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NEPHROLOGY FORUM

Erythropoietin in chronic renal failure

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Case presentation

A 33-year-old man was admitted to the Nephrology Department at the Hospital General Universitario Gregorio Marañón because of progressive renal failure, severe anemia, and intense fatigue.

At age 29, gross hematuria for several days followed by ankle edema prompted study at another center. He was normotensive and his renal function was normal (serum creatinine, 1.2 mg/dl; creatinine clearance, 95 ml/min). The 24-hour urinary protein excretion was 7.3 g. Serum total protein was 4 g/dl and serum albumin was 1.5 g/dl. Renal biopsy was performed; light microscopic examination revealed diffuse and uniform thickening of the capillary wall, without cell proliferation. There was mild interstitial infiltration by mononuclear cells. Silver methenamine staining revealed the presence of spikes. Immunofluorescent examination showed uniform granular deposits of IgG and C3 outlining all the capillary loops. A histopathologic diagnosis of membranous nephropathy was made.

Antinuclear antibodies and anti-DNA antibodies were negative, as was hepatitis B viral antigen testing. An abdominal CT scan was normal. A diagnosis of nephrotic syndrome secondary to idiopathic membranous nephropathy (with normal renal function) was made, and the patient was treated conservatively with a low-salt diet.

One year later, at age 30, the serum creatinine was 1.8 mg/dl and urinary protein excretion remained greater than 7 g/day. At age 32, the serum creatinine was 2.2 mg/dl, and 6 months before admission it rose to 3.3 mg/dl.

When the patient was admitted to our hospital, he presented with intense fatigue, pallor, and loss of appetite. He had begun to lose weight and was forced to stop working. The hematocrit was 24.6%; red blood cell count, 2,800,000/mm^3; hemoglobin, 8.3 g/dl; mean corpuscular volume, 87.7 fl; white blood cell count, 7200/mm^3; and platelet count, 313,000/mm^3. The serum creatinine was 5.3 mg/dl and creatinine clearance 17.4 ml/min. Serum ferritin was 190 μg/liter; iron, 89 μg/dl; transferrin, 195 mg/dl; transferrin saturation, 23%; serum vitamin B_{12}, 784 pg/ml; folic acid, 7.7 pg/ml; and erythropoietin, 15 mIU/ml. Serum PTH was 263 ng/ml; total protein, 4.6 g/dl; albumin, 2.4 g/dl; total cholesterol, 286 mg/dl; triglycerides, 87 mg/dl; and alkaline phosphatase, 152 U/liter.

There was no evidence of hemorrhage, decreased iron stores, or folic acid or vitamin B_{12} deficiency. Treatment with recombinant human erythropoietin was begun at a dose of 1000 IU three times per week, subcutaneously. Ferrous sulfate (270 mg; 80 mg Fe^{++}) three times daily was administered simultaneously.

In the following weeks, the patient began to improve. Two months after beginning treatment with recombinant human erythropoietin, his hematocrit was 36%; hemoglobin, 12.1 g/dl; and mean corpuscular volume, 87.7 fl. The patient returned to work and his appetite improved greatly. The decrease in serum total protein persisted (4.3 g/dl); serum ferritin was 88 μg/liter; and the serum creatinine continued to rise (6.7 mg/dl). Total serum calcium was 6.7 mg/dl; phosphorus, 5.6 mg/dl; and PTH, 354 pg/ml. Oral calcitriol was started at a dose of 0.25 μg/day.

The patient maintained that he was taking oral ferrous sulfate as prescribed, but 6 months after the beginning of treatment with erythropoietin, the serum ferritin had fallen to 3 μg/liter. His hematocrit fell to 26%, hemoglobin to 8.9 g/dl, and mean corpuscular volume to 82.2 fl. Oral administration of ferrous sulfate was stopped, and treatment with intravenous ferrous gluconate was initiated; a dose of 62.5 mg, diluted in 250 ml of 5% dextrose (administered over one hour) was repeated every week. One month later, the hematocrit was 39.6%; hemoglobin, 13.3 g/dl; and mean corpuscular volume, 88 fl. The serum ferritin increased to 88 μg/liter. Throughout the following months, the dose of recombinant human erythropoietin was reduced to 1000 IU twice weekly and later to once weekly. Administration of intravenous ferrous gluconate (62.5 mg) was continued every month, and serum ferritin levels exceeded 250 μg/liter. The hematocrit level remained between 33% and 39%.

Sixteen months after the initiation of treatment with recombinant human erythropoietin, the serum creatinine had increased to 11.5 mg/dl, and renal replacement therapy was begun using hemodialysis three times per week. Treatment with erythropoietin and intravenous iron was continued. Residual renal function decreased after hemodialysis commenced; by six months later, the serum total protein was normal.

During the following three years, the patient remained stable and in good clinical condition. Erythropoietin was given in a dose ranging from 1000 to 2000 IU per week subcutaneously, and ferrous gluconate was administered every two to four weeks; the aim was to maintain a serum ferritin level between 100 and 200 μg/liter. His hematocrit remained above 30% and the hemoglobin concentration exceeded 11 g/dl.

At age 38, four years after starting hemodialysis treatment, his hematocrit fell below 30%; the serum ferritin was between 128 and 215 μg/liter. The dose of erythropoietin was increased to 4000 IU three times per week. Nonetheless, his hematocrit fell to 22% and the hemoglobin to 7.3 g/dl, with a mean corpuscular volume of 89 fl. The PTH level had increased over the preceding years and by this point was 825 pg/ml. The total serum calcium was 10.6 mg/dl; phosphorus, 6.5 mg/dl; alkaline phosphatase, 835 U/liter; and serum aluminum, 6 μg/liter. Intravenous calcitriol was started at a dose of 2 μg three times per week. After three weeks of treatment, the patient developed intense pruritus; the total serum calcium was 13.5 mg/dl and intravenous calcitriol was stopped. The hematocrit remained between 20% and 22% with no evidence of hemorrhage; the serum ferritin level was 180 μg/liter. Gastroscopy revealed normal esophageal and gastric mucosa. The patient underwent a subtotal parathyroidectomy with removal of the four glands and implantation of ten small fragments of

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parathryoid tissue in the forearm. The total weight of the four glands was 2850 mg. Three months later, his hematocrit had risen to 37%, the PTH level had fallen to 110 pg/ml, and the dose of erythropoietin was decreased to 2000 IU three times per week.

Discussion

DR. FERNANDO VALDERRÁBANO (*Professor of Medicine, and Chairman, Department of Nephrology, Hospital General Universitario Gregorio Marañón, Madrid, Spain*): A decade has passed since the first patients with end-stage renal disease (ESRD) were treated with recombinant human erythropoietin (Epo). Thousands of patients have received this treatment all over the world during this time. In Europe, more than 50% of patients receiving hemodialysis treatment were given Epo therapy in 1992 [1]; in some European countries, the percentage of patients treated with Epo was higher than 80%. When Epo use began in 1985, the objective was to eliminate blood transfusions and thereby the risks of iron overload, sensitization, and transmission of viral diseases [2]. In the last few years, however, we have learned that Epo treatment can improve the feeling of well-being in ESRD patients and, consequently, their quality of life; Epo also can eliminate symptoms commonly attributed to uremia but probably the result of anemia.

However, Epo treatment is costly. Therefore the percentage of ESRD patients who receive Epo in different countries is a function of the country's economic level. Abundant clinical experience has defined the best way to use this hormone to maximize its benefits and avoid its adverse effects. Even so, aspects of the optimal use of Epo remain to be elucidated. The varied beneficial effects of Epo treatment range from improving cognitive and sexual function to ameliorating left-ventricular hypertrophy. In the short term, these effects are clearly manifested. Nevertheless, long-term effects have not yet been determined. Optimal use of Epo should achieve the greatest benefits at the lowest cost. For this reason, it is important that we diagnose the conditions that produce hyporesponsiveness to Epo.

As I said, Epo is efficacious in ESRD patients who are undergoing renal replacement therapy, but it currently is used more and more frequently in ESRD patients who have not yet started dialysis. As in today's case, the main objective of Epo use in pre-dialysis patients is to maintain the patient free of symptoms and in the best possible clinical condition; the goal is to enable the patient to make the transition from severe chronic renal failure (CRF) to renal replacement therapy with minimal symptoms. Unanswered questions remain. Does Epo treatment accelerate the progression of chronic renal failure? Or, to the contrary, can Epo delay the start of dialysis treatment? The case presentation shows two aspects of Epo treatment that have not yet been fully explored. The first is the importance of restoring iron stores in Epo-treated patients, including pre-dialysis patients. Oral iron administration is not always sufficient, because iron absorption can be abnormal in these patients. Available data clearly demonstrate that intravenous iron administration has a salutary effect on the response to Epo [3], but this maneuver is rarely necessary in pre-dialysis patients. In today's patient, intravenous ferrous gluconate administration allowed a normalization of serum ferritin levels, thereby prompting an excellent response to Epo.

A second aspect of the case presentation is the patient's lack of response to Epo treatment that appeared four years after he started hemodialysis treatment, and which resulted from severe secondary hyperparathyroidism. A sixfold increase of the weekly dose of Epo (4000 IU three times/week) was not successful in restoring the hematocrit to its previous level. Only parathyroidectomy succeeded in improving the patient's hematocrit and in allowing us to decrease the dose of Epo. Let us now turn to the use of Epo in pre-dialysis patients, different causes of hyporesponsiveness, optimal use of Epo, and its beneficial effects both short- and long-term, with special emphasis on quality of life and the target hematocrit.

Epo treatment in pre-dialysis patients

Several groups have reported an improvement in general clinical status as well as increased appetite and physical activity in CRF patients treated with Epo before beginning dialysis [4–8]. Symptoms of anemia usually appear when the hematocrit falls to below 30%, or with higher hematocrit levels if heart failure or angina pectoris is present. In one study, work capacity increased significantly—by 62%—in Epo-treated pre-dialysis patients, as assessed by questionnaires filled out by the patients [4]. We concur with the authors who maintain that instead of asking whether these patients should be treated, we should ask, why not? If beneficial and adverse effects, proven in dialysis patients, are the same in pre-dialysis patients, the most important potential hazard is the possibility of worsening renal function.

In a Spanish multicenter study, we treated 34 pre-dialysis patients. This study consisted of two protocols of treatment; in Protocol A, Epo was administered by the subcutaneous route at an initial dose of 75 IU/kg/once weekly. In Protocol B, three doses of 25 IU/kg were administered every week [8]. Self-administration of subcutaneous Epo at home was possible after short preparatory conversations with the patients.

Although daily doses have been used [9], our experience showed that similar results were obtained when the entire weekly dose was administered all at once. Patients treated according to Protocol A (Epo dose administered once weekly) increase their hemoglobin level from a mean of 8.3 g/dl to 10.7 g/dl at three months, and patients treated according to Protocol B (three doses weekly) increased their hemoglobin level from a mean of 7.9 g/dl to 10.6 g/dl.

Oral iron administration, in the form of ferrous sulfate or fumarate frequently is enough to support erythropoiesis, but not all patients tolerate it well, and gastrointestinal absorption is not always sufficient. In these cases, intravenous iron administration is necessary, with either iron dextran or iron gluconate. It is possible that in the patient presented today, edema of the gastrointestinal mucosa—a consequence of the nephrotic syndrome—caused the low iron absorption. Chronic renal failure patients with a functioning renal graft who need Epo treatment can have higher iron requirements as a consequence of the administration of azathioprine [6]. However, ferrokinetic studies show that treatment with azathioprine increases ineffective erythropoiesis: erythrocytes are destroyed within the bone marrow before maturation and release [10].

