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Therapy with Recombinant Human Erythropoietin (rEPO) in Hemodialysis Patients with Transfusion-Dependent Anemia. Report of a European Multicenter Trial

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SUMMARY

The effect of recombinant human erythropoietin (rEPO) on transfusion-dependent anemia was investigated in a multicenter trial including 351 hemodialysis patients of 59 centers. The average increase of hematocrit was 1.0 vol.%/week (3 × 80 U/kg i.v.) and 1,2 vol. %/week (3 × 120 U/kg i.v.). After 3 months of therapy, lees than 2 % required further transfusions, mostly accounted for by unusual blood loss and infections. The degree of transfusion dependency and of iron overload significantly modulated the response characteristics. Iron overload was markedly reduced. However functional iron deficiency, indicated by transferrin saturation < 20 % developed in up to 30 % of the patients with ferritin levels > 700 ng/ml and in 50 % with ferritin levels < 700 ng/ml. Data indicate that rEPO is effective even in transfusion-dependent renal anemia at a rate of success which aproaches 100 % in a selected cohort. Despite iron overload, functional iron deficiency develops frequently, requiring transitory iron supplementation to increase hematocrit levels.

Key words: ***Erythropoietin. Transfusion-dependent anemia. Hemodialysis. Iron overload.***

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TRATAMIENTO CON ERITROPOYETINA HUMANA RECOMBINANTE (rEPO) EN PACIENTES EN HEMODIALISIS CON ANEMIA DEPENDIENTE DE TRANSFUSIONES. ENSAYO MULTICENTRICO EUROPEO

RESUMEN

Ha sido estudiado el efecto de la eritropoyetina humana recombinante (rEPO) sobre la anemia dependiente de transfusiones en una población de 351 pacientes en hemodiálisis procedentes de 59 hospitales europeos. El incremento medio del hematócrito fue de 1,0 vol. %/semana (3 × 80 U/kg i.v.) y de 1,2 vol. %/semana (3 × 120 U/kg i.v.). Después de tres meses de tratamiento, menos de un 2 % requirió transfusiones, todas ellas casi siempre relacionadas con inusuales pérdidas de sangre e infecciones. El grado de dependencia de las transfusiones y de la sobrecarga de hierro moduló las características de la respuesta. Se redujo considerablemente la sobrecarga de hierro. Sin embargo, la deficiencia funcional de hierro, indicada por saturaciones de transferrina inferiores al 20 %, apareció en más del 30 % de los pacientes con niveles de ferritina mayores de 700 ng/ml y en el 50 % de aquellos con niveles de ferritina menores de 700 ng/ml.

Estos datos indican que la rEPO es efectiva incluso en la anemia renal dependiente de transfusiones, con una tasa de éxito que se aproxima al 100 % en una población seleccionada. A pesar de la sobrecarga de hierro, aparece frecuentemente deficiencia funcional de hierro, que obliga a la utilización de suplementos del mismo para inducir incremento en los valores del hematócrito.

Palabras clave: ***Eritropoyetina. Anemia dependiente de transfusiones. Hemodiálisis. Sobrecarga de hierro.***

Introduction

Renal anemia is an almost inevitable consequence of end-stage renal disease. Although the pathogenesis is multifactorial, deficiency of erythropoietin has been recognized as the principal cause[1,2].

Within less than 3 years after the first pioneer studies[3,4], substitution of recombinant human erythropoietin (rhEPO) has been the subject of extensive clinical investigations and has been introduced to the basic therapy of patients on maintenance hemodialysis. Encouraging results have been observed also in predialysis patients[5,6].

Due to its high therapeutic potency and its broad therapeutic range, the rate of primary success is very high, leaving up a small number of patients with insufficient clinical response or complete therapeutic failure. Amoung other reasons like infection, gastrointestinal blood loss, aluminium overload[4,7,8] and development of iron deficiency has been identified[4,7,9,10].

