INTRODUCTION

The purpose of this chapter is to summarize and analyze the clinical literature on the safety and efficacy of recombinant erythropoietin. First, the etiology of and treatment method for anemia associated with chronic renal failure are discussed. Next, the efficacy of recombinant erythropoietin is analyzed with information from clinical trials in chronic renal failure patients. Issues discussed include the effect of recombinant erythropoietin on physiologic parameters, such as hematocrit level, and on the quality of life. This section also examines the efficacy of various doses and routes of administration of the product, including intravenous and subcutaneous routes. Other anemic conditions in which recombinant erythropoietin may be clinically useful are reviewed. The final section considers safety issues related to the use of recombinant erythropoietin, including adverse reactions.

TREATMENT FOR ANEMIA ASSOCIATED WITH CHRONIC RENAL FAILURE

Anemia is characterized by a significant reduction in red blood cell mass and a corresponding decrease in the oxygen-carrying capacity of the blood (23). Red blood cells are the cellular components of blood responsible for the transport of oxygen to body organs and tissues. Sustained lack of tissue oxygenation results in hypoxia, which is characterized by fatigue, weakness, lethargy, decreased ability to exercise, difficulty breathing, loss of appetite, and a overall decreased sense of well-being. Severely anemic patients may have these symptoms at rest and be unable to tolerate any level of exercise. Some may develop heart failure or transient loss of consciousness, while individuals with mild cases of anemia may or may not exhibit these symptoms.

In addition, due to decreased blood flow to the skin, anemic patients are often sensitive to cold and have pale skin color. Anemic males may complain of impotence, while anemic females may have irregular menstrual cycles. Other signs of anemia are dizziness due to lack of oxygen to the brain, irritability, and difficulty in sleep and concentration (23).

One criterion for the diagnosis of anemia is the hematocrit level, which is the volume of red blood cells expressed as a percentage of total blood volume. The average hematocrit level in men is 42-53 percent, and in women 37-47 percent (12).

There are many causes of anemia: loss of red blood cells, decreased production of red blood cells, and increased destruction of red blood cells (hemolytic anemias). Bleeding from surgery or trauma are examples of anemia associated with red blood cell loss. In hemolytic anemias, red blood cells are rapidly destroyed by the body and have a short survival time. Decreased production of red blood cells may occur through lack of iron, vitamins, or naturally occurring hormones, such as erythropoietin.

When the body detects hypoxia, erythropoietin, a hormone produced primarily by the kidneys, is released into the blood stream.[1] This hormone stimulates the release of red blood cell precursor cells from the bone marrow into the blood stream. These precursor cells work with iron stores in the body, assuming these are sufficient, to develop into mature red blood cells, and the hypoxia is corrected (23).

Successful treatment for anemia depends on the underlying causes of the condition in the patient. One method for treating anemia caused by iron deficiency is through the administration of supplemental iron. Other anemias, such as those due to insufficient bone marrow stores of precursor cells, or insufficient endogenous erythropoietin, are usually irreversible and have been historically treated with other measures, primarily periodic blood transfusions.

[1] About 90 percent of endogenous erythropoietin is produced by the kidneys, and 10 percent is produced by the liver (63).

Box 2-A--Dialysis Treatment Methods

The two major forms of treatment for individuals with chronic renal failure are kidney transplantation and some form of dialysis. The term dialysis refers to any process in which the components of a liquid or solution are separated on the basis of the selective movement of different kinds of molecules through a semipermeable membrane. The movement of the molecules through the membrane is caused by the differences in concentrations of salts and toxins in the blood and in the dialysate that is used to cleanse the blood (27).

The different methods of dialysis and the frequency of their use in the U.S. dialysis population are listed in table 2-1. The most commonly used form of dialysis is hemodialysis, in which a machine pumps blood from the patient's body and returns it through an external blood loop. Waste products and other molecules are passed through a semi-permeable membrane, so that blood can be faltered and cleaned. Hemodialysis patients usually require a total of 13 to 15 hours of dialysis weekly, for sessions of about 3.5-4 hours each (27). In 1988, approximately 85 percent of all dialysis patients, both Medicare and non-Medicare, used this method of dialysis (156).