We have not seen any significant variation in arterial blood pressure or in serum creatinine in pre-dialysis patients treated with Epo in up to one year followup [8]. There were no differences in serum creatinine or in blood pressure in pre-dialysis patients receiving three doses per week compared with those receiving the total weekly dose at once [8]. Similar results in clinical studies have been described by other authors [4, 5]. However, we have

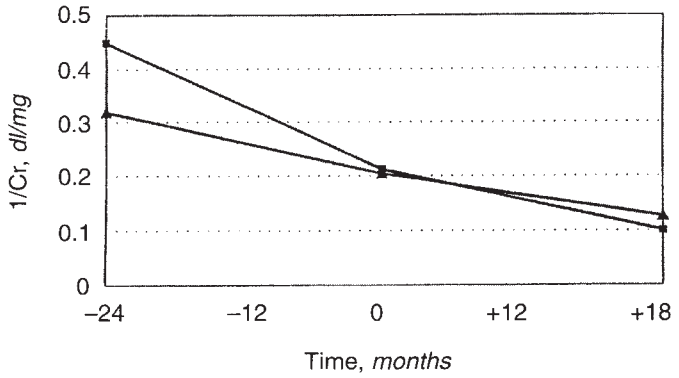

Fig. 1. *Slope of the inverse of serum creatinine in a group of pre-dialysis, Epo-treated patients (■, N = 12), compared to a control group of pre-dialysis, non-treated patients (▲, N = 15).* Note the significant improvement of the slope in Epo-treated patients (−0.0098 vs. −0.0062 dl/mg month, $P < 0.05$). There was no significant change in the slope of non-treated patients (−0.0045 vs. −0.0043 dl/mg month, NS).

Table 1. Evolution of the Sickness Impact Profile (SIP) scores in 54 pre-dialysis patients treated with Epo (Epo group) and in 26 pre-dialysis patients not receiving Epo (Control group)[a]

	Epo group	Control group
Number	54	26
Mean age (*years*)	56.4 ± 14.9	48.8 ± 10.5
Sex (*% males*)	40.9	44.4
Basal serum creatinine (*mg/dl*)	6.0 ± 1.6	7.3 ± 1.7
Basal hemoglobin (*g/dl*)	8.2 ± 0.9	10.0 ± 1.4
Hemoglobin at 3 months	10.6 ± 1.4[b]	9.8 ± 1.7
Basal hematocrit (%)	24.6 ± 2.8	30.6 ± 4.7
Hematocrit at 3 months (%)	31.4 ± 5.3[b]	29.2 ± 5.2
Basal GS of SIP	17.7 ± 2.4	12.7 ± 4.6
GS of SIP at 3 months	14.5 ± 2.1[c]	14.9 ± 2.3
Basal PhD of SIP	16.8 ± 3.0	7.9 ± 4.1
PhD of SIP at 3 months	12.8 ± 2.1[c]	11.9 ± 3.8
Basal PsD of SIP	16.0 ± 2.2	20.7 ± 6.1
PsD of SIP at 3 months	13.1 ± 1.8[c]	17.7 ± 3.9

[a] Mean starting subcutaneous Epo dose: 67.8 ± 20.3 IU/kg/week. PhD, physical dimension; PsD, psychosocial dimension; GS, global score. Data as mean ± error standard of mean. Lower scores mean better quality of life.

[b] $P < 0.001$.

[c] $P < 0.01$.

seen a decrease of serum ferritin levels three months after starting treatment, although these patients were receiving oral iron supplements. This is a usual finding reported in hemodialysis patients treated with Epo [11].

The most important aspect of the use of Epo in pre-dialysis patients is the possibility of worsening their renal function. In rats submitted to five-sixths nephrectomy, anemia retarded the progression of proteinuria and glomerular sclerosis, and also reduced systemic hypertension. When these animals were treated with Epo, glomerular injury accelerated and renal failure progressed rapidly [12]. These animals also showed a considerable increase in systemic blood pressure. In other animal experiments in which Epo-induced hypertension was controlled with antihypertensive drugs, the progression of renal failure was prevented [13].

Human studies have not been able to demonstrate that Epo treatment in pre-dialysis patients worsens renal function [14–18]. Our first experience in 12 patients, followed for two years before starting Epo treatment until one-and one-half years after therapy began, showed no variation in the slope of the inverse of serum creatinine [18]. To assess whether the improvement in hemoglobin concentration did not have a negative effect on renal function loss, we selected a group of 12 patients with chronic renal failure followed for two years before starting the study. They were treated with low doses of Epo (68 ± 13 IU/kg) once weekly subcutaneously. This group of patients was compared with a control group of 15 patients with chronic renal failure but not treated with Epo. The progression of renal insufficiency was measured by the slope of the regression line of the inverse of serum creatinine. We found no differences in serum creatinine between the groups at the beginning of treatment (4.7 ± 1.9 mg/dl in the treated group versus 4.9 ± 1.7 mg/dl in the control group). In the control group, the slope of the inverse of serum creatinine did not change; in the Epo-treated group, this slope improved slightly [18] but significantly (Fig. 1).

Patients who received Epo treatment had a faster progression of renal failure during the two years before Epo treatment compared to the control group. This faster progression likely would have caused more intense anemia. In fact, the mean hematocrit when patients began Epo treatment was 24.2% ± 2.5% compared to 29.5% ± 3.6% in the control group.

After 15 months of followup, the mean serum creatinine in the treated group was 7.29 ± 1.8 mg/dl, and two of the twelve patients needed to start dialysis therapy. The mean serum creatinine of the control group was 6.57 ± 1.8 mg/dl, and three of the fifteen patients started dialysis (*P*, NS). We do recognize, however, the limitations of measuring the progression of renal disease by the slope of the inverse of serum creatinine [19].

Studies published to date have not been able to demonstrate that Epo treatment in pre-dialysis patients worsens renal function [14–18]. An increase in the glomerular filtration fraction seemingly related to an increase in blood pressure was shown in one study [14]. However, in another similar study, in which blood pressure was carefully controlled, filtration fraction did not increase [15]. Another controlled study did not find deterioration of renal function when glomerular filtration rate was measured with ^{125}I-iothalamate [17].

If, then, Epo administration does not worsen renal function, we can ask a related question: Can Epo treatment delay the start of dialysis? At this moment, we have no clear answer. We do have evidence that the quality of life of pre-dialysis patients improves with Epo treatment. In a Spanish multicenter pre-dialysis study, we used the Sickness Impact Profile (SIP) to measure the quality of life of these patients. Our results showed that the global score improved significantly in Epo-treated patients; no variations in this score occurred in the control group of pre-dialysis patients who did not receive Epo. Similar results were observed in the physical dimension and the psycho-social dimension of the same test. Table 1 summarizes the characteristics of these patients as well as their hematocrit and hemoglogin levels (pre and post treatment) and the physical dimension, psycho-social dimension, and global score of the SIP.

One of the objectives of that study was to determine whether Epo therapy can delay the start of dialysis. The decision to start renal replacement therapy is usually based on analytic data but

Table 2. Causes of Epo hyporesponsiveness

Iron deficiency	B_{12}/folate deficiency
Absolute	Vitamin C deficiency
Functional	Malnutrition
Blood loss	Immunosuppression
Hyperparathyroidism	Chemotherapy
Aluminum intoxication	ACE inhibitors?
Inflammatory states	Theophylline?
Malignant diseases	Bioincompatible dialysis?
Hemolysis	Oxalosis
Myelodysplastic syndromes	Hypothyroidism
	Premature birth

also depends on the clinical status of the patient. We want to know whether the improvement in the patient's quality of life could allow us to delay the start of dialysis without producing negative clinical effects for the patient. At this moment, we have no results, but we consider the question extremely important because of its economic consequences. In effect, if Epo treatment allows a delay in initiation of dialysis with impunity, the cost-benefit ratio will improve.

The increasing number of publications on pre-dialysis treatment with Epo suggests that the number of patients undergoing Epo treatment before dialysis is increasing. In the last EDTA Registry Report [1], the number of pre-dialysis patients receiving Epo treatment was equivalent to 7% of all dialysis-treated patients in Europe. It is difficult to know what percentage of pre-dialysis patients receive Epo, because evaluation of pre-dialysis patients is not included in the different international registries of patients.

Finally, one might suppose that the beneficial effects observed in Epo-treated dialysis patients are the same as those in pre-dialysis patients. However, prospective studies are necessary to elucidate whether the beneficial cardiovascular effects of Epo accrue in pre-dialysis patients. If left-ventricular hypertrophy could be reversed before a patient starts renal replacement therapy, overall morbidity and mortality might be improved.

Hyporesponsiveness to erythropoietin

In the first studies of Epo treatment in dialysis patients, a small percentage of patients, less than 5%, showed a total or partial resistance to Epo therapy [11, 20, 21]. Now, only eight years later, many possible causes of an inadequate response to Epo have been documented (Table 2). The most common cause is an unsuspected iron deficiency [22]. The beginning of hemodialysis treatment generally coincides with a rapid decrease in previously normal iron stores, probably as a consequence of blood loss in the dialyser and blood lines. On the other hand, iron deficiency does not always mean that iron stores are diminished. The availability of iron can be diminished; this situation is known as functional iron deficiency. The best indicator of iron availability is the percentage of transferrin saturation [23]. Serum ferritin is a good index of the amount of iron stored. The best parameter for determining a real or functional iron deficiency is the percentage of hypochromic red cells in the peripheral smear. Other parameters for monitoring iron deficiency are the transferrin receptor concentration in blood, red cell ferritin level, free erythrocyte protoporphyrin, and red cell zinc protoporphyrin [24–26]. I will comment shortly on clinical aspects of diagnosing iron deficiency and presenting iron supplementation during Epo treatments. I will discuss this topic further when describing the optimization of Epo therapy.

Blood loss is a frequent cause of apparent hyporesponsiveness to Epo as well as of iron deficiency. Gastrointestinal blood loss, as well as blood loss during the dialysis procedure, are the most common causes of hidden bleeding. The increased risk of occult gastrointestinal bleeding is a consequence of the increased bleeding tendency and of the higher prevalence of gastritis, peptic ulcer, and gastrointestinal telangiectasia in patients with ESRD. Occult blood loss must be excluded and gastrointestinal endoscopy is sometimes necessary. Metrorrhagia also must be taken into account in women with iron deficiency and Epo hyporesponsiveness.

