individually as the difference between the final value of the respective phase minus the baseline value, divided by the individual number of weeks.

The primary variable of the maintenance phase was the individual mean epoetin beta dose per week to maintain the corrected PCV. The individual maintenance dose was estimated by the mean dose in the maintenance phase excluding the first 90 days.

The slope of the reciprocal of serum creatinine versus time was determined by linear regression methods for each patient before and after the start of epoetin beta treatment. Two-sided Wilcoxon signed rank tests on the differences of the slopes were used to analyze the effect of epoetin beta treatment on progression of renal failure in all patients and in the various subgroups.

Results

275 uremic predialysis patients with distinct hypogenerative anemia were enrolled (242 patients in Germany, 33 patients in the Netherlands).

Nine patients dropped out of the study during the run-in phase (need for dialysis [n = 3], personal reasons [n = 6]). 266 patients were treated with epoetin beta and analyzed for safety. Patients were excluded from the efficacy analysis if the mean PCV value in the run-in phase was above 30% without blood transfusions (n = 15), if they were treated with epoetin beta for less than four weeks (n = 18), or if the initial administration frequency deviated from the study plan. (n = 8 patients treated neither 3 times nor 7 times a week). Therefore 225 patients fullfilled the criteria for the efficacy analysis. The underlying diseases, basic demographic data and laboratory parameters are summarized in Table 1.

Efficacy

The median duration of therapy in the 225 patients evaluated for efficacy was 211 days (interquartile range: 105 to 350 days); 129 patients were treated for more than half a year and 54 patients for more than one year.

The renal anemia was corrected by epoetin beta in both frequency groups. During the first 6 weeks the increase in PCV was 0.403% (median) with treatment three times a week and 0.648% (median) with treatment seven times a week. When calculated for the whole correction phase, the increases in PCV were 0.519% (median) and 0.515% (median), respectively.

During the correction phase, the PCV rose from 25.6% to 33.7% (median) in the group treated three times a week and from 25.6 to 33.0% (median) in the group treated seven times a week. The PCV remained stable during the maintenance phase when the dosage was adjusted individually.

The median epoetin beta dose required to maintain the target PCV was 55 U/kg body weight per week (three times a week) and 61 U/kg body weight per week (seven times a week). The median maintenance dose for the total

Table 1 Underlying diseases, basic demographic data and laboratory parameters for uremic predialysis patients treated with rhEPO (median, interquartile ranges)

Efficacy population

		Treatment		
		3 ×/week	7×/week	total
Sex	Male	n = 17	n = 67	n = 84
	Female	n = 31	n = 110	n = 141
Age (years)		54 (43–68)	56 (46–65)	56 (46–66)
PCV (%)		25.6 (23.7–27.0)	25.6 (23.7–27.7)	25.6 (23.7–27.4)
Hb (g/dl)		8.6 (8.0–9.0)	8.6 (7.8–9.1)	8.6 (7.8–9.1)
Corrected reticulocytes (‰)		6.8 (4.1–9.9)	7.3 (5.1–10.2)	7.2 (5.0–10.2)

	Treatment					
	3 ×/week		7×/week		total	
Underlying disease	n	%	n	%	n	%
Chronic glomerulonephritis	7	14.6	28	15.8	35	15.6
Diabetic nephropathy	2	4.2	36	20.3	38	16.9
Hereditary nephropathy	7	14.6	9	5.1	16	7.1
Interstitial nephritis	10	20.8	19	10.7	20	12.9
Nephrosclerosis	1	2.1	8	4.5	9	4.0
Pyelonephritis	3	6.3	15	8.5	18	8.0
Renal failure due to chronic graft rejection	5	10.4	18	10.2	23	10.2
Unknown and other	13	27.1	44	24.9	57	25.3
Total	48	100	177	100	225	100

population was 58 U/kg body weight per week (interquartile range: 42 to 81 U/kg body weight per week).

Transfusion requirement

During the last month before enrollment into the study, 8.4% of the patients received at least one blood transfusion. This transfusion need was nearly eliminated (≤ 1% per month) after one month of treatment. Only individual patients required transfusions on single occasions for acute bleeding.