In the following, preliminary results of a european multicenter trial on the effect of rhEPO on transfusion-dependent anemia in patients on maintenance hemodialysis shall be reported with special regard to a) the demand of transfusions, b) the assessment of the correction and maintenance dose in transfusion-dependent renal anemia, c) the reduction of iron overload and d) changes of iron metabolism during treatment with rhEPO.

Patients

351 patients in 59 centers have been included in the study between August 17, 1987 and May 17, 1988. The deadline for the interim evaluation of the data presented here was July 15, 1988. Data set analyzed is shown in the patients analyzed flow chart (fig. 1). The mean duration of therapy was 114 days (6-313 days). The correction period lasted for 6-213 days and the maintenance period 1-288 days.

Criteria for inclusion were a) adult patients, b) at least 6 months on maintenance hemodialysis, c) hematocrit ≤28 vol.%, defined as a mean of the pretreatment controls, d) at least 3 blood transfusions (1 U = 200 ml packed red cells) during the last six months and/or, e) ferritin levels above 700 ng/ml.

The distribution of the total transfusion volume within the 6 month prior to rhEPO is shown in figure 2. Approximately 70 % of the patients had received 600 ml or more packed red cells (fig. 2). Patients with infections, malignomas, poorly controlled hypertension, epilepsy, deficiency of vitamin B_{12} and folic acid and a positive allergy test to intracutaneous rEPO (200 U EPO dissolved in 2 ml sterile water, 0.2 ml i.c.) should be excluded.

Protocol

The study was designed as an open, non-randomized multicenter trial in Europe. After a two weeks run-in pe-