Table 2-l--Dialysis Treatment Methods Used in the United States by Medicare[a] and Non-Medicare[b] Patients, December 31, 1988

Hemodialysis		
In-unit	86,250	(81.7%)
Home	3,197	(3.0%)
Subtotal	89,447	(84.7%)
Peritoneal		
In-unit intermittent	365	(0.4%)
Home intermittent	326	(0.3%)
Home CAPD	13,318	(13.0%)
Home CCPD	1,922	(2.0%)
Subtotal	15,931	(15.0%)
Self-Training		
Subtotal	580	(0.3%)
Total U.S. dialysis population	105,958	(loo%)

a As of Dec. 31, 1988, 91,820 dialysis patients were covered by Medicare and 6,371 had Medicare coverage pending. The percentage distribution of dialysis patients by dialysis method is for the total U.S. dialysis
b population.
Patients in the non-Medicare category may include those who are covered by the Veterans Administration, private insurance (including those who have employer group health insurance coverage for the first year of ESRD, with Medicare's becoming the primary insurer thereafter), and Medicaid; foreign nationals; and individuals with no coverage.

KEY: CAPD = continuous ambulatory peritoneal dialysis; CCPD = continuous cycling peritoneal dialysis.

SOURCES: Sagel, 1990 (124); US DHHS, HCFA, 1989 (156).

Although most patients receive hemodialysis treatments in dialysis facilities, some have been trained to perform hemodialysis at home. Home dialysis requires self-reliance, but permits freedom from a facility's dialysis schedules. Because of the possibility of medical complications resulting from hemodialysis, patients with severe medical problems are usually not considered candidates for home hemodialysis (27). Only 4 percent of all dialysis patients are on home hemodialysis (157).

Box 2-A--Dialysis Treatment Methods--Continued

In the other major dialysis method, peritoneal dialysis, a dialysate or cleansing fluid is introduced into a permanent catheter that has been inserted into the abdomen or peritoneal cavity (146). After remaining in the cavity for a period of time, the dialysate is drained out and discarded. Approximately 15 percent of patients utilize some form of peritoneal dialysis (157).

There are three commonly used forms of peritoneal dialysis. Intermittent peritoneal dialysis involves the use of a machine to deliver sterile dialysate to the patient's peritoneal cavity and, after the prescribed time, to remove the dialysate. This technique, which can be performed both in the facility and at home, is usually carried out for 10 to 12 hours 3 times weekly (146). As the patient's renal function declines, longer treatments are needed with this method.

Continuous ambulatory peritoneal dialysis (CAPD) involves continuous, manual exchange of dialysate, roughly every 4 to 6 hours. CAPD requires no machine, and the patient can usually perform the task without additional assistance. In CAPD, the patient empties a 2-liter bag of dialysate fluid into the peritoneal cavity and then proceeds with usual activities for the next 4 to 8 hours or overnight (146). At the end of the cleansing time, the dialysate is drained. The process is repeated 3 to 5 times daily, 7 days a week. The patient must be cautious to use sterile technique at all times. Due to the number of bag changes, the major risk to the patient with this form of dialysis is peritonitis, an infection of the lining surrounding the abdomen.

Continuous cycling peritoneal dialysis (CCPD) is a combination of the intermittent and CAPD methods. CCPD uses a machine to warm and cycle the dialysate in and out of the peritoneal cavity automatically about every 4 hours as the patient sleeps. The dialysate is instilled in the cavity in the morning and remains there until connection to the machine in the evening. Although still small in total number of patients, CCPD is the fastest growing method of dialysis, increasing 26 percent in use during the period 1982-1987. This method does not predispose the patient to peritonitis as much as CAPD, due to the fewer number of connection changes to the dialysis machine (146). Both CAPD and CCPD are home methods of peritoneal dialysis.