Hyperparathyroidism exacerbates anemia in chronic renal failure. High levels of parathyroid hormone might have a deleterious effect on erythroid progenitors in bone marrow [27, 28], and they also can increase hemolysis or provoke bone marrow fibrosis consequent to cystic osteitis fibrosa [29]. Today's patient had responded adequately to Epo treatment for four years, but when he developed severe hyperparathyroidism, his anemia increased in spite of increased doses of Epo. He had no iron deficiency, aluminum intoxication, or inflammatory or neoplastic disease. Parathyroidectomy improved the anemia and allowed a lowering of the Epo dose. These findings have been confirmed in other patients of ours in whom parathyroidectomy permitted an increase in the hematocrit despite lowered Epo dosing [30]. In seven of our hemodialysis patients treated with Epo who presented with severe hyperparathyroidism and were submitted to subtotal parathyroidectomy, the mean hematocrit before parathyroidectomy was 27.9% ± 5.7%; six months later it increased to 35.1% ± 6.4%. These changes permitted lowering the weekly mean Epo dose from 136 ± 12.5 IU/kg to 94 ± 10.5 IU/kg. Other authors have made the same observations [29]. Rao et al showed that the mean dose of Epo required to maintain a target hematocrit of 35% ± 3% was 174 ± 33 IU/kg three times weekly in a group of seven patients with poor response to Epo and severe hyperparathyroidism (mean PTH level of 800 ± 648 pg/ml), versus a group of 11 patients who needed only an Epo dose of 56 ± 18 IU/kg three times weekly in whom the mean PTH level was 266 ± 322 pg/ml [29]. These authors also found a correlation between the doses of Epo needed and the percentage of osteoclastic and eroded bone surfaces and the degree of bone marrow fibrosis [29]. Experimental data are not conclusive, however. In effect, some authors reported an inhibitory effect of PTH on erythroid colony growth [31]; this effect has not been confirmed by others [32, 33]. The rapid improvement in Epo responsiveness after parathyroidectomy supports the hypothesis that elevated parathyroid hormone levels have a toxic effect on red cells or on erythroid progenitors.

Aluminum intoxication also blunts the response to Epo. Fortunately, aluminum intoxication is not very frequent nowadays. The principal source of intoxication is inadequate treatment of water for dialysis, but phosphate binders also can contribute. Anemia provoked by aluminum overload is usually normocytic but, in the case of severe intoxication, it is microcytic. On the other hand, gastrointestinal aluminum absorption is increased in iron-depleted patients [34]. We must not forget that aluminum and iron can share common metabolic routes and that each can regulate uptake of the other. Both are bound to serum transferrin [34]. Aluminum intoxication reduces absorption and cellular uptake of iron [35]. The diagnostic procedures for aluminum overload

include the monitoring of serum aluminum concentration and, above all, a deferoxamine (DFO) test using low doses (5 mg/kg) if the serum aluminum level exceeds 60 μg/liter. Patients with a positive DFO test have a serum aluminum increment higher than 150 μg/liter and should undergo DFO treatment with the same dose once weekly. The patient should be dialyzed with high-flux membranes [36]. Therapy with DFO in aluminum-induced resistance to Epo therapy enhances the erythropoietic response to Epo in dialysis patients [37].

Other common causes preventing a response to Epo are infections, inflammatory states, and neoplastic diseases. Acute or chronic infections of bacterial, viral, or fungal origin usually are accompanied by a lower response to Epo. Many infections are accompanied by a limited iron availability and a consequent inability of the patient to produce heme [38]. Occult infections as well as inflammatory disorders such as rheumatoid arthritis [39], systemic lupus eythematosus [40], inflammatory bowel disease [41], and malignant neoplastic diseases [42] can decrease the response to Epo. An increased production of cytokines seems to be involved in this decreased response to Epo. In effect, it has been shown that IL-1, TNFα and interferon γ have a suppressor effect on erythropoiesis. Some studies suggest an effect of these inflammatory cytokines on endogenous Epo production [43], but a resistance to the effect of Epo on erythroid progenitor cells also has been demonstrated [44]. Macdougall recently proved that IL-6 also lowers response to Epo [45] and that IL-3 and IGF-1 potentiate erythropoiesis [46]. Furthermore, several chronic inflammatory diseases also raise serum TNFα and IL-1 concentrations [28, 39]. The increase in serum fibrinogen over 4 g/liter is a good clinical indicator of the presence of an inflammatory process and of the response to exogenous Epo [25].

Hepatitis B viral infection is one inflammatory disease in which anemia is not worsened [47]; nor is anemia exacerbated in drug-induced hepatitis or other types of viral hepatitis. Liver inflammation seems to increase endogenous erythropoietin production as a consequence of the capacity of the newly formed hepatocytes to secrete this hormone [48]. An increase in serum immunoreactive erythropoietin has been described in anephric dialysis patients during an episode of acute non-A, non-B hepatitis [48]. Hepatitis C viral infection also is accompanied by an increased responsiveness to exogenous Epo [49]. However, an increase in serum erythropoietin levels as an index of endogenous erythropoietin production has not been observed in other reports [50], despite the improvement of anemia. An alternative explanation could be an increased responsiveness to Epo of the erythroid cells or the production of some cytokines with erythropoictic activity such as IGF-1 [50]. Resistance to Epo treatment also has been reported in an AIDS patient treated with zidovudine (AZT) [51].

Chronic graft rejection frequently causes chronic renal failure and can be considered a chronic inflammatory state. It is not unusual to observe a lack of response to Epo in patients who have undergone transplantation and who have chronic rejection [52]. Also resistance to Epo treatment has been observed in transplant patients who returned to hemodialysis; this hyporesponsiveness can be improved after graft removal [53] or by maintaining cyclosporine treatment [54]. In these cases, the possible effects of immunosuppression must be taken into account. I will return to this topic.

Malignancy must be ruled out in patients who don't respond adequately to Epo. In a group of 81 patients with solid malignant tumors, the serum concentration of immunoreactive erythropoietin decreased, although there was not an absolute inability to produce erythropoietin because hypoxemia induced adequate crythropoietin production [42]. Further, immunosuppressive and chemotherapeutic drugs can interfere with Epo. In fact, chemotherapeutic agents further decrease Epo production. This effect is not only observed with the nephrotoxic agent cis-platinum, but also with other chemotherapeutic agents [42]. Multiple myeloma causes ESRD in a small percentage of patients and is usually accompanied by severe anemia, which can be improved with Epo therapy, albeit at doses higher than usual [55, 56].

The presence of hemolysis also can decrease a patient's response to Epo. The causes of hemolysis are varied, from antibody-mediated hemolysis to hypersplenism to toxic or mechanical hemolysis. Hemoglobinopathies, such as thalassemia and sickle-cell disease, are another frequent cause of hyporesponsiveness to Epo treatment. In all these processes, red cell destruction produces a need for higher Epo doses to combat anemia in these patients [57]. The diagnosis and correction of the cause, when possible, will improve Epo response. Hydroxyurea can improve the response to Epo in sickle-cell disease [58]. A resistance to the response to Epo has been observed in myelodyplastic syndromes [59] and in premature infants [60].

Vitamin B_{12} and folic acid deficiency can each aggravate anemia in ESRD. We do not consider it necessary to administer vitamin B_{12} and folic acid supplements to all dialysis patients. Serum levels of these vitamins are useful for diagnostic purposes. Some patients with vitamin C deficiency have high levels of serum ferritin with low transferrin saturation. Vitamin C supplementation can improve iron availability in patients with functional iron deficiency [61]. Severe malnutrition also can interfere with Epo response [62].

Therapeutic agents can induce Epo resistance. Chemotherapy for malignant disease inhibits erythropoiesis [42]. The effect of immunosuppressive treatment has been studied in patients who have received transplants. Cyclosporine A can reduce the endogenous secretion of erythropoietin in cultured Hep3B cells [63], and in phenylhydrazine-induced anemia in mice [64], but no evidence has shown a decreased response to Epo in patients receiving cyclosporine A [65]. Furthermore, some patients who have received a transplant have had an improved response to Epo treatment after cyclosporine was added to the treatment regimen [54]. This effect might occur because cyclosporine inhibits cytokine secretion. Azathioprine clearly worsens anemia in patients who have undergone transplantation [10].

Angiotensin-converting-enzyme (ACE) inhibitors diminish the production of endogenous erythropoietin in patients with chronic renal failure of different causes [66], including transplant patients with chronic renal failure [67, 68]. However, it appears that Epo requirements are not increased in ESRD patients treated with ACE inhibitors [69]. We have not found any differences in hematocrit and hemoglobin levels, or in the weekly doses of Epo, in hemodialysis patients receiving treatment with ACE inhibitors, compared to others receiving another antihypertensive therapy or those receiving no antihypertensive therapy. Other recent studies also have found no increase in the doses of Epo needed in patients treated with ACE inhibitors [69].

Theophylline, an adenosine antagonist, diminishes the renal production of Epo and lowers hematocrit [70]. It remains to be

proved, however, that patients treated with theophylline need higher doses of Epo.

The literature contains only a few reports on ESRD patients with oxalosis who have received Epo, but the majority of the cases show a poor response to the therapy [71]. Hypothyroidism, a frequent cause of anemia, can worsen anemia in ESRD patients, necessitating higher doses of Epo [72]. Exogenous thyroid therapy can improve hypothyroidism, thereby decreasing the Epo requirements and raising the hematocrit.

Bioincompatible dialysis membranes result in monocyte activation and cytokine secretion [73]. But even the use of biocompatible dialysis membranes can be accompanied by an increase in serum IL-6 and TNFα in the presence of bacterial contamination of the dialysate [74]. Such cytokine activation must be a consequence of the passage of bacterial endotoxins into the blood through a highly permeable membrane. Therefore, when using biocompatible (and highly permeable) membranes, one absolutely must have a sterile dialysate. The possible effect of this cytokine activation on Epo responsiveness has not yet been studied.

Optimizing the use of Epo

Three important points should be kept in mind when one uses Epo in patients with ESRD. First, the factors that aggravate anemia in chronic renal failure, and thus induce hyporesponsiveness to Epo, must be eliminated. I have already addressed these factors (Table 1). Second, iron supplementation must be adequate. This point requires that iron stores be carefully monitored. Serum ferritin is synthesized in the reticulo-endothelial system and secreted into the plasma. The rate of ferritin protein synthesis is governed by the iron concentration in the intracellular iron pool, which is related to the intracellular iron stores [75]. When iron metabolism is balanced, serum ferritin levels reflect the state of the iron stores. Erythropoietin administration acutely decreases serum ferritin levels within a few hours of administration [75]. On the other hand, serum ferritin also can be raised in inflammatory states, infection, and liver disease [76]. One must keep in mind, however, that patients can have a functional iron deficiency with normal or high serum ferritin levels. Transferrin saturation measures the amount of iron joined to transferrin and, although it is not related to iron stores, the saturation level provides a more exact idea of iron availability.

Much attention has recently focused on the percentage of hypochromic red blood cells (defined as an individual cell hemoglobin concentration lower than 28 g/dl [26]) as a reliable index of iron deficiency. When the percentage is higher than 10%, an iron deficiency (absolute or functional) is present [26, 77]. Other parameters that seem more exact in diagnosing iron deficiency are the transferrin receptor concentration in blood, the red cell ferritin concentration, free erythrocyte protoporphyrin, and red cell zinc protoporphyrin. Iron-deficient erythropoiesis can be recognized by an elevation of serum transferrin receptor concentration [25]. Transferrin receptor concentration, as well as the percentage of hypochromic red blood cells, are more accurate for detecting a functional iron deficiency than is the transferrin saturation level [25, 26]. Red cell ferritin concentration could be a valid support to serum ferritin evaluation in the determination of patients with a real iron deficiency erythropoiesis [78]. Free erythrocyte protoporphyrin level is an early marker of iron deficiency in nonuremic patients. Increased levels in uremic patients are a consequence of a defective heme transferrin receptor concentration [79, 80]. Red cell zinc protoporphyrin is a poor marker for iron deficiency [80]. Most of these analyses are not available in the majority of laboratories, however. Although formulas have been devised for calculating the level of iron reserves and iron needs in patients to be treated with Epo [22], clinical experience shows that iron requirements in patients receiving Epo are higher than those derived from theoretical calculations.