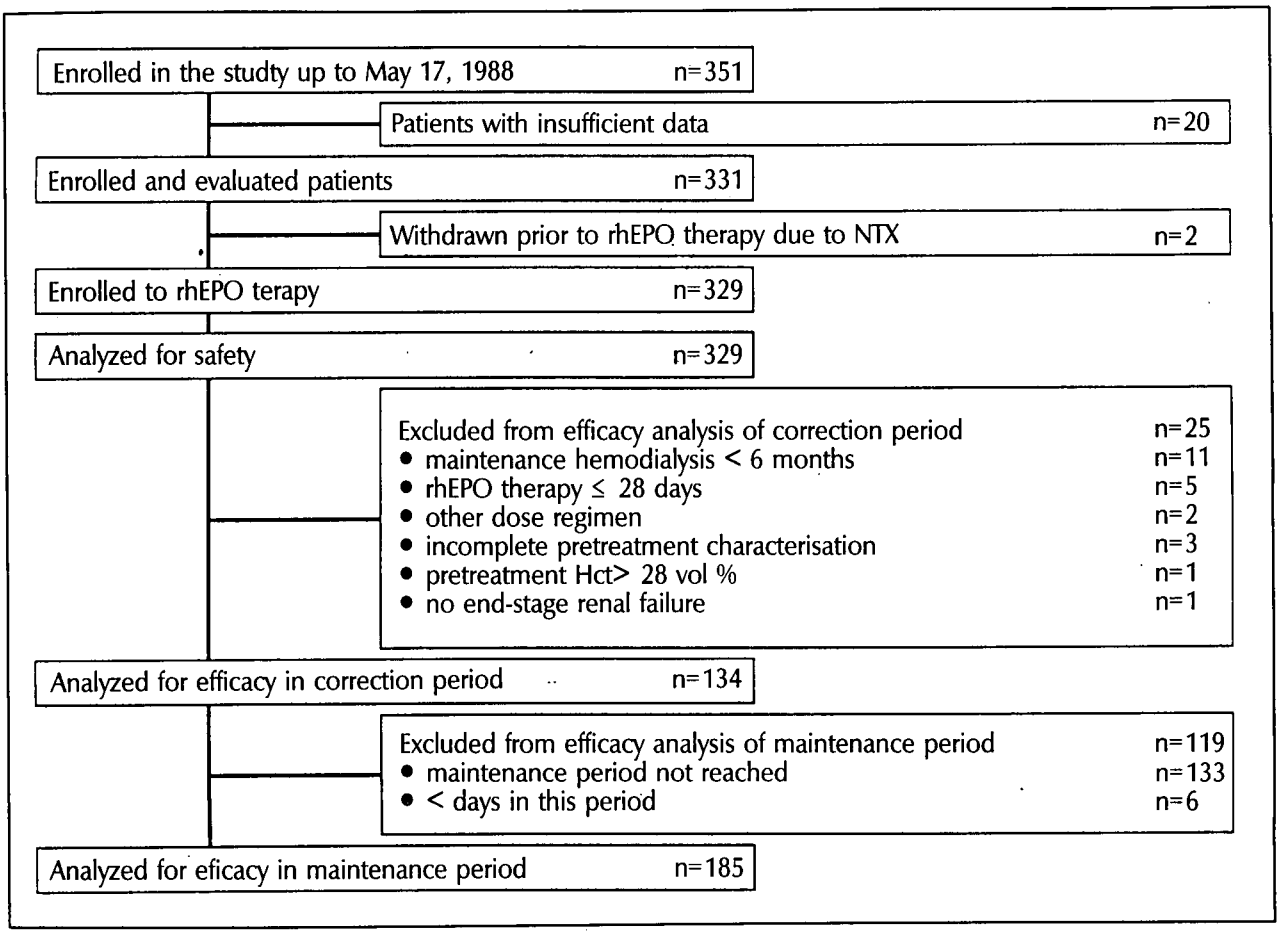

Fig. 1.—Patients Flow Chart.

riod, patients were treated with rhEPO using an initial dose of 80 (n = 244) or 120 U/kg (n = 60) bodyweight 3x weekly intravenously, till hematocrit values between 30 and 35 vol. % were reached and no further transfusions were necessary (correction period).

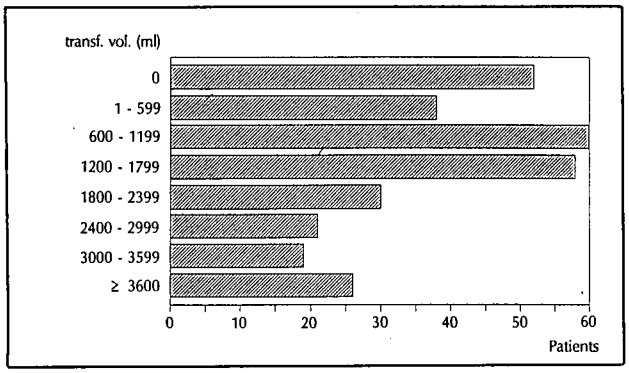

Fig. 2.—Requirement of transfusions within 6 months prior to rhEPO therapy, expressed as total packed red cell volume/6 months.

For the first patients enrolled 120 U/kg b.w. were given for correction of anemia 3 times weekly i.v. On the basis of preliminary data on safety and efficacy from another multicenter trial[18], patients enrolled after January 21st received 80 U/Kg b.w. rhEPO was administered as a bolus intravenously within 1-2 minutes. If after 12 weeks the desired target hematocrit was not achieved and/or further blood transfusions were needed, the dosage was increased every 4 weeks by 40 U/kg b.w. Thereafter, the EPO-dose was uniformly reduced to 30 U/kg b.w. initially and individually adapted to maintain a stable hematocrit of 30-35 vol. %.

Parameters Studied

Hematocrit, hemoglobin, erythrocytes, reticulocytes and platelets were controlled 3x/week during run-in and correction period. Blood pressure, bodyweight and temperature were also controlled 3x/week.

Ferritin, transferrin, iron, iron-binding capacity and safety parameters (total protein, LDH, haptoglobin, creati-

nine, urea, sodium, potassium, calcium, phosphate, AP, SGPT, SGOT, gamma GT, leukocytes, differential blood count) were controlled 2 x resp. 3 x during run-in period and every 1 resp. 2 weeks during correction period. During the maintenance period, these parameters were controlled at constant intervals of 1 to 4 weeks. The demand of transfusions was recorded 6 months prior to and during rhEPO therapy. Corrected reticulocyte counts were calculated after Ganzoni[12] and transferrin saturation was calculated as the ratio of serum iron level to iron-binding capacity.