The choice of patient dialysis treatment and setting depends on the patient's medical condition, ability to participate in self-care, the level of support from friends and family at home, and treatment preferences (16). Home dialysis can give those patients needing dialysis a certain measure of independence and may reduce the cost of in-unit personnel needed for dialysis. Approximately 18 percent of all dialysis patients utilize some form of home dialysis (157). Home hemodialysis training takes from 3 weeks to 3 months, and home peritoneal dialysis training takes from 1 to 2 weeks. A profile of home dialysis patients is provided in table 2-2.

Table 2-2--Home Dialysis Treatment Methods Used in the United States by Medicare and Non-Medicare Patients, December 31, 1988

Dialysis method	Number of patients	Percent of home dialysis patients
Hemodialysis	3,197	17
Peritoneal	15,566	83
Intermittent	326	2
CAPD	13,318	71
CCPD	1,922	10
Total	18,763	100

KEY: CAPD = continuous ambulatory peritoneal dialysis; CCPD = continuous cycling peritoneal dialysis.
SOURCE: US DHHS, HCFA, 1989 (156).

Anemia is frequently associated with chronic renal failure, a progressive condition that results in permanent and irreversible destruction of the kidneys. Chronic renal failure progresses from a predialysis phase, where the kidneys continue to function but at a reduced rate, to a later phase, where there is little or no kidney function and continuous dialysis is needed to remove waste products from the blood stream (21) (see box 2-A and tables 2-1 and 2-2).

In most chronic renal failure patients, the survival time of red blood cells is only slightly decreased, and anemia results primarily from underproduction of red blood cells. This is due to insufficient production of endogenous erythropoietin by failing kidneys (21). The anemic condition worsens as kidney function declines?

The prevalence of anemia in dialysis patients is substantial. Among approximately 13,000 dialysis patients tested by National Medical Care (NMC)[3] in 1989, for example, approximately 93 percent had a hematocrit level less than 35 percent, 74 percent had a hematocrit less than 30 percent, and 70 percent had a hematocrit between 20-29 percent (see table 2-3). For predialysis patients, estimates of the prevalence of anemia vary widely, from 10-44 percent (see ch 3. and table 3-5). The symptoms of anemia associated with predialysis are, in general, not as debilitating as the symptoms of anemia associated with later-stage chronic renal failure (123).

Until recently, the treatment of anemia associated with chronic renal failure had been limited to the use of blood transfusions, androgen therapy, and administration of supplemental iron (57).

2Other factors associated with the anemia of chronic renal failure include unavoidable blood loss during the dialysis procedure, decreased red blood cell survival time, and iron deficiency (80).

3 NMC is the nation's largest chain of dialysis centers (11).

Table 2-3-Distribution of Hematocrit Levels of Dialysis Patients, by Age, January 1988[a]

	Percentage of patients with specified hematocrit level						
Age	< 1 4	15-19	20-24	25-29	30-34	≥35	Cumulative percent by age[b]
0-14	0.00	0.02	0.07	0.11	0.02	0.02	0.23
15-24	0.00	0.32	1.00	0.57	0.14	0,05	2.30
25-34	0.05	0.63	2.92	2.73	0.99	0.43	10.05
354..	0.02	0.48	4.06	4.68	2.07	o.%	22.38
45-54	0.02	0.50	4.60	6.06	3.06	1.36	37.97
55-64	0.02	0.75	6.97	10.01	4.94	2.03	62.69
65-74	0.00	0.41	6.51	11.26	5.11	1.75	87.73
≥75	0.00	0.25	3.66	5.68	2.20	0.54	100.06
Cumulative percent by hematocrit level	0.10	3.46	33.25	74.34	92.87	100.00	

[a]Based on data from approximately 13,200 patients tested by National Medical Care. Data do not distinguish among patients' method of dialysis.
b Total does not sum to 100 because of rounding.
SOURCE: Berger, 1989 (11).