Erythropoietin should not be given if iron deficiency exists. Patients must receive iron supplementation before Epo treatment if the following conditions exist: the serum ferritin is lower than 100 μg/ml, the transferrin saturation is lower than 20%, or more than 10% of hypochromic red cells are present. Even with iron supplementation, serum ferritin levels virtually always decrease after Epo therapy. In our experience, after six months of Epo treatment, ferritin levels are at the bottom of the normal range in patients who have received oral iron supplementation. Furthermore, several years ago we observed that high levels of serum ferritin decreased significantly after one year of Epo treatment in renal failure patients with iron overload (polytransfused patients). There is no doubt that Epo treatment is a good therapy for iron overload [81].

Controversy exists regarding whether orally administered iron is adequately absorbed from the gut. Early studies suggested that iron absorption from the gut was increased in dialysis patients who were iron deficient [46, 82]. Other studies suggest that iron absorption increases with Epo therapy [83], but we frequently observe patients, like today's case presentation, for whom oral iron administration is insufficient to maintain adequate iron stores because despite oral iron administration, serum ferritin levels decrease during Epo therapy; this situation also has been observed by other authors [75]. In fact, some studies suggest that iron absorption is impaired in dialysis patients taking Epo [84]. We usually administer intravenous iron supplementation before Epo treatment to patients whose serum ferritin levels are lower than 100 μg/liter or who have a transferrin saturation lower than 20% or a percentage of hypochromic red cells higher than 10%. In these cases, we administer three successive intravenous doses of 62.5 mg of ferrous gluconate during hemodialysis. Periodic monitoring of iron metabolism indicates the frequency of successive doses of intravenous iron. Similar dosage schedules of intravenous iron have been proposed by other authors using, in some cases, iron dextran [46, 84]. In a randomized prospective study on iron supplementation in renal patients treated with Epo, intravenous iron was compared with oral iron and no iron supplementation. Patients receiving regular intravenous iron had a significantly increased hemoglobin response, better maintained serum ferritin, and lower Epo dosage requirements [3]. In my opinion, intravenous iron avoids gastrointestinal side effects and poor compliance with oral iron, as well as possible poor absorption from the gut.

The third important point in optimizing Epo therapy is determining the best route and dose of administration. The intraperitoneal route for peritoneal dialysis patients has the disadvantage of the low bioavailability of Epo administered by this route (less than 10% compared to the intravenous route [7, 85]). However, some studies show that Epo can be useful when administered by the intraperitoneal route, if the overnight peritoneal fluid volume is reduced to one liter and Epo is administered in this fluid [7]. The intraperitoneal route can be useful in patients in whom subcutaneous administration poses problems, such as peritoneal

dialysis-treated children. The intravenous route was the first used, but studies soon showed that the subcutaneous route allowed a reduction in doses of approximately 30% with similar results [86] and with considerable economic savings. Other studies confirm these findings, but most of them are difficult to interpret because of flaws in study design and methods [87]. Recent prospective, randomized, cross-over studies show the same elevation of hemoglobin level whether the Epo is given by intravenous or subcutaneous route [88]. Other authors also observed no difference in hematocrit in patients treated either by intravenous or subcutaneous route [89]. In both studies intravenous iron supplementation was administered [89]. In fact, in Europe, according to the EDTA Registry Report of 1993 [1], nearly 50% of the dialysis patients receiving Epo receive the hormone intravenously [1]. There are important variations from one country to the next. In Austria and Spain, more than 50% of the patients receive Epo by the intravenous route; in the United Kingdom, the majority of patients receive the treatment subcutaneously [1].

A conventional starting intravenous dose is 40–50 IU/kg thrice weekly (2000–4000 IU/dose). When the subcutaneous route is used, the usual starting dose is 20–30 U/kg thrice weekly (1000–2000 IU/dose). When the target hematocrit is reached, the doses can be lowered and a much lower dosage is sufficient to maintain the desired hematocrit.

The bioavailability of subcutaneously administered Epo is higher when the injection is made in the thigh compared to the arm or abdomen [90]. The intravenously administered maintenance dose (when the target hematocrit has been achieved) is best administered two or three times per week. For the subcutaneous route, when the weekly dose is low (less than 4000 IU), the entire dose can be administered at one time. We have not observed significant variations in hematocrit levels in hemodialysis patients receiving Epo in three doses per week who later received it in one weekly dose. In a group of 21 hemodialysis patients, we changed the dosage schedule from three doses per week to one dose per week when the mean hematocrit of the patients was 32.5% ± 3.8%. After 12 months with one dose per week, the mean hematocrit was 32.5% ± 3% [91]. Other studies have shown similar observations [92]. The principal reason for administering one dose per week is to decrease pain, although the pain is also related to the amount injected; therefore the one dose per week regimen is recommended only for patients on a low dose. The differences observed in the pain produced by epoetin-α (Epo diluted in an aqueous solution containing sodium chloride, citrate buffer, and human serum albumin) and epoetin-β (lyophilized Epo without citrate buffer and human serum albumin) seem to disappear when citrate is eliminated as the vehicle in epoetin-α [7]. In summary, we can conclude that both intravenous and subcutaneous routes are appropriate for hemodialysis patients, but that the subcutaneous route is preferable for pre-dialysis or peritoneal dialysis patients. Regarding a maintenance dosage schedule, two or three times/week seems to be acceptable and, in patients receiving a low dose, one weekly dose suffices.

Eschbach has recently emphasized that adjunctive therapies can increase the efficiency of Epo [72]. Among these, the use of androgenic steroids has been proposed by several authors [93]. Testosterone, nandrolone decanoate, and fluoxymesterone have been used for this purpose. Economic arguments have been used to propose their use in developing countries to reduce the Epo dose and to reach the same results with less cost. However, the adverse effects of androgenic steroids cannot be disregarded. Among them, acne, liver disease, elevation of serum triglycerides, hirsutism, virilization, and priapism have been described [94]. While IL-1 and IL-6 inhibit the effect of Epo, IL-3 and IGF-1 stimulate erythroid progenitor cells. Animal studies have demonstrated that it is possible to decrease the dose of Epo when IL-3 is administered [95]. Interleukin-3 acts with Epo in stimulating erythroid progenitor cells. In any case, we must consider the possible toxic effects of IL-3 as well as its cost. It is also not clear what the possible effect of L-carnitine administration is on improving the response to Epo [96]. Thymopentin, administered concomitantly with Epo, ameliorates anemia in hemodialysis patients resistant to Epo therapy alone [97]. More experience is necessary to evaluate the usefulness of this pentapeptide as an adjunctive therapy to Epo.

Finally, dialysis efficiency must be taken into account in any attempt at maximizing the effectiveness of Epo therapy. It is a well-known fact that the improvement in hemodialysis efficiency by using high-efficiency or high-flux dialysis is usually accompanied by an improvement in anemia; longer hemodialysis is associated with a higher hematocrit [98]. It has not been determined whether this improvement in anemia is related to better uremic toxin removal, biocompatibility, or other factors related to dialysis efficiency. Peritoneal dialysis patients also have higher hematocrit levels than do patients undergoing conventional hemodialysis, possibly because of the removal of some larger toxic molecules, although these patients have higher iron stores because of less blood loss [72]. Moderate physical exercise also might have a positive effect on dialysis patients, because regular, fairly strenuous exercise can improve erythropoiesis [99], although the mechanism for this has not been clarified.

Beneficial effects

An improved hematocrit in Epo-treated patients provides both non-cardiovascular and cardiovascular benefits. The non-cardiovascular effects include a reduction in fatigue and increased working capacity and exercise tolerance [100]. Muscular fatigue during exercise might be caused by ATP or substrate (glycogen) depletion, by a limited flux of oxygen due to acidosis, alterations in electrolytes, or insufficient muscle mass [101]. Skeletal muscle shows a reduced oxidative capacity in chronic renal failure patients [101], but a normal glycogen content has been found in the muscle of patients with ESRD [102]. The ATP production capacity is increased in anemic hemodialysis patients [103]; this suggests that mitochondrial respiratory capacity does not limit maximal performance in chronic renal failure. In fact, this increase might be a form of metabolic adaptation to the decrease in oxygen delivery [103]. The rise in hemoglobin concentration as a consequence of Epo administration is associated with a rise in maximal oxygen uptake (VO_2 max) [104]. Maximal exercise capacity increases during Epo treatment [105] as does the anaerobic threshold.

Coagulation parameters improve. Platelet aggregation, factor VIII, and fibrinogen levels improve due to the increase in the red cell mass [106]. These changes, however, might confer a risk of thrombotic events, such as vascular access clotting and an increase in the need for heparin during hemodialysis [107]. Long-term controlled studies do not demonstrate a higher incidence of thrombotic episodes, however [108]. The usual immunosuppression of chronic renal failure improves with Epo therapy. A rise in

blood viscosity can worsen microcirculation and is probably one of the factors implicated in the peripheral vascular resistance increase that affects these patients. Some studies have shown a deficit of cognitive function in anemic ESRD patients that can be assessed psychometrically, such as by the trailmaking test and by evoked potentials [109]. Evoked potentials are useful in the evaluation of cognitive brain dysfunction. The elevation of hematocrit from 22% to 30% during Epo treatment improved stimulus-related evoked potentials and trailmaking in 15 chronic hemodialysis patients [109]. This improvement in cognitive function could explain, at least in part, the feeling of well-being and the increase in working capacity of the patients.

Other non-cardiovascular benefits also accrue with Epo therapy. An improvement in sexual function has been observed, especially in males [110]. This change in male sexual function might be due not only to an improvement of anemia, but also to an increase in serum testosterone levels related to a decrease in luteinizing hormone [111]. Erythropoietin therapy also can improve appetite, the feeling of well-being, depression, and the sleep/awake pattern. Raynaud's phenomenon decreases or disappears in some patients. An improvement in the lipid profile of hemodialysis patients was recently described; serum total cholesterol, ApoB lipoprotein, and serum triglycerides decrease with Epo treatment [112]. Finally, cytotoxic antibodies diminish in sensitized polytransfused patients [113]. We have observed this phenomenon in 42 patients after two years of Epo treatment in parallel to the striking decrease in the number of transfusions [114].

Nutritional status improves in patients treated with Epo [115]. A short-term, randomized study showed an improvement of pruritis in 10 hemodialysis patients; itching returned after one week of discontinuation of Epo therapy [116]. This improvement was not related to the change in hemoglobin level. These patients had elevated plasma histamine levels, as compared with hemodialysis patients without pruritis and with normal subjects. Therapy with Epo decreased plasma histamine levels, and recurrence of pruritus after Epo discontinuation was accompanied by an increase in plasma histamine concentration [116]. Other authors have seen an improvement of pruritus in hemodialysis patients treated with an anti-allergic drug (azelastin HCl) without changes in the plasma histamine levels during azelastin treatment [117].