Iron stores

Of the total of 266 patients 131 received iron substitution at the start of the study. Iron substitution was initiated in 40 of 135 patients not originally receiving iron medication, i.v. in six of them. During the correction phase there was a decrease in body iron stores as a result of stimulation of erythropoiesis; the median serum ferritin fell from 143.0 μg/ml to 94.0 μg/ml and transferrin saturation fell from 20.7 to 17.5%. During the maintenance phase body iron stores recovered; the serum ferritin level increased from 79 μg/ml to 129.5 μg/ml, and transferrin saturation also showed a tendency towards baseline.

Progression of renal failure

The course of 1/serum creatinine versus time was analyzed to assess the impact of epoetin beta treatment on the progression of renal failure. With regard to the total study population, no difference could be detected when comparing the slope of 1/serum creatinine before and after epoetin beta treatment (Table 2), showing that there was no change in the rate of progression of renal failure during epoetin beta therapy compared with that before.

Analysis of patients stratified by underlying disease (Table 3, Figure 1) showed no relevant differences in the

Table 2 Regression of 1/creatinine ($\times 10^{-4}$ dl/mg) slope before and under treatment with rhEPO in anemic, uremic predialysis patients (n = 253)

	Median	Minimum	1st quartile	3rd quartile	Maximum
Before	−1.828	−58.310	−3.652	−1.001	+17.761
Under	−1.660	−37.447	−4.626	−0.353	+25.189
Δ slope	+0.303*)	−31.376	−1.858	+1.838	+83.499

Acceleration of progression (Δ slope <0) n = 115 (45.5%)
Deceleration of progression (Δ slope >0) n = 138 (54.5%)
*) Wilcoxon Signed Rank Test p = 0,8537

Table 3 Differences in slopes of 1/creatinine ($\times 10^{-4}$ dl/mg) after start minus before start of epoetin beta treatment in anemic, uremic predialysis patients

		N	Median	1. Quartile	3. Quartile	p-value*
Total		253	0.303	−1.858	1.838	0.854
Chronic glomerulonephritis		40	0.096	−1.612	1.802	0.732
Diabetic nephropathy		42	0.846	−2.166	3.274	0.398
Hereditary nephropathy		20	0.519	−0.706	2.526	0.216
Interstitial nephritis		32	0.559	−3.146	1.491	0.546
Nephrosclerosis		10	−2.191	−4.125	0.807	0.160
Pyelonephritis		21	0.957	−1.071	2.726	0.511
Renal failure due to chronic graft rejection		25	0.584	−3.857	1.838	0.824
Unknown and other		63	−0.241	−1.580	1.503	0.389
Baseline creatinine	≤4 mg%	51	0.701	−2.875	2.151	0.775
	>4 – ≤6 mg%	88	0.387	−2.655	2.102	0.941
	>6 mg%	114	0.085	−1.420	1.673	0.981
Duration of treatment >180 d		130	0.752	−0.405	1.858	0.0001
Duration of treatment >360 d		58	0.798	−0.151	1.838	0.0001

A positive slope means deceleration of the progression of renal disease
*) Wilcoxon Signed Rank Test