Statistics

Analysis of efficacy of the correction period excluded patients without end-stage renal failure, maintenance hemodialysis <6 months, hematocrit > 28 vol.% in the pretreatment period, incomplete pretreatment characterization, rhEPO therapy ≤ 28 days, or other dose regimen. Analysis of efficacy and tolerability of the maintenance period excluded patients without data for at least 14 days in this period. Descriptive statistical methods were used to analyze the data of the study. As most variables are neither normally nor symmetrically distributed, medians and interquartile ranges are preferred parameters for location and dispersion. As the correction and maintenance period varied markedly from patient to patient, the «last-observation-carried-forward» method was used, even if the patients dropped out before the target hematocrit was reached the time needed for the correction of anemia (i.e. till hematocrit values between 30 and 35 vol. % were reached and no further transfusions were necessary) was analyzed by non-parametrics survival time methods[11].

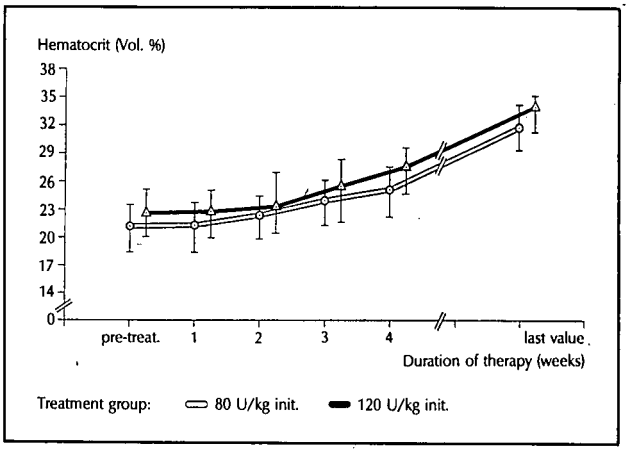

Fig. 3.—Hematocrit levels during the first 4 weeks and at the end of the correction period. Calculation includes only patients with no further transfusions after starting rhEPO therapy, using a dose of 80 U/kg (n= 200) or 120 U/kg (n = 37) 3 × weekly as correction dose.

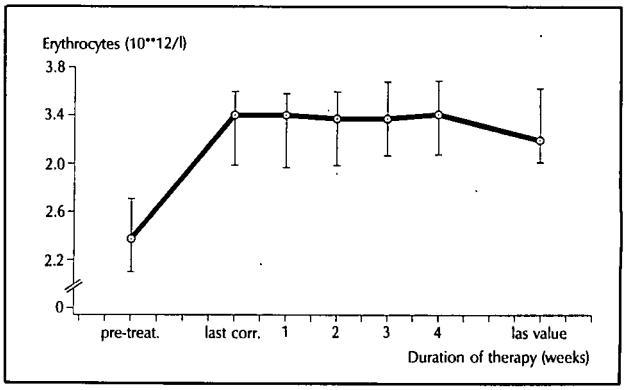

Fig. 4.—Erythrocyte counts at the end of the correction period and during maintenance therapy (including only patients with no transfusions in the maintenance period, n = 155).

Results

All patients had marked normochromic and normocytic anemia with a median hematocrit level of 22 vol. % prior to rhEPO therapy. From 2 weeks of therapy onwards, hematocrit levels increased continuously, reaching a median level of 32 vol. % at the end of the correction period.

The average increase of hematocrit during the first 4 weeks of rhEPO therapy was 1,02 vol. %/week in patients treated with 80 U/kg and 1,21 vol. %/week in patients treated with 120 U/kg b.w. (fig. 3).

Hemoglobin concentration and erythrocyte counts behaved accordingly. Median erythrocyte counts increased from 2,36 to 3,4 · 10^{12}/l and remained stable for 4 weeks after dose reduction; at the end of the evaluation period erythrocyte counts slightly declined to 3,2 · 10^{12}/l (fig. 4).