The cardiovascular effects of Epo therapy are evident in different short-term studies at one or two years. In ESRD patients, the prevalence of left-ventricular hypertrophy (LVH) is between 50% and 80%; the prevailing functional disturbance associated with LVH is left-ventricular diastolic dysfunction. Left-ventricular hypertrophy is an important and independent risk factor for mortality in these patients [118]. On the other hand, anemia is associated with an increased heart rate and left-ventricular stroke volume, which result in an elevated cardiac output, an important stimulus for ventricular hypertrophy. Several studies have shown an improvement in LVH during Epo treatment. Left-ventricular end-diastolic diameter decreases, as does interventricular septum thickness and left-ventricular mass index [119, 120]. In most studies, a reduction of left-ventricular mass index from 170–190 g/m^2 to 130 g/m^2 has been observed after 6 to 12 months of Epo treatment [121]. Taking into account that more than 50% of deaths in ESRD patients are due to cardiovascular causes [1], and that left-ventricular mass is an important risk factor for mortality in these patients, it is reasonable to anticipate that LVH reduction with Epo therapy will improve long-term survival [122]. In one study, the survival of ESRD patients with a left-ventricular muscle index lower than 125 g/m^2 was significantly better at five-year followup compared to that in patients with a left-ventricular muscle index higher than 125 g/m^2 [118]. However, the hypothesis of an improvement of patient survival after Epo treatment has not yet been substantiated. Cardiac output decreases as a consequence of stroke volume decrease or heart rate reduction [119, 123, 124]. Another beneficial effect of Epo treatment is the reduction in the incidence of angina in patients with coronary heart disease after anemia is corrected [125].

Peripheral vascular resistance increases markedly in parallel with a reduction of cardiac output [123, 126, 127]. This elevated systemic peripheral resistance is the main cause of hypertension in patients receiving Epo (see later). Several factors can contribute to increased peripheral vascular resistance. The increased blood viscosity can contribute to this effect [128] as well as to the improvement of hypoxia, which would decrease hypoxic vasodilation. Erythropoietin also increases pressor responsiveness to noradrenaline and angiotensin II and improves the anemia-mediated disturbance of alpha-2 receptor function [129]. Alpha-2 adrenoceptor density and plasma catecholamines are increased in ESRD patients, who likely have a defective receptor-ligand interaction [129]. When anemia is corrected by Epo therapy, both catecholamine concentration and alpha-adrenoceptor density decreased and vascular resistance increased [129]. Lastly, the increase in vascular resistance has been related to an elevation of platelet cytosolic free Ca^{++} [130] and to increased endothelin-1 production [131]. Figure 2 summarizes the potential mechanisms involved in Epo-related hypertension.

Total blood volume remains constant, but plasma volume decreases during Epo therapy. The decrease in plasma volume can influence hemodialysis efficiency, although significant variations have not been reported in studies using urea kinetic modeling [132]. The incidence of hemodialysis-related hypotension decreases in parallel with the correction of anemia [133], probably as a consequence of the improvement of the autonomic nervous system dysfunction observed during Epo therapy [134].

Hypertension was the most frequent adverse effect in the early experience with Epo treatment, appearing in previously normotensive patients or in those with worsening pre-existing hypertension; the prevalence rate can reach 30% [135]. More recently, however, probably because of less-aggressive dosage schedules, the reported prevalence of hypertension is about 20% [122]. Hypertension that develops during Epo treatment and worsening of previously existing hypertension generally are easy to control via a careful adjustment of the hemodialysis patient's "dry weight," initiation of antihypertensive therapy, or an adjustment of the dosage schedule of the antihypertensive agents previously used. The improvement in appetite usually is a cause of weight gain in dialysis patients treated with Epo. A reduction in dry weight by removal of fluid during dialysis can be sufficient to control hypertension. If this is not sufficient, antihypertensive agents must be added or, if the patient was previously under antihypertensive treatment, the doses must be increased or another agent must be introduced. Epo doses can be reduced, but only in very exceptional cases must Epo therapy be stopped. Erythropoietin imposes no contraindications for any specific drug;

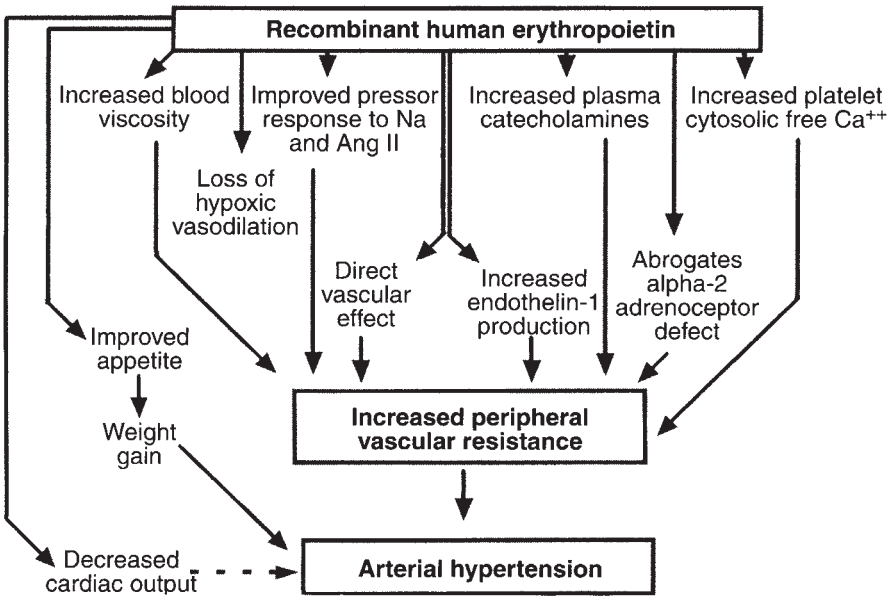

Fig. 2. *Mechanisms involved in Epo-related hypertension.* Epo induces an increase in blood viscosity, plasma catecholamine levels, platelet cytosolic free calcium, and endothelin-1 production. The pressor response to noradrenaline (Na) and angiotensin II (Ang II) improves, as does the alpha-2 adrenoceptor defect. Hypoxic vasodilation decreases, and Epo probably has a direct vascular effect. All these facts may contribute to the increase of peripheral vascular resistance. Epo improves appetite, thus possibly inducing weight gain. The decrease of cardiac output is overrun by the increase of peripheral vascular resistance, and arterial hypertension appears or worsens in the previously hypertensive patient.

neither ACE inhibitors nor calcium antagonists are contraindicated. One recent study showed a 5.8% prevalence of hypertension in 34 hemodialysis patients under Epo treatment who also were receiving antiplatelet therapy; in another group of 57 hemodialysis patients receiving Epo but not antiplatelet therapy, the prevalence of hypertension was 56%. The antiplatelet drugs received by the patients studied were ditazole, ticlopidine, and dipyridamole plus aspirin [136]. There is no clear explanation for this beneficial effect of antiplatelet therapy in Epo-related hypertension; one can infer that changes in platelet aggregability induced by Epo might be involved in the pathogenesis of Epo-related hypertension. Other adverse effects, such as thrombotic events, clotting of the vascular access, seizures, and cerebrovascular accidents, have a similar prevalence to that observed in non-Epo-treated patients [135].

Quality of life seems to improve in patients receiving Epo. Several studies using quality of life questionnaires have reported significant improvement [137–139]. Our own prospective study evaluated quality of life in hemodialysis patients with ESRD, both before starting Epo treatment and at three and six months after therapy was begun [140]. A control group of "non-anemic patients" was studied. The tests used for this study were the Karnofsky Performance Scale (KS) and the Sickness Impact Profile (SIP). The KS is a well-known and simple global indicator of self-sufficiency and functional capacity [141]. The SIP, a more complex questionnaire, is based on criteria that evaluate dysfunctional behavior related to the illness [142]. It comprises 136 items in 12 activity categories in which dysfunctional behavior can occur. The 12 categories are grouped to obtain physical and psychosocial dimensions and a global SIP score. In this study, we used the Spanish version of the SIP, done by F. Moreno, adapted from the "Spanish" version by W. Hendricson [143] for our environment. We observed a significant improvement in the KS as well as in the physical and psychosocial dimensions and the global SIP score at three and six months in a group of 57 non-diabetic hemodialysis patients treated with Epo, whose mean hematocrit increased from 21.03% ± 0.3% to 29.0% ± 0.4%, after six months; we did not detect a similar response in the control group of 29 hemodialysis patients not treated with Epo whose mean hematocrit was 30.0% ± 0.8% before starting the study, and 31.0% ± 0.8% after six months [140] (Table 3). We used a multivariate analysis by stepwise linear regression to evaluate improvement in specific factors related to the quality of life. Improvement in quality of life was inversely related to the basal quality of life indicators; patients with a worse clinical condition before treatment experienced a more intense feeling of improvement. Work disability before Epo treatment is also related to a higher improvement in quality of life, probably because work disability may be an indicator of poor quality of life. The hematocrit at six months of treatment also was related to an improvement in quality of life. Co-morbidity, measured by the index proposed by Friedman [144], was another factor related to a poor quality of life [140].

Table 3. Hematocrit and quality-of-life scores in a group of hemodialysis patients treated with Epo and a control group of hemodialysis patients not receiving Epo[a]

	Epo group	Control group
Number	57	29
Mean age (*years*)	50 ± 2	53 ± 2
Basal hematocrit (%)	21.0 ± 0.3	30.0 ± 0.8
Hematocrit at 6 months (%)	29.0 ± 0.4[b]	31.0 ± 0.8
Basal KS score	68.4 ± 1.8	79.7 ± 2.6
KS score at 6 months	81.0 ± 1.4[b]	76.9 ± 2.6
Basal GS of the SIP	19.8 ± 1.6	16.6 ± 2.4
GS of the SIP at 6 months	13.5 ± 1.2[b]	15.1 ± 2.2
Basal PhD of the SIP	15.4 ± 1.8	11.6 ± 2.4
PhD of the SIP at 6 months	9.6 ± 1.4	10.6 ± 2.5
Basal PsD of the SIP	19.0 ± 1.9	16.0 ± 3.0
PsD of the SIP at 6 months	10.8 ± 1.3[b]	14.3 ± 2.9

[a] Diabetic patients were not included in either group. (From Ref. 140). Data as mean ± standard error of mean. KS, Karnofsky scale; SIP, sickness impact profile; GS, global score; PhD, physical dimension; PsD, psychosocial dimension. Higher KS scores mean better quality of life. Lower SIP scores mean better quality of life.

[b] $P < 0.0001$.

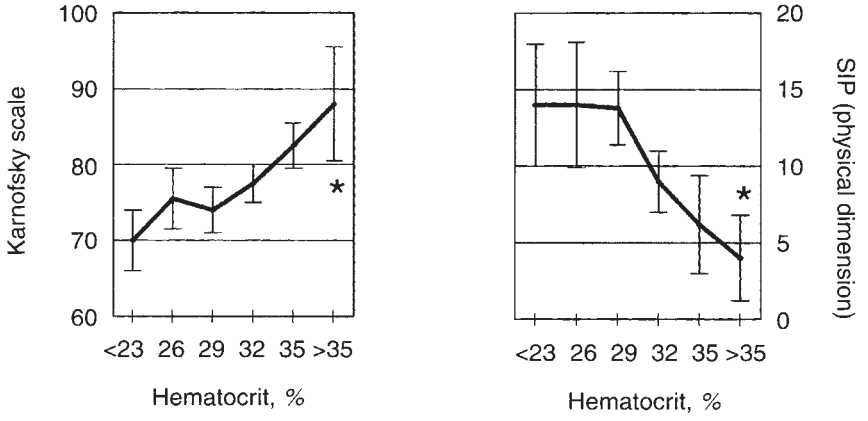

Fig. 3. *Relation between quality-of-life scores and hematocrit.* The Karnofsky scale scores and the physical dimension of the Sickness Impact Profile scores are better in patients with higher hematocrit. This effect is particularly evident with hematocrits higher than 29% (In the Karnofsky scale, higher scores mean better quality of life, and in the Sickness Impact Profile, lower scores mean better quality of life.) $*P < 0.01$. (Results were obtained from 275 quality-of-life questionnaires filled out by 102 hemodialysis patients. Scores are represented as mean ± SD. From Ref. 148.)