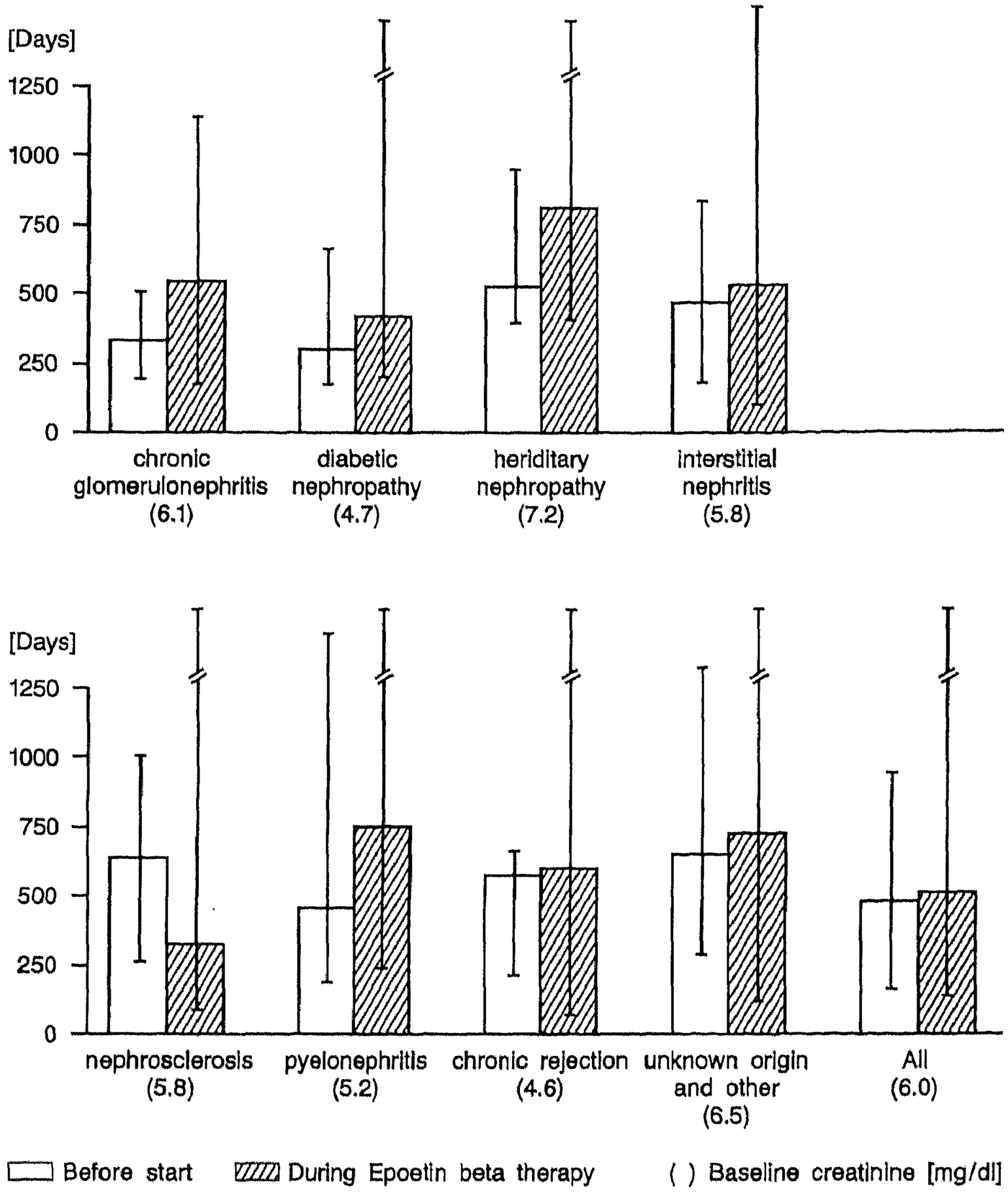

Fig. 1 Time to double the serum creatinine at day 0, using slopes before start of epoetin beta therapy and under epoetin beta therapy in anemic uremic patients (median, interquartile range)

slopes. However, in patients with nephrosclerosis, a distinct acceleration of the progression of renal failure was observed in five of the nine patients. Due to the small number of patients in this subgroup, a general conclusion cannot be drawn. Regarding baseline creatinine values, no influence on the course of progression of renal function was observed. Analysis of patients who were treated for more than half a year or more than one year with epoetin beta showed a significant deceleration of the progression of renal failure. However, it has to be considered that this population is a "positive" selection, because only patients with rather stable renal function could be kept in the study for longtime treatment.

Adverse events

90 serious adverse events were reported in 65 patients and 160 non-serious adverse events in 97 patients. 10 patients died; seven of heart failure, one of pneumonia, one of acute kidney failure and one of pulmonary edema. All the AEs leading to death were classified as unrelated to epoetin beta therapy.

Seven patients discontinued the study due to an adverse event; four were serious adverse events: one case of hypertension with clinical symptoms, two cases of cardiovascular disease and one case of subarachnoid hemorrhage. The remainder were non-serious adverse events: continuous deterioration of retention values, pruritus and headache. All adverse events classified as being possibly related to epoetin beta therapy are listed in Table 4.

The course of blood pressure was analyzed using the documented blood pressure values and antihypertensive treatment. During the correction phase two patients became hypertensive without requiring antihypertensive therapy (AHT); in 10 patients AHT was initiated and the dosage of AHT was increased in 51 patients, i.e. 24% of

Table 4 Adverse events classified as being possibly related to epoetin beta therapy

Adverse event	Number of patients	Number of AEs
Hypertension	18	20
Headache	5	6
Terminal renal failure	3	3
Shunt thrombosis	2	2
Deep-vein thrombosis	1	1
Menorrhagia	2	2
Stenocardia	2	3
Flu-like-syndrome	1	2
Deterioration in retention values	2	2
Pruritus	1	1
Vertigo, fatigue	2	2

patients showed a hypertensive reaction. During the maintenance phase, one patient became hypertensive without requiring AHT; AHT was initiated in four patients and in 35 patients the dosage was increased, i. e, 26% of patients showed a hypertensive reaction.