It is estimated that one-fourth of dialysis patients undergoing hemodialysis require regular or intermittent blood transfusions to maintain acceptable hematocrit levels (57). At initial administration, blood transfusions produce a quick increase in hematocrit, but as the red blood cells die, the hematocrit level drops and another transfusion is required. Thus, it is difficult to stabilize a patient's hematocrit level with blood transfusions. In addition, many risks are associated with repeated blood transfusions, such as iron overload and the potential for transmission of various types of hepatitis virus or the human immunodeficiency virus (HIV) (65). A more detailed discussion of the risks associated with blood transfusions is found later in this chapter. Whether a patient receives a blood transfusion depends on several factors, such as the patient's hematocrit level, signs and symptoms of anemia, and the clinician's judgment. Androgens are male hormones capable of stimulating erythropoiesis, but are associated with side effects, such as liver toxicity and masculinization, and are used infrequently (104).

EVALUATION OF THE EFFICACY OF RECOMBINANT erythropoietin

A safe and efficacious treatment for anemia associated with chronic renal failure has been unavailable. Efficacy refers to the probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use (143).

The efficacy of recombinant erythropoietin has been assessed primarily by physiologic factors, including changes in hematocrit level and reduction in the need for blood transfusions, an indication that anemia has been alleviated. Although information from studies does not indicate that use of recombinant erythropoietin increases length of life, evidence suggests that the biologic increases the hematocrit level, reduces the need for blood transfusions, and improves aspects of the quality of life of dialysis patients, such as well-being and activity level. The efficacy of recombinant erythropoietin for conditions besides chronic renal failure is being explored.

Physiologic Effects of Recombinant erythropoietin in Chronic Renal Failure Patients

Studies in the United States to determine the efficacy of recombinant erythropoietin were first performed in chronic renal failure patients, including dialysis and predialysis patients. Three different classes of studies were done: randomized studies in which there was an untreated or placebo-treated control group; randomized studies in which there was no untreated control group and a before and after effect was examined; and studies in which there was no randomization, and a before and after effect was examined.[4] Important characteristics of some of these studies are listed in table 2-4.

The studies indicate that recombinant erythropoietin produces a dose-dependent increase in hematocrit levels and can reduce or eliminate the need for blood transfusions in most patients.[5] The time required to increase the hematocrit level (rate of increase) and the amount of increase depend on the dose.

In June 1989, the Food and Drug Administration (FDA) approved recombinant erythropoietin for administration by the intravenous route in dialysis patients[6] and by both the intravenous and subcutaneous routes in predialysis patients (160).

A In a randomized trial, patients are randomly assigned to a control group, which receives standard or no therapy, or to an experimental group, which receives the intervention being assessed. In a before and after trial, the patients' physiological parameters serve as the baseline to assess the impact of the intervention.

5 According to the Food and Drug Administration (FDA), transfusion-dependency was defined as requiring at least six transfusions per year (159).

6 The intravenous route of administration of recombinant erythropoietin was used in hemodialysis patients because of the availability of an access site to the blood stream to which the dialysis machine is connected. The subcutaneous route of administration of recombinant erythropoietin, which is used for both predialysis patients and peritoneal dialysis patients, is more practical for these patients because of the unavailability of an intravenous access site.

