Does treatment of pre-dialysis patients with recombinant-human erythropoietin compromise renal function?

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¿COMPROMETE LA FUNCION RENAL EL TRATAMIENTO CON ERITROPOYETINA EN ENFERMOS EN PREDIALISIS?

RESUMEN

En los enfermos con insuficiencia renal crónica la anemia suele aparecer cuando el aclaramiento de creatinina cae por debajo de 25 ml/min. Estudiamos la eficacia y posibles efectos indeseables del tratamiento con r-HuEPO en enfermos en prediálisis durante la corrección de la anemia con una atención especial a las modificaciones en la función renal y en los parámetros hemodinámicos. A 24 enfermos con CCr entre 5 y 22 ml/min se les distribuyó de forma randomizada en tres grupos con dosis de 50, 100 y 150 unidades/kg durante diez semanas, a razón de tres dosis semanales, para pasar posteriormente a una pauta de mantenimiento de una vez por semana.

El tratamiento con r-HuEPO aumentó el hematócrito en todos los grupos, aunque en el de menor dosis lo hizo más lentamente. No se registraron variaciones significativas en las cifras de presión arterial media, si bien el consumo de hipotensores se incrementó significativamente a las diez semanas de tratamiento. Las cifras medias de creatinina y aclaramiento no se modificaron, y tampoco lo hicieron el flujo plasmático ni el filtrado glomerular.

Los resultados de este y otros estudios similares ponen de manifiesto que los enfermos en prediálisis pueden beneficiarse igualmente del tratamiento con eritropoyetina. Se precisan estudios a largo plazo para valorar los efectos de este tratamiento sobre la función renal.

SUMMARY

In patients with chronic renal failure, anemia usually develops when the creatinine clearance has decreased below 25 ml/min. We studied the efficacy and safety of r-HuEPO treatment in pre-dialysis patients during correction of the anemia with special attention to changes in renal function and renal hemodynamics. Twenty four patients with CCr from 5-22 ml/min were randomly assigned to 3 dosage groups (50, 100 and 150 units/kg) during 10 weeks, 3 times a week and after that once a week on a maintenance regime.

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Treatment with r-HuEPO increased hematocrit in all groups, but with different rates. There were no significant changes in mean arterial blood pressure, although antihypertensive drugs were prescribed more frequently after 10 weeks of therapy. The mean serum creatinine and creatinine clearance did not change significantly during the correction phase. Effective renal plasma flow and glomerular filtration rate were not significantly modified.

The results of this and other studies show that anemic pre-dialysis patients will also benefit from treatment with r-HuEPO. Long term studies are required to assess the effect of this treatment on renal function.

Introduction

Recombinant-human erythropoietin (r-HuEPO) has proved to be an effective drug in the treatment of anaemia in patients with end-stage renal failure undergoing chronic haemodialysis of peritoneal dialysis. In many patients with chronic renal failure not yet on dialysis anaemia starts to develop when the creatinine clearance has decreased below 25 ml per min. With the further progression of renal failure signs and symptoms of anaemia appear that are not different from those in dialysis patients. It can therefore be expected that treatment with r-HuEPO will also be of benefit to anaemic pre-dialysis patients as it is for the dialysis-dependent population.

The most important question that needs to be answered is whether correction of the haematocrit to almost normal values in these patients will be hazardous to the kidney and will increase the rate of progression of renal failure. Experiments in animals have demonstrated that an acute increase of the haematocrit causes a rise in glomerular capillary pressure [1]. As pointed out by Brenner a constantly elevated glomerular capillary pressure may be responsible for the most often unrelenting progressive course of renal failure by causing focal glomerulosclerosis [2]. A few studies in rats treated with r-HuEPO have indeed shown that such a treatment may accelerate the development of renal failure [3, 4]. Before r-HuEPO can be prescribed routinely to anaemic patients with chronic renal failure not yet on dialysis, it is thus of utmost importance to establish whether a damaging effect will also occur in the clinical situation.

We have studied the efficacy and safety of r-HuEPO treatment in pre-dialysis patients during correction of the anaemia and during maintenance therapy. Special attention was paid to changes in renal function and renal haemodynamics. Together with a review of the available literature on pre-dialysis patients this will be the subject of the current report.