Except for the laboratory parameters that reflect the progression of renal failure, none of the safety laboratory parameters monitored showed any notable changes during epoetin beta.

No anti-EPO antibodies were detected.

Discussion

Efficacy of subcutaneous epoetin beta in uremic predialysis patients

In the two studies reported, therapy was started with low dosages of epoetin beta (approx. 60 IU/kg/week). The basic reasons for the low dosages were:

- There is no medical need to rapidly correct chronic renal anemia; by a moderate correction the body can adapt to the new PCV more readily and with fewer or even no side effects.
- If therapy is started with high dosages of epoetin beta the rate at which the PCV rises can be increased, but the efficacy calculated in relation to the cumulative dose of epoetin beta (= cumulative erythropoietin dose until the target PCV is reached) is reduced.

The dose regimen used in the studies is sufficient to reach a satisfactory target PCV within a reasonable time. Therefore the following dosage recommendations can be made: Start with 3 × 20 IU/kg body weight and week s.c. in the correction phase. Thereafter, the dosage may be increased every 4 weeks by 3 × 20 IU/kg body weight and week if the increase in PCV is not adequate (< 0.5% per week). In these anemic predialysis patients, no differences in the required weekly dosages were observed between the administration scheme of three times a week and daily administration of epoetin beta. The maintenance dosage was 55 IU/kg body weight per week and 61 IU/kg body weight per week, respectively. These findings correspond with published data [Eschbach et al. 1989, Scigalla et al. 1990, Graf et al. 1992].

Investigations of renal function under epoetin beta therapy in predialysis patients

One of the objectives of the studies was to investigate whether the correction of renal anemia in patients with uremia not yet requiring dialysis, leads to an acceleration in the progression of renal failure. The linear regression of the reciprocal values of serum creatinine levels before and after epoetin beta therapy was calculated for each patient. The slope of the regression line was taken as a measure of the progression of renal failure. This approach is based on the results of various studies, which showed that the reciprocal of the serum creatinine levels declines linearly with time. The decline is approximately proportional to the reduction of creatinine clearance [Walser 1990, Gretz et al. 1983]. However, when using this method one must take into account the fact that the serum creatinine level is influenced by many factors, e. g. functional and drug-induced tubular secretion of creatinine and changes in creatinine metabolism. Nevertheless, observation of the slope of the regression line is the only practical way of obtaining an indication of the progression of renal failure in the long-term.

Under epoetin beta therapy the slope of 1/creatinine tended slightly to be less steep, indicating a slower progression of renal failure compared to pretreatment time; however, this difference is not statistically significant. The result of our studies agree with data from other studies. In all these studies, some of which were conducted over one year and more, the decline in the reciprocal serum creatinine level was found to be constant, i. e. the progression of renal failure was not affected by rhEPO therapy [Frenken et al. 1989, Lim et al. 1990, Eschbach et al. 1989, Koene and Frenken 1990, Graf et al. 1992, Stone et al. 1988, Teehan et al. 1991, Abraham et al. 1990].

The above results are also confirmed by other kidney function studies [Koene and Frenken 1992, Abraham et al. 1990]. These study groups determined or calculated the glomerular filtration rate, renal plasma flow, extrarenal plasma flow and the filtration fraction before and during rhEPO therapy. They found no changes within 8 to 18 weeks of rhEPO therapy. It is worth emphasizing that the blood pressure of these patients remained normal with or without antihypertensive therapy.

Up to now only one study has been published showing a deterioration of kidney function [Onoyama et al.

1989]. In this study, kidney function was determined by means of inulin and PAH clearance before and after 4 weeks of rhEPO therapy. After an increase in PCV from 21 to 27%, a slight decrease in the extrarenal plasma flow and a slight increase in the glomerular filtration rate was found. The filtration fraction was thus significantly increased. However, it must be stressed that blood pressure rose from 171/73 mmHg to 190/105 mmHg.

To summarize, the clinical results agree with the results from animal experiments [Myers et al. 1975, Gretz et al. 1987, Garcia et al. 1988, Ruedin et al. 1991]. In both animal experiments and clinical trials, accelerated progression of renal failure was only observed when systemic blood pressure rose significantly. The increase in PCV alone did not lead to a deterioration in kidney function.