A Spanish cross-sectional multicenter study of 1013 dialysis patients showed that the principal factors related to quality of life are age, co-morbidity and, again, hemoglobin and hematocrit levels [145, 146]. Other factors related to a better quality of life are higher socioeconomic and cultural levels. Diabetes, female gender, and intermittent claudication related to a lower quality of life. Patients with hemogloblin levels over 12 g/dl had significantly higher quality-of-life scores. These differences were observed both in the physical and psychosocial dimensions as well as in the global score of the SIP. Although this study evaluated more than 1000 patients, no relationship was observed between quality of life and dialysis technique (conventional hemodialysis, hemodiafiltration, or peritoneal dialysis), the use of synthetic or cellulosic membranes, or bicarbonate or acetate hemodialysis. No relationship was observed between quality of life and dialysis efficiency (as measured by KT/V), or protein intake, measured by protein catabolic rate (PCR). In any case, we must not forget that this study was cross-sectional and that the patients had not been randomly assigned to a particular technique. Prospective studies are necessary to clarify whether dialysis efficiency and biocompatibility (including biocompatibility of dialysate) have an influence on quality of life.

The target hematocrit

Our own study first yielded firm evidence that quality of life improved during Epo treatment when the hematocrit level rose. Although aged patients had a higher co-morbidity index, a group of 23 non-diabetic hemodialysis patients older than 60 years had a significant improvement in quality-of-life scores measured by the KS and SIP, in parallel with their hematocrit increase during Epo therapy [140]. A similar improvement in quality-of-life scores also was observed in 15 patients older than 65 years [140, 147]. This is an important finding: age is not a contraindication for Epo treatment.

What should the target hematocrit be for patients receiving Epo? This is one of the controversies related to EPO treatment. In Europe, according to the EDTA Registry, 50% of the centers had a target hemoglobin level between 9.5 g/dl and 10.4 g/dl, but the percentage of centers reporting higher target hemoglobin levels (10.5 g/dl–11.4 g/dl) is increasing [1]. The target hemoglobin and hematocrit levels usually have been chosen empirically. Unfortunately, at present, there are no long-term morbidity and mortality studies relating to hematocrit in patients receiving Epo. Currently, the best available index for deciding target hematocrit is based on quality of life and working capacity. A Canadian multicenter study showed a small improvement in quality of life and exercise capacity in patients with a mean hemoglobin level of 12 g/dl [137]. As I mentioned, in our own experience, hematocrit level is one of the factors related to the improvement in quality of life [146].

In another study using the same KS and SIP instruments, we showed a direct relationship between hematocrit and quality of life scores. We compared KS and SIP scores for 57 hemodialysis patients receiving Epo treatment and 29 untreated patients with various hematocrits. Both groups were matched for age and co-morbidity. The physical dimension of the SIP (as well as the global score and the KS) improved markedly at hematocrits ranging from 29% to over 35%. The KS and SIP scores were similar in patients with hematocrits up to 29%, but with hematocrits higher than 31%, a direct relationship existed between hematocrit and the quality-of-life scores. This relationship did not disappear at the higher hematocrit levels (Fig. 3). We concluded that a direct relationship exists between quality of life and hematocrit, which was preserved even at the higher hematocrit levels [148].

Other authors have measured maximum oxygen supply to the brain at different hematocrit levels during Epo treatment [149]. They calculated the maximum oxygen supply to the brain from measurements of regional cerebral blood flow using positron emission tomography and arterial oxygen content. The optimal hematocrit for maximum oxygen supply in this study was around 40%. Eschbach et al increased Epo doses to raise hematocrit from a mean of 32.6% to 42% in 13 hemodialysis patients and noted a significant improvement in quality of life, exercise capacity, and cardiac function [150]. Cardiac output decreased from 5.1 liter/min to 4.3 liter/min, exercise duration increased by 20%, and maximal oxygen consumption increased by 24%. There were no adverse effects. However, the mean increase in Epo dose was 69% [150].

We can summarize by saying that a conventional target hematocrit of about 30%, or a target hemoglobin of about 9 g/dl, must be considered insufficient. One might reasonably consider that the conventional normal hematocrit should be the target hematocrit for patients with ESRD. However, the biggest problem in obtaining a "normal" hematocrit in ESRD patients is the increase in the required dose of Epo and therefore the cost of treatment. It is

probable that the most reasonable position is to individualize target hematocrit. Young patients who carry out physical activities or patients with heart disease would need a nearly normal hematocrit. However, older patients without heart disease or sedentary patients would not need such high hematocrit levels. Eschbach's idea of letting patients decide what hematocrit is best for them is very enticing [72] and would rationalize the idea of individualizing target hematocrit. Erythropoietin therapy must be individually optimized to achieve maximal benefits at a lower cost.

Can Epo treatment lengthen survival?

The long-term benefits of Epo have not been determined. A recent study showed that anemia can predict mortality in ESRD patients independently of age, presence of diabetes, cardiac failure, serum albumin and creatinine levels, blood pressure, and cardiac disease [151]. Anemia increases left-ventricular end-diastolic diameter, which promotes LVH [151], and LVH increases mortality by more than three times in hemodialyis patients [152]. Thus correcting anemia and therefore normalizing cardiac size and decreasing cardiac output should improve survival in patients with ESRD. Patients with polycystic kidney disease have a better survival rate than do other ESRD patients [153], and patients with polycystic kidney disease have higher levels of hemoglobin [153]. We should seriously consider the recently made suggestion that we should "adapt the dialysis unit to increased hematocrit levels" [154], because sufficient evidence now indicates that higher hematocrits reduce long-term morbidity and mortality. Finally, Epo therapy can reverse many uremic (probably, in large part, anemic) symptoms and improve the quality of life of chronic renal failure patients before dialysis and after dialysis is initiated. It is not an exaggeration to say that Epo has been the most prominent medical advance in the treatment of ESRD patients since maintenance dialysis treatment was introduced 36 years ago.

Questions and answers

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts, U.S.A.*): Regression of left-ventricular hypertrophy following Epo treatment is obviously of great clinical importance. How rigorously has this effect been documented and how consistent is it? Has it been dissociated from the effect of certain antihypertensive medications, which by themselves can lead to regression of cardiac hypertrophy?

DR. VALDERRÁBANO: The best answer to your question would have been evidence that Epo therapy decreases the long-term cardiovascular mortality rate in dialysis patients. But we have no evidence of that. Two factors could reduce left-ventricular hypertrophy. One is the improvement of anemia. It is well proven that the improvement of anemia with Epo decreases left-ventricular hypertrophy [119–121], and that this effect is independent of the effect of antihypertensive agents, such as ACE inhibitors or calcium antagonists. The second factor is hypertension. We must be especially careful to achieve excellent control of hypertension when treating dialysis patients with Epo. If hypertension is well controlled, left-ventricular hypertrophy will improve and ventricular mass will decrease [155]. But the balance between anemia and hypertension must be carefully maintained. On the other hand, anemia per se is an independent mortality risk factor, irrespective of left-ventricular hypertrophy or hypertension [151]. This means that we must take both factors into account to achieve the best results from Epo treatment.

DR. F. PAOLO SCHENA (*Institute of Nephrology, Polyclinic, Bari, Italy*): Do you believe that it is important to measure endogenous (native) Epo in uremic patients undergoing periodic dialysis before starting Epo treatment, since this therapy is very expensive?

DR. VALDERRÁBANO: From the practical point of view, it is not necessary to have serum Epo levels before starting treatment with Epo. Of course, to maintain a positive cost-benefit relation, the optimal use of Epo is fundamental. Thus therapy should include adequate iron monitoring and iron supplementation, correct dosage of Epo, and the exclusion of all the causes of Epo hyporesponsiveness. In the majority of cases, knowing the pre-treatment Epo level is not necessary because it is not predictive of the response to exogenous Epo.

DR. SCHENA: Does Epo treatment improve graft survival in uremic patients who receive Epo therapy before renal transplantation?

DR. VALDERRÁBANO: I do not know of any studies regarding the effect of Epo therapy before transplantation on graft survival. I should note that azathioprine decreases the response to Epo [10]. On the other hand, cyclosporine does not have this effect; in fact, cyclosporine sometimes improves the response to Epo, likely because it decreases cytokine production [54]. More and more pre-dialysis patients are treated with Epo, and one of the causes of end-stage renal disease, and thus starting dialysis, is a failed renal graft. Erythropoietin does not seem to hasten the progression of renal dysfunction in such patients. However, we need prospective and controlled studies to clarify this point.

DR. FERNANDO CARRERA (*Department of Nephrology, Hospital SAMS, Lisbon, Portugal*): Is there a correlation among level of anemia, need for Epo, and the type of dialysis membrane used? If so, is there any relation between quality of life and the type of dialysis membranes used?

DR. VALDERRÁBANO: The use of high-permeability and biocompatible membranes, as well as longer hemodialysis sessions, has been associated with higher hematocrit in patients not treated with Epo [98]. I don't know of any correlation between quality of life and the type of membrane used. Moreover, in the multicenter study carried out in Spain, more than 1000 patients were included, and no relationship was apparent between quality of life and the type of dialysis membrane used [145]. We expected to find a higher quality of life in patients treated with the more sophisticated, more expensive, and more advanced dialysis techniques, that is, biocompatible membranes, hemodiafiltration, and other techniques. However, this is not what we found. A possible explanation is that this study was retrospective and not randomized; it was a cross-sectional study.

DR. DONALD SILVERBERG (*Department of Nephrology, Tel Aviv Medical Center, Tel Aviv, Israel*): Did you obtain blood pressure data showing no change in blood pressure in Epo administration with 24-hour blood pressure monitoring or just with usual blood pressure measurements obtained in the clinic? Recent 24-hour blood pressure studies have shown almost uniform elevation of blood pressure with Epo, particularly at night [156].

DR. VALDERRÁBANO: We measured our patients' blood pressure during dialysis sessions or at office visits. We did not do 24-hour blood pressure monitoring on our patients. Twenty-four hour blood pressure monitoring is the best method of evaluating blood

pressure control in any hypertensive patient as well as the efficiency and safety of any antihypertensive drug [156]. In my opinion, the problem you raised seems to be related to the type of antihypertensive agent used more than to the hypertensive action of Epo.

DR. SILVERBERG: To what level do you increase ferritin or transferrin saturation in pre-dialysis or hemodialysis patients? If you had increased ferritin to 400 μg/liter before giving Epo, would you have achieved the same elevation of hematocrit as with Epo?

DR. VALDERRÁBANO: One of the main ways of improving a patient's reponse to Epo is with intravenous iron repletion [3, 46, 84]. We also must monitor the patient to prevent iron overload. In our experience and in published studies [46], intravenous iron administration produces no adverse effects if the transferrin saturation and ferritin levels are periodically monitored. Isolated administration of iron without Epo does not achieve the same elevation of hematocrit, and in this situation there is a risk of iron overload. In your paper, you showed an increase of hematocrit from 29.4 ± 3.2% to 32.4 ± 2.2% in a group of 22 pre-dialysis patients treated with 200 mg of intravenous ferric saccharate, once monthly for five months, without additional Epo treatment [157]. In these 22 patients, the mean serum ferritin level increased from 94 ± 81 μg/liter to 296 ± 172 μg/liter. The experience in pre-dialysis patients treated with Epo and with oral iron supplementation showed higher increments in hematocrit [4, 5] than that described administering only I.V. iron supplements.