Patients and methods

Twenty-four patients were included in the trial: 13 females and 11 males, aged 23 to 68 years. They all had a known history of progressive chronic renal failure, whereas other clinically significant diseases were absent. Endogenous creatinine clearances ranged from 5 to 22 ml/min. All patients were anaemic with haemoglobin ranging from 5.3 to 10.2 g/dl and haematocrit from 0.16 to 0.30 lg/l. The anaemia could not be attributed to other causes. Hypertension was either absent or medically controlled. The patients received stable doses of oral iron supplementation (up to 200 mg of elemental iron per day) and folic acid for 2 weeks before study entry and for the duration of the study. The patients were randomly assigned to three dosage groups each containing eight patients. The doses were 50, 100 and 150 units of r-HuEPO per kilogram of body weight (U/kg) per injection. After a two week period of base-line measurements the patients were given intravenous injections of r-HuEPO three times a week for eight weeks. At the completion of this eight week study, or whenever a patient's haematocrit exceeded the target values (37 % for female, 39 % for male) by two percentage points, the patient was entered into a maintenance study. During the maintenance phase r-HuEPO was injected intravenously once a week. The starting dose was three times the dose given per injection during the correction phase, adjusted for response. Haemoglobin, haematocrit, and blood cell counts were determined twice weekly in the correction phase and at least once monthly in the maintenance phase. Blood pressure (supine, before venepuncture) was monitored before each dosing.

The serum creatinine values of the individual patients during the two years preceding the study were retrieved from the clinical records. The reciprocal of serum creatinine can be used to estimate the rate of deterioration of the glomerular filtration rate. We used the equivalent 1000 divided by serum creatinine (μmol/l) to calculate this rate. When sufficient values of serum creatinine recorded before therapy were available, linear regression was applied to the reciprocal of serum creatinine versus time (days) data. In eight patients we were able to determine haemodynamic parameters before and after eight weeks of treatment with r-HuEPO. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR)

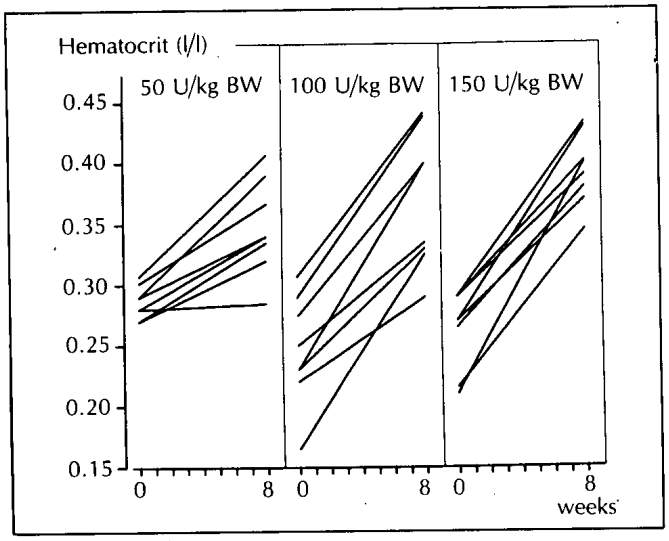

Fig. 1.—Effect of three different dosages of recombinant-human erythropoietin on the mean haemoglobin levels in pre-dialysis patients (correction phase).

were determined using standard renal clearance techniques with continuous infusion of para-aminohippurate and inulin.

Differences from base-line levels within groups were evaluated using Student's t-test for paired data. The slopes of the regression lines obtained before and after the start of r-HuEPO therapy were compared with analysis of covariance. Comparison of several groups of data was done with analysis of variance. A P value of less than 0.05 was considered significant. Unless otherwise stated all values are expressed as means ± standard deviation.

Results

Treatment with r-HuEPO increased haematocrit in all dosage groups (fig. 1). An increase in haematocrit was observed in all patients, except in one in the 50 U/kg dosage group. The rate of increase in haematocrit was significantly smaller in the 50 U/kg dosage group, whereas rates were comparable in the two other dosage groups. Anaemia was corrected during the eight week study period in 87.5 % of patients in the 150 U/kg dosage group, and in 50 % of patients in the two lower dosage groups. This difference was not significant. In the two highest dosage groups an increase in reticulocyte counts was seen within one week of the start of the treatment. In these groups there was also a small but significant increase in thrombocyte counts. However, the increase was transient and values never exceeded the upper limit of the normal range.

The mean subjective scores for ability-to-do-work and energy level increased in all dosage groups during r-HuEPO treatment.

During the correction phase there were no significant changes in mean arterial pressure (MAP) in either of the three dose groups. Also, mean systolic and diastolic blood pressure and MAP did not change during the maintenance phase. Additional data from the maintenance phase revealed that the mean number of antihypertensive drugs prescribed increased significantly from 1.5 ± 1.1 before the start of r-HuEPO treatment to 2.0 ± 1.4 after 10 weeks of therapy ($P < 0.05$). This was caused by the increase of antihypertensive medications in 9 of 18 previously hypertensive patients. The remaining six patients who were normotensive at the start of the therapy reamined so during the whole trial period.