In general, no difference could be detected when comparing the progression of renal failure before treatment with that during epoetin beta treatment, nor was there an influence of the baseline state of renal failure.

Considering the groups with specific underlying renal diseases separately, a tendency towards acceleration of the progression of renal failure cannot be ruled out entirely in patients with nephrosclerosis.

Adverse events during epoetin beta in uremic predialysis patients

The evaluation of the adverse events in the safety population of 266 patients treated with epoetin beta in the two clinical trials was difficult because the patients were enrolled in studies without a placebo control and the uremic predialysis patients were polymorbid patients with an impaired function and structure of many organs.

In order to obtain an optimum assessment of safety, the individual clinical course of the patients and thus all adverse events were analyzed in consultation with the investigators and were assessed taking into account the patients' medical histories.

In dialysis patients the incidence of thromboembolic events, including shunt thrombosis, is not higher with epoetin beta therapy than without. Nevertheless, thromboembolic complications are of special interest in a therapy which leads to an increase in PCV. In the two studies available there was only one case of a deep vein thrombosis and two cases of shunt thrombosis, which therefore are regarded as being possibly related to epoetin beta therapy.

During epoetin beta therapy a total of 24% of patients in the correction phase and 26% of the patients reaching the maintenance phase had a hypertensive reaction. These results show that the effects of epoetin beta on blood pressure are similar in patients with ESRF and uremic predialysis patients. The above-mentioned incidence of hypertensive reactions is, however, undoubtedly an overestimation of the epoetin beta effect. The main reason for this is that the incidence of hypertension usually rises as renal failure progresses, mainly due to an increase in hyperhydration.

It is important to state that the antihypertensive reactions were controlled adequately by antihypertensive therapy and that serious hypertensive crises occurred only rarely. This finding is also important mainly because it was clearly demonstrated in other studies that systemic hypertension significantly accelerates the progression of renal failure [Raine 1988].

Conclusions

The results of the two multicenter studies can be summarized as follows:

- Renal anemia in uremic predialysis patients can be corrected and the need for regular transfusions eliminated with epoetin beta.
- In general, there was no acceleration of the progression of renal failure during epoetin beta therapy.
- The most important adverse event during epoetin beta therapy is the development or aggravation of hypertension. Hypertensive patients should only be treated with epoetin beta if their blood pressure is properly controlled.
- In predialysis uremic patients no clinically relevant changes are to be expected in laboratory parameters other than retention values.
- Since the risks of treatment can be identified and managed, the risk-benefit ratio of epoetin beta for renal anemia in predialysis patients is favourable.

REFERENCES

Abraham PA, Opsahl JA, Rachael KM, Asinger R, Halstenson CE 1990 Renal function during erythropoietin therapy for anemia in predialysis chronic renal failure patients. Am J Nephrol *10:* 128

Bommer J, Barth H-P, Zeier M, Mandelbaum A, Bommer G, Ritz E, Reichel H, Novack R 1991 Efficacy comparison of intravenous and subcutaneous recombinant human erythropoietin administration in hemodialysis patients. In: *Gurland HJ, Moran J, Samtleben W, Scigalla P, Wieczorek L* (eds) Contrib Nephrol. Karger, Basel, vol 88, p 136

Bommer J, Kugel M, Schoeppe W, Brunkhorst R, Samtleben W, Bramsiepe P, Scigalla P 1988 Dose-related effects of recombinant human erythropoietin on erythropoiesis. In: *Koch KM, Kuehn K, Nonnast-Daniel B, Scigalla P* (eds) Contrib Nephrol. Karger, Basel, vol 66, p 85

Canadian Erythropoietin Study Group 1988 A prospective randomized double-blind study of recombinant human erythropoetin (r-HU-EPO) in chronic hemodialysis. Kidney Int *33*

Canadian Erythropoietin Study Group: Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving hemodialysis. Br Med J *300:* 573

Eschbach JW, Kelly MR, Haley NR, Abels RI, Adamson J 1989 Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. N Engl J Med *321:* 158

Eschbach JW Egrie JC, Downing MR, Browne JK, Adamson JW 1991 The safety of Epoietin-Alpha: Results of clinical trials in the United States. In: *Gurland HJ, Moran J, Samtleben W, Scigalla P, Wieczorek L* (eds) Contrib Nephrol. Karger, Basel, vol 88, p 72