DR. SILVERBERG: Could you clarify the parameters that guide iron administration?

DR. VALDERRÁBANO: A ferritin level lower than 100 μg/liter or transferrin saturation lower than 20% indicates iron deficiency. Several intravenous iron doses are necessary to replete iron stores. When the serum ferritin level is higher than 100 μg/liter or transferrin saturation higher than 20%, we continue administering intravenous iron at a different dosage; that is, we give 62.5 mg of ferrous gluconate once weekly, once every two weeks, or once per month according to the serum ferritin levels. Also we monitor the serum ferritin level and avoid ferritin levels above 300 μg/liter.

DR. SILVERBERG: You said a subcutaneous Epo dose is more effective than one given intravenously in hemodialysis patients. Yet studies have shown that if the level of ferritin is equal, the response to the two methods is similar [88].

DR. VALDERRÁBANO: This problem has not been fully clarified. Several studies have shown that lower doses administered subcutaneously can produce similar results as higher intravenous doses [86, 158]. However, recent cross-over randomized studies showed a similar response whether Epo is given intravenously or subcutaneously [87, 88].

DR. FRANTISEK KOKOT (*Professor of Medicine, Department of Nephrology, Silesian University of Medicine, Katowice, Poland*): You stressed the problem of hyporesponsiveness to Epo. As you know, there is a small population of patients who are *hyper*responsive to Epo, in whom, in spite of discontinued Epo administration, the hematocrit is maintained or even increased for several months. Of course, in these patients the presence of a renal cyst cannot be excluded. Could you comment on the problem of hyperresponsiveness to Epo in hemodialyis patients without renal cysts?

DR. VALDERRÁBANO: This problem was reported in the case you recently published, in which renal cysts were not present [159]. I had a similar experience, but in patients with renal cysts. We stopped giving Epo to two patients treated with Epo for more than one year, because the hematocrit level exceeded 50%. Six months later, both patients' hematocrits exceeded 40% without Epo treatment or iron supplementation. Both of our patients had acquired cystic disease in their native kidneys. The serum Epo levels in these two patients were normal for their hematocrit levels. Serum Epo levels in dialysis patients before treatment with Epo are lower than those observed in healthy controls when correlated with their hematocrit or hemoglobin levels [18]. Our two patients with renal cysts had normal serum Epo levels and normal hematocrits, but there are many other dialysis patients with acquired cystic disease who are anemic. I have not seen hyperresponsiveness to Epo in other patients.

DR. MADIAS: Your data suggest that administration of Epo to pre-dialysis patients retards the progression of renal disease. Given the various shortcomings of using the 1/Cr ratio as an index of GFR, do you know of any studies on progression that have used direct measurements of GFR?

DR. VALDERRÁBANO: Yes, a 1994 study shows that renal function did not worsen in pre-dialysis patients treated with Epo [17]. The authors measured the GFR with ^{125}I-iothalamate. The majority of the studies in humans monitored renal function by the slope of the inverse of serum creatinine, but these did not find a decline in renal function in pre-dialysis patients receiving Epo when they periodically measured GFR.

DR. PIETRO ZUCCHELLI (*Professor of Medicine, Malpighi Department of Nephrology, S. Orsola-Malpighi Hospital, Bologna, Italy*): You said that Epo can reverse left-ventricular hypertrophy and that data suggest that left-ventricular hypertrophy and left-ventricular diastolic dysfunction are the main causes of hemodialysis-related hypotension. Have you data on Epo's effect on the frequency of hemodialysis-related hypotension?

DR. VALDERRÁBANO: I mentioned a decrease in the frequency of hemodialysis-related hypotension as a beneficial effect of Epo (unpublished observations). Our own patients have experienced this effect, and they tolerate hemodialysis better. Patients with severe anemia are prone to hemodialysis-related hypotension, and Epo improved hemodialysis-related hypotension in a group of hemodialysis patients [133]. In this study, however, the patients were also shifted from acetate hemodialysis to bicarbonate hemodialysis, and it is well known that bicarbonate hemodialysis improves dialysis tolerance. The improvement of hemodialysis tolerance during Epo treatment might be explained through the improvement of anemia itself or through the different vascular effects of this hormone, which increases peripheral vascular resistance (see Fig. 2). On the other hand, hemodialysis-related hypotension also is related to the autonomic nervous system dysfunction existing in end-stage renal disease, and this dysfunction improves during Epo therapy [134]. In fact, Epo therapy significantly raised the blood pressure in a group of 8 patients with non-renal disease and orthostatic hypotension (4 patients with type-I diabetes mellitus and autonomic neuropathy, 3 patients with pure autonomic failure, and one patient with sympathotonic orthostatic hypotension) at a dose of 50 IU/kg thrice weekly [160]. On the other hand, London et al showed that Epo not only improved left-ventricular end-diastolic diameter, but also significantly increased the venous tone [127]. This venoconstriction observed during correction of anemia with Epo contributes to an adequate venous return and cardiac filling [127]. All these factors might participate in the improvement of hemodialysis-related

hypotension, although other authors did not find any change in the incidence of hypotensive episodes in hemodialysis patients receiving Epo in spite of an increase in the total peripheral resistance index of 62.3% [161].

DR. JORGE CANNATA (*Professor of Medicine, Head of the Research Unit, Hospital Central de Asturias, Oviedo University, Oviedo, Spain*): I want to come back to a practical point, that is, the target hematocrit level in patients receiving Epo. According to the data you have shown from the EDTA Registry, it seems that 50% of the European centers have selected a target hematocrit of around 30%. Looking at your results on quality of life, it seems that it should be useful to raise the hematocrit higher. Is this a useful or safe policy as a general practice in dialysis units?

DR. VALDERRÁBANO: Approximately 50% of European centers are using a conventional target hematocrit of about 30%, but the EDTA Registry report also showed a significant number of centers using higher target hematocrit levels. The main question regarding the target hematocrit is, why isn't a normal hematocrit the target hematocrit? If a relatively healthy person feels poorly with a low hematocrit, why shouldn't a patient with end-stage renal failure? The main reason for individualizing the target hematocrit is the high cost of erythropoietin. Eschbach et al showed in 13 hemodialysis patients that increasing Epo doses significantly raised the hematocrit in some patients, but most of these patients needed a greater than 60% increment in the dose of Epo to achieve a hematocrit higher than 40% [150]. This means that the cost of treatment was increased significantly. Young patients doing physical exercise require a higher hematocrit level. But this is not the case with old patients living a sedentary life. In these cases it is probably not necessary to increase the hematocrit to the same levels as in more active patients. On the other hand, angina can occur at different hematocrit levels for any patient, and the objective should be to maintain the patient free of symptoms. Finally, we must not forget that a clear relationship between the hematocrit level achieved during Epo treatment and the incidence of adverse effects (that is, hypertension) has not been reported.

DR. JOSEPH W. ESCHBACH (*Professor of Medicine, University of Washington, Minor and James Medical Clinic, Seattle, Washington, U.S.A.*): Thank you, Fernando, for your excellent review today. My question relates to the issue of how to optimize the hematocrit and the dose for our patients. Why is there a range in which patients respond to a given Epo dose? Is this variation in response any different between subcutaneous or intravenous route of administration? In general, is there a need for more Epo after the initiation of hemodialysis compared with a stable dose administered prior to dialysis? Epo dose requirements vary, even in the absence of obvious reasons. At what upper dose of Epo do you look for causes of "resistance?"

DR. VALDERRÁBANO: These are very good questions; I do not know whether I have good answers. It is usual to start with a conventional dose for all patients. Our practice is always to administer iron if iron parameters are low, so that the patient has good iron repletion before starting Epo therapy. The iron level is one of the main factors related to Epo response. After Epo treatment has been started, it is difficult to determine all the factors involved in the various responses observed in different patients. The different causes of hyporesponsiveness (absolute or functional iron deficiency, blood loss, hyperparathyroidism, aluminum overload, presence of inflammation, hemolysis, cytokine activation, etc.) can be present in each patient but with a different intensity. In consequence, these can be the factors involved in the different response to Epo. A different response to a standard dose occurs when Epo is given by the intravenous or subcutaneous route. In general, dialysis patients treated via the subcutaneous route responded more slowly than did those in whom the intravenous route was used, although final results were similar. With regard to a possible change in the dose of Epo needed when a pre-dialysis patient starts dialysis, this change is not necessary if iron supplementation is adequate. We must take into account that iron needs usually increase after hemodialysis begins, probably as a consequence of higher blood loss. Finally, it is not clear at which dose of Epo one must search for a cause of hyporesponsiveness. We must bear in mind all possible causes of hyporresponsiveness in every Epo-treated patient. If the patient does not respond well after the induction period, we must exclude the major causes of Epo resistance.

DR. NETAR P. MALLICK (*Professor of Medicine, Manchester Royal Infirmary, University of Manchester, Manchester, U.K.*): How do age, activity level, and co-morbidity influence the time of initiation and target level for Epo?

DR. VALDERRÁBANO: In the multicenter Spanish study on quality of life in hemodialysis patients, the main factors related to quality of life were age and co-morbidity [145]. The older the age, the worse was the quality of life of the patient. But an improvement in quality of life has been observed in different age groups of patients, including patients older than 65, when the hematocrit increases during Epo treatment [140]. Young patients improve, but older patients also can improve. In consequence, there is a clear indication for treatment in elderly patients. Co-morbidity is the other main factor related to quality of life in hemodialysis patients. A third factor is hematocrit or hemoglobin level. We cannot change the age of the patient, nor can we alter the morbidity of the patient, but we can improve the hematocrit and thus the quality of life. The target hematocrit will depend on physical activity, and usually elderly patients have less physical activity than do younger patients.

DR. MADIAS: You have all but discarded any effect of ACE inhibitors on Epo levels and the anemia of chronic renal failure. Yet, as you know, there are well-documented interrelationships between the renin-angiotensin axis and erythropoietin. What observations have been made on the effects of ACE inhibitors on erythropoietin levels and anemia in pre-dialysis and dialysis patients?

DR. VALDERRÁBANO: Patients with chronic renal failure from different primary renal diseases, including chronic graft rejection, had lower serum levels of endogenous Epo and more anemia when treated with ACE inhibitors [66–69]. In our experience and in published studies, these patients do not need higher doses of Epo, and this is also the case for dialysis patients treated with ACE inhibitors [69]. Low endogenous Epo levels do not seem to influence the patient's response to exogenous Epo. In consequence, these patients can be treated with ACE inhibitors without interfering with their response to Epo.

DR. GIOVANNI SELVAGGI (*Assistant in Nephrology, Fatebenefratelli Hospital, Rome, Italy*): Is it possible that the long-term use of Epo and the consequent overstimulation of bone marrow can cause dyserythropoietic anemia or leukemia? Have you ever observed anti-Epo antibodies?

DR. VALDERRÁBANO: Myeloproliferative syndromes have not

been reported as a consequence of Epo treatment. I have never observed anti-Epo antibodies in any patient.

DR. VLADIMIR TEPLAN (*Associate Professor of Medicine, Department of Nephrology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic*): How can we improve the nutritional status (malnutrition) of patients with chronic renal failure and anemia who ingest a low-protein diet and take low doses of Epo?