None of the 24 patients required haemodialysis during the first eight weeks of the study period. The mean serum creatinine and creatinine clearances did not change significantly during the correction phase. Additional information on the evolution of renal function can be derived from the six month maintenance study that followed the correction phase. In 14 patients sufficient data could be obtained to compare the time course of renal function (as measured by 1000/creatinine versus time) before and during r-HuEPO therapy. The periods reviewed included 20 months before and seven months during therapy. There were no significant differences between the slopes of 1000/creatinine versus time before therapy (−0.036 ± 0.002) and during therapy (−0.031 ± 0.004), indicating that there was no significant change in the progression of renal failure during the observation period.

In addition to the measurements of serum creatinine a special study on renal haemodynamics was done. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were determined in eight patients before and after 12 weeks of treatment with r-HuEPO. The results of this study are shown in figure 2. There were no significant changes of these parameters after 12 weeks of treatment. Moreover, the filtration fraction (FF) and the fractional excretion excretion of albumin did not change significantly.

Discussion

The results of this therapeutic trial in pre-dialysis patients demonstrate that r-HuEPO treatment can effectively correct anaemia in these patients. This is in accord with the results obtained by three other groups that have so far published their experience[5-7]. A summary of all studies is given in table I.

The haematologic response does not appear to differ from that in patients with end-stage renal failure who are treated by chronic dialysis. In almost all cases in

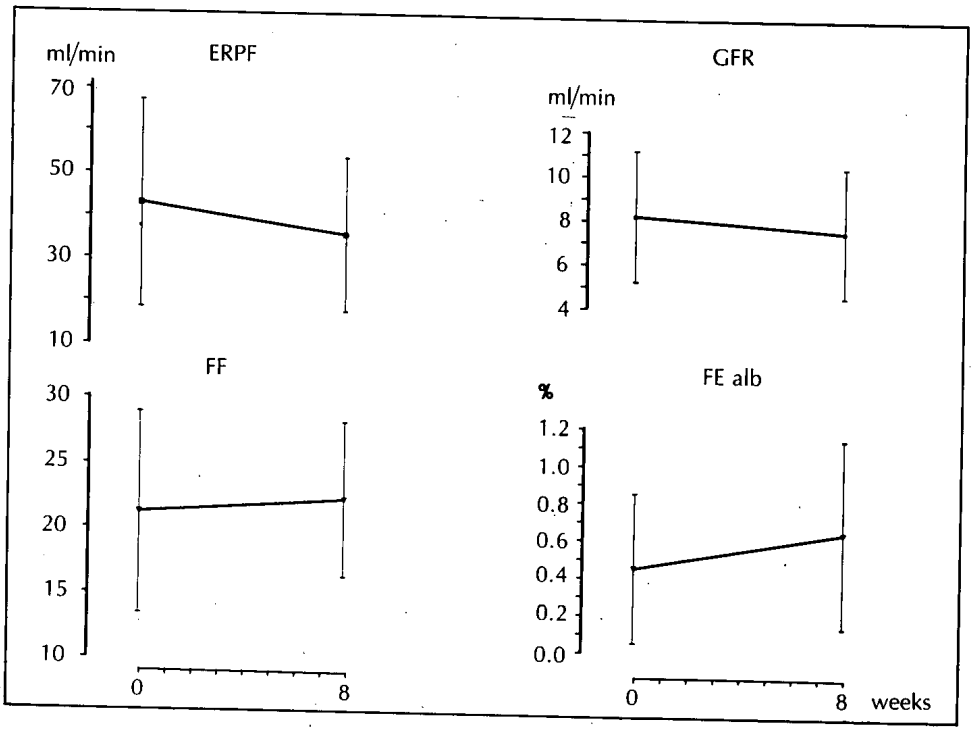

Fig. 2.—Renal haemodynamic studies in 8 patients before and after 8 weeks of treatment with recombinant-human erythropoietin.

which a response was absent this could be attributed to intercurrent illnesses or early withdrawal from the trials. All studies show that treatment with r-HuEPO improves the patients' subjective ratings of well-being, ability-to-do-work, and energy level. The exact dose requirements for r-HuEPO in pre-dialysis patients cannot be simply derived from these studies. There may be considerable differences between individual patients. A dose of 50 U/kg, three times a week intravenously, seems to be the preferable approach during the correction phase. In the study that included a maintenance phase of six months the dose requirements decreased. This may, at least partly, be related to the change from intravenous to subcutaneous administration. There is preliminary evidence that during subcutaneous administration dose requirements are about 30 % less than during intravenous administration [8]. More experience is needed before the exact dosing schedule and the optimal route of administration can definitively be established.