Frenken LAM, Verberckmoes R, Michielsen P, Koene RAP 1989 Efficacy and tolerance of treatment with recombinant human erythropoietin in chronic renal failure (pre-dialysis) patients. Nephrol Dial Transplant *4:* 782

Garcia DL, Anderson S, Rennke HG, Brenner BM 1988 Anemia lessens and its prevention with recombinant erythropoietin worsens glomerular injury and hypertension in rats with reduced renal mass. Proc Natl Acad Sci *85:* 6142

Graf H, Barnas U, Stifter S et al. 1992 Effectiveness and safety of recombinant human erythropoietin in predialysis patients. Nephron *61:* 399

Granolleras C, Branger B, Shaldon S, Nonnast-Daniel B, Koch KM, Pollok M, Baldamus CA 1991 Subcutaneous erythropoietin: A comparison of daily and thrice weekly administration. In: *Gurland HJ, Moran J, Samtleben W, Scigalla P, Wieczorek L* (eds) Contrib Nephrol. Karger, Basel, vol 88, p 144

Gretz N, Manz F, Strauch M 1983 Predictability of the progression of chronic renal failure. Kidney Int *24,* Suppl 15: 2

Gretz N, Lasserre JJ, Meisinger E, Strauch M, Waldherr R, Kraft K, Weidler A 1987 Potential side-effects of erythropoietin. Lancet *I:* 46

Koene RAP, Frenken LAM 1990 Does treatment of predialysis patients with recombinant human erythropoietin compromise renal function? In: *Schaefer RM, Heidland A, Hoerl WH* (eds) Contrib Nephrol. Karger, Basel, vol 87, p 105

Koene RAP, Frenken LAM 1992 Role of rHuEPO in treatment of uremic anemia prior to end-stage renal disease. Kidn Int *42,* Suppl 38: 142

Lim VS, Fangman J, Flanigan MJ, DeGowin RL, Abels RT 1990 Effect of recombinant human erythropoietin on renal function in humans. Kidney Int *37:* 131

Myers BD, Deen W, Robertson CR, Brenner BM 1975 Dynamics of glomerular ultrafiltrtion in the rat. VIII. Effects of hematocrit. Circ Res *36:* 425

Onoyama K, Kumagai H, Takeda K, Shimamasu K, Fujishima M 1989 Effects of human recombinant erythropoietin on anaemia, systemic haemodynamics and renal function in predialysis renal failure patients. Nephrol Dial Transplant *4:* 966

Raine AE 1988 Hypertension, blood viscosity and cardiovascular morbidity in renal failure: Implications of erythropoetin therapy. Lancet *I:* 97

Ruedin P, Lemoine R, Boillie M, Leslie M, Kaufer A 1991 Prevention of accelerated progression of renal failure induced by recombinant human erythropoietin in the rat remnant kidney. (Abstract) Nephrol Dial Transpl *6:* 828

Samtleben W, Ehmer B, Lutz-Knochenhauer I, Hagmann Ch, Scigalla P, Gurland HJ 1991 Side effects during recombinant human erythropoietin therapy in 2000 ESRD patients. In: *Gurland HJ, Moran J, Samtleben W, Scigalla P, Wieczorek L* (eds) Contrib Nephrol. Karger, Basel, vol 88, p 107

Scigalla P, Messinger D, Wieczorek L 1990 Reasons for differences in dose requirements of recombinant human erythropoietin in haemodialysis patients. In: *Tanaka H* (ed) Contrib Nephrol. Karger, Basel, vol 82, p 55

Scigalla P, Wieczorek L, Bicker U 1990 Treatment of renal anemia with recombinant human erythropoietin: European experience. In: *Garnick MB* (ed) Erythropoietin in clinical applications: an international perspective. Marcel Dekker, New York, p 141

Stone WJ, Graber SE, Krantz SB, Dessypris EM, O'Neil VL, Olsen N, Pincus TP 1988 Treatment of the anemia of predialysis patients with recombinant human erythropoietin: A randomized, placebo-controlled trial. Am J Med Sciences *296;* 171

Teehan B, Krantz SB, Stone WA, Graber S, Abels R et al. 1991 Double-blind, placebo-controlled study of the therapeutic use of recombinant human erythropoietin for anemia associated with chronic renal failure in predialysis patients. Am J Kidn Dis *18:* 50

Walser M 1990 Progression of chronic renal failure in man. Kidney Int 37: 1195