Reticulocyte counts were transformed to the reticulocyte index given by Ganzoni[12]. The median index was distinctly below 10 %, indicating hyporegenerative anemia in the majority of patients. Under rhEPO, reticulocyte index increased from 6,2 to 19,5 % at the end of the correction period and remained elevated in the range of 12 % during maintenance therapy (fig. 5).

The demand of blood transfusions was almost stable within the last 6 months prior to rhEPO therapy; in each month about 50 % of the patients required at least one transfusion (fig. 6).

After the onset rhEPO therapy, a total of 49 (16 %) patients received at least one more transfusion during a mean observation period of 114 days. 32 patients (10,5 %) received at least one transfusion in the first month, in the second and third month this number decreased to approximately 2 % of the patients.

The transfusion requirement after at least one month of rEPO therapy is mostly accounted for by unusual blood loss, temporarily reduced response due to infections or temporary discontinuation of therapy during vacation or hospitalisation (fig. 6).

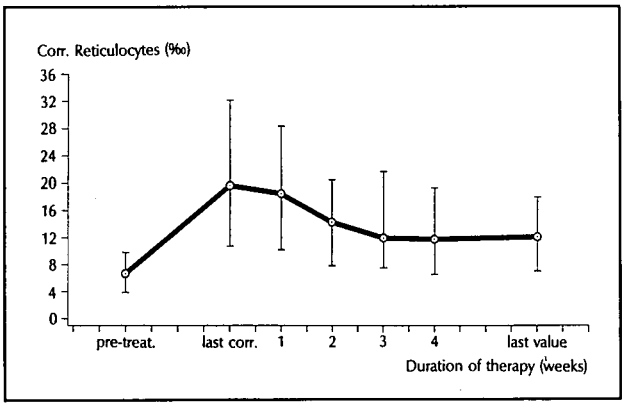

Fig. 5.—Corrected reticulocytes at the end of the correction and during maintenance period (including only patients with no transfusions during maintenance period, n = 147).

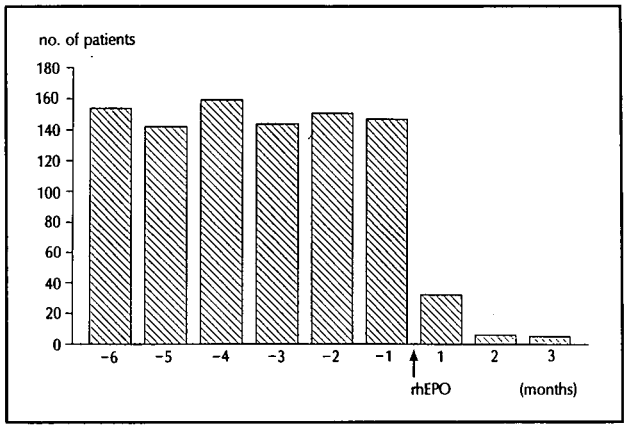

Fig. 6.—Effect of rhEPO therapy on transfusion requirements. The number of patients with at least one transfusion/month within the last 6 months prior to rhEPO was almost stable at 50 %; within 3 months of rhEPO therapy, more than 95 % of the patients became independent of blood transfusions.

In order to determine whether the degree of transfusion dependency and/or iron overload has an effect on the response to rEPO therapy, patients were divided into four subgroups according to their baseline data (table I).

All patients with a transfusion demand of <600 ml (group 3 and 4) were independent of further blood transfusions within 2 months of rhEPO therapy. In patients requiring >= 600 ml packed red cells during the last six months only (group 1 and 2) 2,1-2,9 % of the patients required further blood transfusions during the first 2-3 months of rEPO therapy (table I).

In order to take into account those patients who dropped out before the end of the correction period, survival rate methodg[11] were used. Response (i.e. the end of «survival of anemia») was defined if at least 80 % of the hematocrit values were >= 30 vol. % over a period of 14 days without receiving any transfusions during the previous month.