Table 2-4-Efficacy and Safety Studies in Chronic Renal Failure Patients

Study design	Number of patients	Target hematocrit	Doses used and results	Significance level (p value)	Source[a]
A	89 HD	see results	IV dose of 100 units/kg produced increase in hematocrit from 22 to 34 vs. placebo (22 to 23).		Sobota, 1989 (131).
A	101 HD	32-38	IV dose of 150 units/kg or placebo TIW for 12 weeks. 97 percent reached target hematocrit.	0.0005	U.S. DHHS FDA 1989 (160).
B	131 HD	see results	IV doses of 25 units/kg, 100 units/k& and 200 units/kg increased the hematocrit from 22 to 28,21 to 32, and 21 to 32 respectively over 138 days.	NA	Sobota, 1989 (131).
C	333 HD	32-38	IV doses of 300 units/kg; or 300 units/kg reduced to 150 units/k& or 150 units/kg for 12 weeks. Mean maintenance dose was 108 units/kg. 97 percent reached target hematocrit.	0.0005[b]	Eschbach, et al., 1989 (56).
A	14 PD	3541	IV doses of 50, 100, and 150 units/kg compared with placebo in 14 patients. Over 8 weeks, increases in hematocrit were 27 to 35,27 to 36,28 to 41, and 24 to 28, respectively.	O.0001	Lim, et al., 1989 (92).
A	12 PD	36	SC dose of 100 units/kg or placebo. Hematocrit increased in 11 patients from 25 to 36 after 3 months. 92 percent reached target hematocrit.	0.001	Teehan, et al., 1989 (140).
A	93 PD	38-40	SC dose of 100 units/kg (45) or placebo (48). 58 percent reached target hematocrit.	NA	U.S. DHHS FDA 1989 (160).
A	117 PD	3540	IV doses of 50,100, and 150 units/kg were compared with placebo in initial phase. Hematocrit increased 0.13,0.20,0.26, and -0.01 points/day respectively. Patients then treated SC or IV (75-150 units/kg) in maintenance phase. 94 percent reached target hematocrit.	NA	U.S. DHHS FDA, 1989 (160).
B	17 PD	3740	SC doses of 50-100 units/kg and IV dose of 150 units/kg in initial phase; SC maintenance doses at levels to sustain hematocrit.	O.0001	Eschbach, et al.,1989 (58).
c	5 CAPD (Pediatric)	32-38	SC dose of 150 units/kg TIW increased hematocrit from 22 to 33.	0.001	Sinai-Trieman, et al., 1989 (130).

[a]Numbers in parentheses refer to list of references.
[b]Compared to patients' initial hematocrit levels.

KEY: A = randomized clinical trial that employed placebo or untreated control; B = randomized clinical trial that did not employ placebo or untreated control and a before and after effect was examined; C = nonrandomized trial in which a before and after effect were composed; CAPD = continuous ambulatory peritoneal dialysis; HD = hemodialysis; IV = intravenous; kg = kilogram; NA = not available; PD = predialysis; SC = subcutaneous; TIW = 3 times weekly.

FDA's approved labeling for recombinant erythropoietin recommends that there be initial dosing and maintenance dosing phases. According to the labeling, therapy should start with 50-100 units/kg of recombinant erythropoietin 3 times a week by intravenous administration for 6 to 12 weeks. When the hematocrit reaches the target range of 30-33 percent, or rises by more than 4 points in any 2-week period, the labeling recommends that the dose be reduced by 25 units/kg. An individual should be maintained in the target range by adjusting the dosage by 25 units/kg of body weight at 2-6 week intervals (160).[7] The maintenance dose is usually lower than the induction dose once the target hematocrit is attained.

At doses of 50 units/kg, the hematocrit increased 0.11 points/day, and at 100 units/kg, it increased 0.18 points/day, clearly establishing a dose-response relationship (160). To maintain patients in the 34-36 percent hematocrit level, 65 percent of patients required fewer than 100 units/kg 3 times weekly; 10 percent each required either fewer than 50 units/kg or more than 200 units/kg 3 times weekly (160).

FDA reviewed data to show the comparability of intravenous and subcutaneous administration for chronic renal failure (62). However, neither the FDA Summary Basis of Approval nor the FDA-approved labeling addresses the relative efficacy of the intravenous route vs. the subcutaneous route of administration, or the relationship between efficacy and dose by these respective routes.