A rise in blood pressure during treatment with r-HuEPO has been observed in both normotensive and hypertensive dialysis patients. Since regulation of volume balance differs between haemodialysis patients and pre-dialysis patients, it is not self-evident that the latter patients will show a similar untoward blood pressure response to r-HuEPO therapy. The experience in haemodialysis patients suggests changes, in case they occur, will become mostly manifest during the correction phase of the anaemia. In the study of Stone et al. [5] hypertension developed in two of 10 pre-dialysis patients. In one patient it was transient whereas in the other patient accelerated hypertension occurred that made hospitalization necessary. Lim et al. [6] did not observe changes in mean systolic or diastolic blood pressure after eight weeks of treatment in 11 pre-dialysis patients. However, they increased antihypertensive medication in three patients. In the study of Eschbach et al. [7] additional antihypertensive medications were required in nine of 14 previously hypertensive patients. Hypertension developed in two of three patients who were normotensive before therapy. In our study hypertension developed in none of the normotensive patients, but in half of the previously hypertensive patients antihypertensive medications were increased during the study. The highest incidence of hypertensive events occurred among patients with the greatest rates of change in haematocrit. These results suggest that, without additional antihypertensive treatment, blood pressure will rise in pre-dialysis patients. Careful monitoring of blood pressure and adjustment of the antihypertensive regime, especially during the correction phase of the anaemia, are therefore indicated when pre-dialysis patients are treated with r-HuEPO. Serious problems with blood presure can probably largely be prevented by a relatively slow correction of the anaemia, because this gives more

Table I. Summary of haematologic responses during the correction phase

Reference	No. of patients	Duration (weeks) *	Haematocrit	
			Start	End
Stone et al. [5]	8	8	0.32	0.40
Lim et al. [6]	11	8	0.27	0.38
Eschbach et al. [7]	17	8-12	0.27	0.37
This study	24	8	0.26	0.37

* Or until the target haematocrit was reached.

time for haemodynamic adaptation and it provides better opportunity for timely adjustment of the antihypertensive medication.

In experimental studies in r-HuEPO-treated rats that underwent five-sixths nephrectomy to induce renal failure, the progression of the disease was accelerated when compared to untreated five-sixths nephrectomized controls[3, 4]. García et al.[4] demonstrated that in these rats an increase in intraglomerular capillary pressure developed, which the investigators thought to be a consequence of an increased vascular resistance due to the rise in whole blood viscosity. These observations have raised concern about the use of r-HuEPO in pre-dialysis patients. However, one should realize that in the rat experiments there was also a considerable increase in systemic blood pressure during r-HuEPO treatment. It seems likely that this hypertension played an important role in accelerating the progression of renal failure in these animals, since hypertension is known to be important in determining the rate of development of renal damage in this model.

In the studies with r-HuEPO in pre-dialysis patients, all investigators have tried to monitor blood pressure meticulously and to adjust antihypertensive treatment when necessary. So far, the experience suggests that under these conditions detrimental effects on renal function as observed in rats do not occur in man. In the studies of Lim et al.[6] and of Eschbach et al.[7] creatinine clearances did not decrease significantly after eight weeks of r-HuEPO treatment. During the correction phase of our study, there was also no significant decrease in creatinine clearances. Our renal haemodynamic studies confirmed the conclusions derived from the creatinine clearance data. Therefore, it can be safely concluded that a relatively rapid correction of the anaemia in 8-12 weeks does not have acute detrimental effects on renal function. With regard to the effects of long-term correction of the anaemia on renal function, the available data do not permit definitive conclusions. Eschbach et al. compared the slopes of the reciprocal serum creatinine values versus time curves during r-HuEPO therapy (median follow-up 12 months) with the pre-treatment slopes in 17 patients, and found no significant change[7].

In our study there was no significant change in the rate of progression of renal failure in 14 patients during seven months of r-HuEPO therapy. However, small changes in the rate of progression will be difficult to detect. Ideally, a placebo-controlled trial with a prolonged observation period in a large group of pre-dialysis patients would be necessary to detect such changes. However, it is highly questionable whether a placebo-treated control group can be recruited. A possible alternative will be to study a large group of predialysis patients in whom pre-treatment follow-up is long enough to permit calculations of the rate of progression of their renal failure and compare these with the progression rate during one or several years of r-HuEPO treatment.

The results of these first studies in anaemic pre-dialysis patients demonstrate that this group will also benefit from treatment with r-HuEPO. Long-term studies are required to assess the effect of this treatment on renal function. On the basis of the current information it can be expected that a possible detrimental effect on renal function will not be very large. Moreover, the benefits of treatment with r-HuEPO will probably outweigh a possible adverse effect on renal function. Therefore, pre-dialysis patients seem to be eligible for treatment with r-HuEPO, provided that blood pressure is carefully monitored and controlled.

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