Table I. Transfusion need in % patients

	n	Pretreatment (mean of 6 months)	After x months rhEPO therapy 1 month	2 months	3 months
G1	163	70.5	15.3	2.7	2.9
G2	51	53.9	11.8	2.1	2.5
G3	37	9.0	0	3.2	0
G4	53	7.2	1.9	0	0

The estimated response rate after 12 weeks of therapy was 55 % (80 U/kg) and 80 % (120 U/kg). The time for correction of the anemia in 50 % of the patients was 81 days (80 U/kg) and 52 days (120 U/kg) (fig. 7).

For the majority of the patients 3 × 40 U/kg b.w. was found to be sufficient for the maintenance of stable hematocrit levels.

Of the 4 subgroups with different transfusion demand and different iron stores, group 3 showed the steepest weekly increment of hematocrit levels, whereas in group 2, the slightest increase was found (table II).

The median ferritin levels decreased by 27-52 % in the four groups during the correction period. Accordingly transferrin saturation decreased in all groups considerably. Functional iron deficiency (transferrin saturation < 20 %) developed in group 1 and 3 (ferritin levels >700 ng/ml) in 25 resp. 30 % of the patients, whereas in group 2 and 4 (ferritin levels < 700 ng/ml), more than 50 % of the patients developed functional iron deficiency. Serum iron levels decreased as well; only minor changes of transferrin levels and total iron binding capacity (TIBC) were observed.

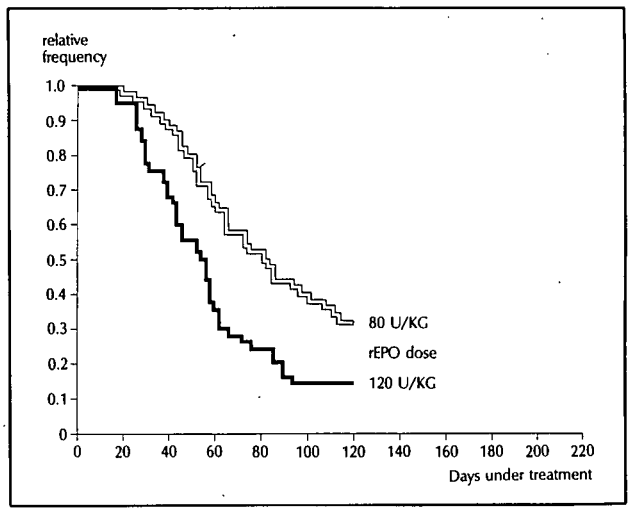

Fig. 7.—Effect of dose regimen on the time to response to treatment, expressed as estimated survival rate of anemia.

Table II

group blood transfusions/6 mo ferritin	1 ≥ 600 ml > 700 ng/ml	2 ≥ 600 ml ≤ 700 ng/ml	3 < 600 ml > 700 ng/ml	4 < 600 ml ≤ 700 ng/ml
n	163	51	37	53
hemoglobin (g/dl)	7.5 6.2 – 8.4	7.2 6.4 – 8.3	7.1 6.2 – 7.9	6.7 5.8 – 7.4
corr. reticulocytes (‰)	6.2 3.9 – 9.4	5.9 3.4 – 8.8	7.8 5.4 – 11.6	7.8 5.1 – 9.9
Δ hct (8 weeks) (vol. %/w)	1.01 0.56 – 1.38	0.87 0.58 – 1.30	1.36 0.62 – 1.52	0.98 0.49 – 1.32
correction period	start n=123 end	start n=42 end	start n=34 end	start n=48 end
ferritin (mg/ml)	1531 (939-2343) 1100 (688-2000)	390 (260-547) 141 (69-302)	1032 (810-1788) 579 (510-1413)	187 (53-430) 68 (37-279)
transferrin saturation (%)	69 (49-85) 26 (19-61)	29 (21-49) 17 (12-23)	44 (27-76) 23 (14-43)	22 (16-37) 15 (12-24)
% patients <20% at the end	25	> 50%	30%	> 50%
iron (µmol fe/l)	29 (37-55) 11 (32-48)	15 (42-54) 7 (37-52)	19 (40-54) 9 (35-48)	14 (49-81) 8 (43-67)
transferrin (g/l)	190 (164-243) 170 (142-213)	200 (185-241) 195 (166-231)	213 (177-240) 192 (156-214)	251 (219-359) 232 (193-300)