Studies clearly indicate that intravenous recombinant erythropoietin produces a significant rise in hematocrit level in those patients who are treated as compared with those not treated. Although the populations used in the studies may be representative of the age distribution of the dialysis population as a whole, little differentiation was made in the interpretation of the results of the studies, however, of the effect by age group. Evaluating this dimension becomes particularly important as the number of elderly dialysis patients increases (46).[8]

In a large clinical study, 101 anemic hemodialysis patients were randomized to receive either placebo or intravenous recombinant erythropoietin, 150 units/kg of body weight 3 times weekly for 12 weeks (160). In the second 12-week phase, the control group was given the same dose of recombinant erythropoietin as the experimental group. The target hematocrit of 35 percent was attained by a cumulative 95 percent of the patients, with the target hematocrit's being achieved by 97 percent of patients in the original treatment group and 93 percent of patients in the control group after crossover to experimental treatment. Information on statistical significance levels was not presented.

In another study without an untreated or placebo-treated control group, 333 patients (ages 18-81) were randomized to receive doses of either 300 or 150 units/kg, which was then reduced to 75 units/kg when the target hematocrit of 32-38 percent was reached (56). In 97.4 percent of patients, hematocrit increased from 22.5 percent to 35 percent ($p<.0005$) within the first 12 weeks. The average hematocrit level was maintained at 33.8 percent after 6 months of treatment ($p<.0005$) and 35.5 percent after 10 months of treatment ($p< .0005$). The group receiving the higher dose reached the target hematocrit more quickly than did the group receiving the lower dose (6-8 weeks for the higher dose group vs. 10 weeks for the lower-dose group).

7 As an alternative to using a higher dose during the initial phase and a lower dose in the maintenance phase, a model was recently developed that may allow clinicians to determine an optimal dose from the initiation of therapy. The model is based on survival time of red blood cells in the body and dose-response cures that were developed in earlier studies (67).

8 Elderly patients are more susceptible to the adverse and toxic effects of most drugs. Changes with aging in body composition and in drug distribution, metabolism, excretion, and response make elderly people more vulnerable to adverse reactions. Since most clinical trials and pharmacological studies are performed in younger people, it is often hazardous to apply drug treatment standards developed for these populations to the elderly (12).

In the same study, after 8 weeks of therapy, none of the treated patients was dependent on blood transfusions, including 116 previously transfusion-dependent patients. An average 0.52 units of blood per patient per month had been required before initiation of recombinant erythropoietin therapy. These requirements were reduced to 0.1 units per patient per month after the first 4 weeks of therapy, and 0.04 units or fewer per patient per month during the study.[9] (The impact of recombinant erythropoietin on reducing blood transfusion requirements in chronic renal failure patients is described in table 2-5).

9 This study did not specify the volume in a unit of blood. For dialysis patients, a transfusion usually consists of 250 ml. of packed red blood cells (77).

In a before and after study, recombinant erythropoietin was intravenously administered over a range of doses between 15 and 500 units/kg to 25 anemic hemodialysis patients (ages 21-69, hematocrits 15 percent to 24.5 percent) (57). Dose-dependent increases in erythropoiesis were noted over 3 to 7 months. Blood transfusions were no longer needed by 12 patients, the only patients that received them before recombinant erythropoietin was used.

A before and after study of 5 transfusion-dependent pediatric peritoneal dialysis patients ages 12-18 was undertaken. In the 6 months preceding recombinant erythropoietin therapy, each patient had received between 5 and 18 blood transfusions to

Table 2-5-Reduction in Blood Transfusions with Recombinant erythropoietin Therapy