DR. VALDERRÁBANO: Nutritional assessment in hemodialysis patients treated with Epo showed an improvement in nutritional parameters [115]. This improvement seems to be related to an increase in appetite in these patients. Similarly, in malnourished pre-dialysis patients, Epo can increase appetite; in consequence, the nutritional state can improve. In these cases, the potential benefit of a low-protein diet on the progression of renal failure is probably less important for the outcome of the patient than is general nutrition, which is the most important risk factor for morbidity and mortality in patients with end-stage renal failure.

DR. ARIS D. EFSTRATOPOULOS (*Professor of Medicine, Athens General Hospital, Athens, Greece*): Let's return to the target hematocrit. You said that the higher the hematocrit, the better the quality of life; however, we have to take into account that increasing the hematocrit more than 33% to 35% produces more frequent hypertension and increases the platelet count, and probably the platelets' ability to aggregate as well. These two factors can worsen cardiovascular morbidity and mortality, mainly stroke and myocardial infarction, in the long term.

DR. VALDERRÁBANO: A relationship between the incidence of hypertension and hematocrit levels has not been described. Nor has an elevation in either platelet count or incidence of cardiovascular accidents been observed in studies analyzing the effect of normalization of hematocrit with Epo treatment [150]. However, the beneficial effect of increasing the hematocrit over 35% must be achieved with strict control of hypertension.

DR. JER-MING CHANG (*Attending Physician, Division of Nephrology, Kaohsiung Medical College, Kaohsiung, Taiwan*): You said that you don't recommend iron supplementation during Epo treatment if the plasma ferritin level is greater than 200 μg/liter. Yet papers published several years ago, using iron stain of bone marrow biopsies as a standard for evaluating the adequacy of iron stores, found that the serum ferritin level must be at least 300 μg/liter to ensure the adequacy of iron stores [162]. Another recently published paper also supported this concept [163]. Some patients with serum ferritin levels greater than 1000 μg/liter still had inadequate iron stores [164]. What is your opinion?

DR. VALDERRÁBANO: Here we have two different issues: the amount of iron stores, and the availability of iron to be utilized by bone marrow. Serum ferritin is a good index of iron stores, and the amount of iron stained on the bone marrow can add information, but we also need information on the availability of iron. The best way to monitor iron metabolism is to determine serum ferritin levels so that one can know the state of iron stores, transferrin saturation (which gives information about iron availability to bone marrow), and the percentage of hypochromic red cells, the best index of absolute or functional iron deficiency. Serum ferritin is not the best parameter for iron metabolism evaluation. Several papers have shown that the erythrocyte ferritin level might be a more reliable way to estimate the actual iron status in patients whose serum ferritin levels are misleadingly elevated as a consequence of chronic inflammatory processes or liver disease [78, 162].

Another study carried out on 65 hemodialysis patients found a resistance to Epo when serum ferritin levels were lower than 300 μg/liter [163]. However, it is unusual to observe Epo resistance when serum ferritin levels are lower than 300 μg/liter. Other causes of Epo hyporesponsiveness must be ruled out in any patient with normal serum ferritin levels.

DR. ESCHBACH: I would like to pursue the last question. There is the perception that iron deficiency can exist despite very high serum ferritin levels [163]. These authors evaluated bone marrow iron stores using decalcified bone biopsies of autopsied iron-overloaded dialysis patients. Chelating agents that decalcify bone generally remove iron as well, although the authors claim that that had not occurred. Because of their findings, the perception has existed that bone-marrow iron stores can be depleted in the face of high serum ferritin levels, and therefore, serum ferritin levels do not reflect marrow iron needs. However, most other studies have shown a good correlation between serum ferritin levels and bone marrow iron as semi-quantitated by Prussian blue iron stains. Iron stores, as reflected by the serum ferritin, are also inversely related to iron absorption, the latter increasing significantly when the serum ferritin level decreases to below 30 μg/liter [165]. Therefore, to maintain adequate iron stores, the serum ferritin should be kept above 100 μg/liter with oral or intravenous iron therapy. However, since the advent of Epo therapy, iron absorption might not be adequate to meet the iron needs for most hemodialysis patients because of the non-physiologic, pharmacologic doses that intravenous Epo provides. But when Epo is given subcutaneously, in which case the peak serum Epo level can be one-tenth of that given intravenously, there may not be as much demand by the marrow for iron, in which case oral iron therapy may be adequate. In my experience, most hemodialysis patients getting intravenous Epo require intravenous iron, whereas predialysis and peritoneal dialysis patients treated with subcutaneous Epo, and who also don't have the tremendous iron (blood) losses of hemodialysis patients, often can maintain iron stores with oral iron alone. I would appreciate knowing your experience as to whether oral iron can maintain iron stores in hemodialysis patients treated with subcutaneous Epo.

DR. VALDERRÁBANO: Your question has several interesting aspects. One is the route of administration of Epo in hemodialysis patients. We have not found differences in iron needs between patients receiving erythropoietin by the subcutaneous route and those receiving it intravenously. I absolutely agree that CAPD and pre-dialysis patients only need intravenous iron occasionally. The patient presented today is an exception because he developed iron deficiency, with very low levels of ferritin, after a few months of treatment. But this patient had a nephrotic syndrome, and it is probable that some other factor such as edema of the gastrointestinal mucosa interfered with iron absorption in this patient. In the majority of pre-dialysis and peritoneal dialysis patients, oral iron supplementation will be enough. But in hemodialysis patients, intravenous iron supplementation is more efficient than oral, improves the response to Epo, and is a safe way to replace iron stores [46].

DR. KASI VISWESWARAN (*Professor of Nephrology, Medical College, Kottayam, India*): Would you advocate the use of low-dose Epo therapy in a young patient with chronic renal failure who is not going to receive chronic hemodialysis or renal transplantation? Such a scenario is very common in many developing

countries. Does the improvement in quality of life justify the use of low-dose subcutaneous Epo?

DR. VALDERRÁBANO: Do you mean in patients with end-stage renal disease who are not going to start renal replacement therapy? In my country there are very few contraindications for starting renal replacement therapy. But in patients in whom, for different reasons, renal replacement therapy was not indicated, we have given low-dose Epo subcutaneously, and these patients were less symptomatic and had a better quality of life than before treatment. This is one indication for Epo therapy in developing countries where renal replacement therapy is not possible for all patients who need it.

DR. BARUCH HURWICH (*Shaare Zedek Hospital, Jerusalem, Israel*): Certainly Epo is one of the most exciting developments since the beginning of chronic dialysis. Little discussion has addressed the rather long list of complications, however, some of which are serious, such as thrombosis of the fistula and myocardial infarction. Is there a way to identify these high-risk patients?

DR. VALDERRÁBANO: If we carefully monitor hypertension, which is the main adverse effect of Epo therapy, the other adverse effects are not a big problem. Some controlled prospective studies showed no differences in the incidence of clotting of vascular access in patients treated with Epo compared with hemodialysis patients not treated with Epo [108]. We have a policy of prevention of clotting of vascular access. When a hemodialysis blood flow of 350 ml/min cannot be achieved, or return blood pressure increases over 150 mm Hg, we routinely obtain a fistulogram. In the majority of cases, we find a stenosis that must be corrected. With our preventive approach, we have found no difference in the incidence or thrombosis of the vascular access in patients treated with Epo compared with patients not receiving the hormone. Regarding myocardial infarction and cerebrovascular accident, no evidence indicates that these frequent complications in end-stage renal disease patients are more likely to appear in patients treated with Epo.

DR. MENELAOS PAPADIMITRIOU (*Professor of Medicine and Nephrology, Department of Nephrology, Aristotelian University, Thessaloniki, Greece*): Let's come back to the case presentation. I was surprised that this patient did not become hypertensive even though his hematocrit rose dramatically after he became hypercalcemic. Therefore I would assume that he might have been taking antihypertensive therapy or that he is an exceptional case. Second, you did not mention his levels of blood urea and urinary urea excretion, which would indicate his nitrogen balance before and after Epo treatment. Before dialysis, the patient did not show any significant change in blood urea and urinary urea excretion.

DR. VALDERRÁBANO: I selected this case for two interesting reasons: the patient's need for intravenous iron during pre-dialysis Epo therapy, and resistance to Epo as a consequence of severe hyperparathyroidism during hemodialysis. During the several years that the patient was on hemodialysis, his hypertension was well controlled with antihypertensive agents. He only became hypercalcemic three weeks after starting treatment with intravenous calcitriol. Hypercalcemia is a frequent complication of calcitriol administered either orally or intravenously, especially when severe hyperparathyroidism exists, as in this patient. In our general experience, calcitriol-induced hypercalcemia is not always accompanied by hypertension. It is also interesting that this patient had an idiopathic membranous nephropathy and that he was normotensive during the first years of evolution of his nephropathy. This patient also was treated with cyclosporine A without any beneficial effect on the evolution of the nephropathy. During the pre-dialysis stage, when the patient was receiving Epo therapy, we did not see variations in his blood urea levels or in his urinary urea excretion.

DR. NORMAN LASKER (*New Jersey College of Medicine, Newark, New Jersey, U.S.A.*): I would like to address the last question. Dr. Papadimitriou was questioning why the patient's blood pressure did not rise with the excessively high hematocrit. We reported in a letter to the *New England Journal of Medicine* a contrary experience: in effect, many patients became hypertensive during Epo therapy without having an increase in hematocrit [166]. Other mechanisms must be involved, contrary to the popular theory about the increase in blood volume. Without going into great detail, the popular theory of the mechanism of hypertension with Epo therapy is that the blood pressure rises because of an increase of blood viscosity and blood volume. We identified many patients whose hematocrit did not rise but who did in fact become hypertensive while receiving Epo therapy. Also, I would like to respectfully disagree with Dr. Eschbach's perception that predialysis and CAPD patients require less iron supplementation. I think it is just a matter of iron balance.

DR. VALDERRÁBANO: Your arguments favor a direct vascular effect of Epo in the genesis of Epo-related hypertension. In your letter you mentioned that your patients did not have an increase in hematocrit, body weight, or fluid overload, but that they became hypertensive during Epo therapy [166]. Your findings do suggest a direct vascular effect of Epo, although some authors did not find hypertension after Epo infusion into arterioles [167]. However, a more recent publication demonstrated that intra-arterial Epo infusion constricted renal and mesenteric vascular beds [168].

On the other hand, we must take into account the other mechanisms involved in Epo-related hypertension, such as the increase in blood viscosity [128], the increase of cytosolic free calcium in platelets [130], the increased production of endothelin-1 [131], and the loss of hypoxic vasodilation [169], which seem to be directly related to an increase in hematocrit.

DR. THOMAS MATHEW (*Professor of Nephrology, Government Medical College, Calicut, India*): What are the commonest reasons for discontinuing treatment with Epo? And generally when do these occur?

DR. VALDERRÁBANO: Some of our Epo-treated patients have had seizures. All of these patients had a history of seizures; in one case we had to stop Epo treatment two months after starting therapy. Our first patient treated with Epo had intense musculoskeletal pain coinciding with the intravenous injection of Epo, and we stopped Epo treatment four months after starting. This patient also had severe hyperparathyroidism. She underwent parathyroidectomy, and her musculoskeletal pain disappeared completely; we then reintroduced Epo treatment without any trouble. We have never stopped Epo therapy due to uncontrolled hypertension. With careful control of dry weight and adjustment of antihypertensive treatment, one rarely needs to stop Epo therapy. In another case we temporarily stopped Epo treatment after the patient had a cerebrovascular accident. The patient recovered and we continued the Epo.

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