20 patients (≅6 %) received regular iron supplementation at the start of therapy. During the correction period, iron substitution was started in a further 21 patients, increased in 4, and discontinued in 6 patients.

Adverse events

58 serious adverse events were reported in 50 patients, 37 of these classified as unrelated and 21 classified as possibly related to rhEPO therapy.

6 patients died, 3 due to myocardial infarction, 1 each due to subarachnoidal bleeding and subdural hematoma, and in 1 case the cause is unknown.

Due to adverse events ten patients were withdrawn: 1 each due to plasmocytoma-like configuration, progression in systemic sclerosis, cerebral convulsion, sensation of general weakness, Wegeners granulomatosis, cerebral vasculitis, combined occurence of malaise, headache and pain over the heart, bone pain and generalized arthralgia, headache and insufficient blood pressure control.

The most important adverse event was the development or aggravation of hypertension. 194 patients were hypertensive prior to rEPO therapy, 176 of which received antihypertensive therapy. In 36 of these, therapy had to be intensified. Of 120 spontaneously normotensive patients, 22 developed hypertension under rhEPO therapy (fig. 8).

Platelets increased from 185 10^9/l to 223 · 10^9/l during correction and decreased to about 200 · 10^9/l during the maintenance period. No evidence of an increased hemolysis rate was observed. Effects on other safety controls resembled those reported from earlier trials.

Development of antibodies to rhEPO, measured in the laboratory of J. H. Thaysen, Rigshospital/Copenhagen according to Kientsch-Engel[13] could not be observed.

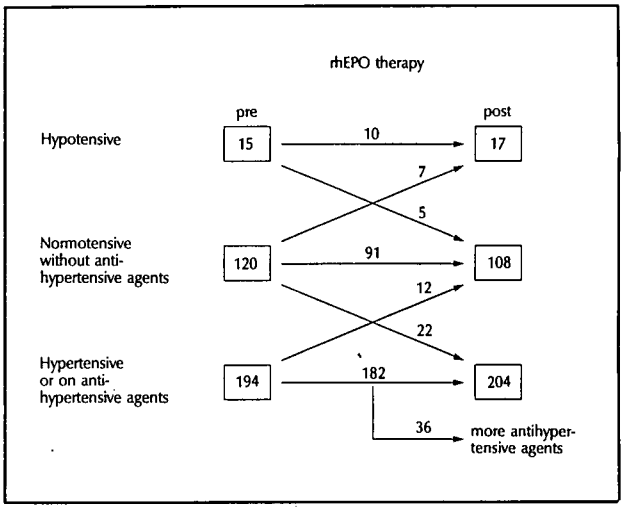

Fig. 8.—Changes of blood pressure status under rhEPO therapy. Patients are grouped according to their status prior to rhEPO therapy and at the end of the correction period (spontaneously hypotensive: systolic blood pressure < 100 mmHg; spontaneously normotensive: BP > 100 mmHg systolic and < 160/95 mmHg; hypertensive: BP > 160/95 mmHg or requiring antihypertensive medication.

Discusion

In several large multicenter trials[14-18] successfull correction of renal anemia by substitution of rhEPO has been shown. In the present trial, rhEPO was used for the correction of transfusion-dependent renal anemia, which can be considered as the most severe expression of anemia of end-stage renal disease. Also here, a surprisingly high rate of primary success has been achieved; within 3 months of rhEPO therapy more than 95 % of the patients became independent of further blood transfusions. Gastrointestinal blood loss, infections and discontinuation of therapy due to vacation or other circumstances unrelated to rhEPO therapy were the most common causes for the persistance of transfusion dependency. The goal seems nearly achieved that maintenance hemodialysis therapy is no longer associated with an increased risk of transfusion-related infections for patients and staff.

It was expected that a high correction dose should be necessary for transfusion-dependent renal anemia; initially 3 × 120 U/kg b.w./week were considered to be necessary to correct renal anemia within 12 weeks. This view was supported by the experience of multicenter trials from America and Europe[14, 19]. Other european studies including a multicenter study on non-transfusion-dependent patients have meanwhile found that an i.v. dose less than 3 × 100 U/kg b.w./week is sufficient in most cases[18, 20, 21]. A rapid increase of hematocrit is associated with a higher complication rate mostly related to blood pressure deterioration[22, 23]. Therefore the correction dose was reduced after the onset of the trial to 80 U/kg b.w. for safety reasons.

In patients treated with 3 × 120 U/kg, the correction time, after which 50 % of the patients had hematocrit levels above 30 vol. % and were > 4 weeks after the last transfusion, was less than 60 days, compared to about 80 days for those treated with 3 × 80 U/kg. However, this lower dose was sufficient and effective enough for most patients.

A dose of approximately 3 × 40 U/kg b.w. i.v. turned out to be sufficient for maintenance in most patients, whereas in non-transfusion-dependent hemodialysis patients an i.v. dose of about 3 × 30 U/kg b.w. has been found[18].

It has been shown recently, that the therapeutic effect of rhEPO can be increased by subcutaneous and more frequent application[24, 25]. This has not been tried here as far as yet.

The degree of transfusion dependency and body iron stores significantly influence the response to rhEPO. Patients with ferritin levels >700 ng/ml and a demand of transfusions < 600 ml packed red cells during the last 6 months showed the most rapid increase of hematocrit whereas patients requiring > 600 ml/6 months and a ferritin level < 700 ng/ml showed the slowest increase of hematocrit. Furthermore, all patients who required < 600 ml packed red cells during the last 6 months prior to study, were independent of blood transfusions within 2 months of rhEPO therapy.

As a special aim of the study was the reduction of siderosis, iron metabolism was closely monitored. The reduction of body iron stores is reflected by a significant decrease of serum ferritin levels of all subgroups under rhEPO therapy in accordance with previous reports[4, 14, 26]. As this became already evident within 3 months of therapy, it can be estimated that additional iron removal by deferoxamine or phlebotomy will not be necessary even in most patients with iron-overload as referred to group 1 and 3.

It is of considerable clinical importance that a functional iron deficiency developed in these patients although iron overload was also present. 25-30 % of the patients with ferritin levels >700 ng/ml displayed a transferrin saturation < 20 % during rEPO therapy whereas this proportion was >50 % in patients with ferritin levels <700 ng/ml. Median transferrin saturation, as well as serum iron levels decreased significantly under rhEPO therapy whereas only minor changes were found for total iron binding capacity and transferrin serum levels. Thus transferrin saturation seems to be the most sensitive parameter for functional iron deficiency.

The high incidence of functional iron deficiency in this study also means that, in these patients, a still lower correction dose should have been as effective, because the bone marrow response to rhEPO is reduced in iron deficiency. Recently, this has also been confirmed by other investigators[9, 10, 14].

The most important adverse effect was the development or an aggravation of hypertension under rhEPO therapy. This has been confirmed by a large number of clinical studies[22, 23]. In regularly transfused patients studied here, the incidence of a development or aggravation of hypertension was 18 % both for spontaneously normotensive patients and patients with hypertension. These figures seemed lowe than those figures reported in previous studies. In patients without regular transfusions the incidence was 13 % for spontaneously normotensive patients and was even 47 % for patients with hypertension prior to rhEPO[27]. It has been suggested, that the effects of rhEPO therapy on blood pressure are not entirely related to changes in hematocrit[22]. However, the incidence of blood pressure effects under rhEPO might be lower when patients are adapted to periodic changes of hematocrit.

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