Study design	Number of patients	Results	Source[a]
A	244 HD[b]	In first randomized arm, the transfusion requirements of 113 treated patients receiving 100 units/kg of recombinant erythropoietin were reduced from 0.17 units per patient per week to 0.09 per week over 6 weeks versus the placebo group, which remained at 0.19 units, per patient per week. In the second randomized arm, transfusion requirements of 131 patients were reduced from 0.09 units per patient per week to 0.04 units per patient per week over 6 weeks vs. the placebo group, which increased from 0.18 units per patient per week to 0.22 units per patient per week after 6 weeks.	Sobota, 1990 (132a).
B	131 HD	After 4 weeks, 4 patients treated with 25 units/kg had a reduction in total transfusions from 69 to 25; 44 patients treated with 100 units/kg had a reduction in total transfusions from 70 to 12; 43 patients treated with 200 units/kg had a reduction in total transfusions from 93 to 18.	Sobota, 1990 (132a).
C	333 HD	Patients needed an average 0.52 units of blood per month prior to therapy; this decreased to 0.1 units per patient per month after 4 weeks, and virtually all patients were transfusion-independent after 12 weeks.	Eschbach, et al., 1989 (58).
C	25 HD	18 patients required transfusions in the 6 months prior to therapy, and 12 were transfusion-dependent, requiring transfusions at least twice a month. These requirements were eliminated in all patients after therapy.	Eschbach, et al., 1987 (57).
C	5 CAPD	In the 6 months before therapy, patients needed 5 to 18 blood (Pediatric) transfusions each; these requirements were eliminated after 12 weeks.	Sinai-Trieman et al., 1989 (130).

[a]Numbers in parentheses refer to list of references. Another report estimated that tranfusion-dependent patients required 7.1 units per year and that these could be eliminated with recombinant erythropoietin therapy (117).

[b]Study consisted of two separate randomized arms.

KEY: A = randomized clinical trial that employed placebo or untreated control; B = randomized clinical trial that did not employ placebo or untreated control and a before and after effect was examined; C = nonrandomized trial in which a before and after effect was examined; CAPD = continuous ambulatory peritoneal dialyis; HD = hemodialysis; kg = kilogram.

maintain a hematocrit of 20 percent and treat symptoms of anemia. The children were treated at home with 150 units/kg recombinant erythropoietin subcutaneously 3 times weekly for 5 to 8 months. The hematocrit level increased from an average of 22 percent to an average of 33 percent ($p < 0.001$), and was maintained in the 32-38 percent range for 5 to 8 months. When the patients reached the target of 35 percent, the dose was decreased in increments of 25 units; when the level reached 40 percent, treatment was discontinued until the hematocrit dropped below 40 percent. The patients were then reinstated on a dose of 150 units/kg once or twice weekly subcutaneously to maintain their hematocrit levels. Further blood transfusions were not required when the target hematocrit was reached (130).

Reflecting the dose-response relationship to recombinant erythropoietin, the time to reach a target hematocrit level and the number of patients reaching any specified target depend on the dose used (see table 2-6). Although the study designs are not presented, it appears from the data that doses of 100 units/kg are needed for 90 percent or more of patients to respond. The data also suggest that with doses of 44 units/kg, slightly more than 50 percent of patients respond. Lower doses seem to produce a lower response rate in a smaller number of patients. In one case, approximately 70 percent of patients (n= 116) in a before and after study without randomization increased their hematocrits to 30 percent over 12 weeks with only 50 units/kg 3 times weekly (18).

Studies to date, as indicated in table 2-7, suggest that subcutaneously administered recombinant erythropoietin is also efficacious at both increasing and maintaining the hematocrit level of most patients to whom it is administered. The current evidence is more voluminous for the efficacy of the subcutaneous route of administration in predialysis patients than in dialysis patients. One report does indicates efficacy in dialysis patients (17).

The evidence is clearly convincing that both the subcutaneous and intravenous routes are efficacious in increasing hematocrit levels. Although some have suggested that target hematocrit levels can be attained with lower doses by the subcutaneous route, there are not enough data to fully support this conclusion. No study compared the same doses by different routes of administration. In most of the studies, both the routes of administration and the doses were varied, making comparison difficult.

In some cases, lower doses of subcutaneously-administered doses of recombinant erythropoietin were able to achieve a similar therapeutic response as higher doses of the intravenously-administered product. This usually occurred, however, over a longer period of time. For example, in one study, the target hematocrit was reached in 8 weeks with 150 units/kg intravenous recombinant erythropoietin as compared with 12 weeks with 100 units/kg of subcutaneous recombinant erythropoietin (58). one possible explanation is that subcutaneously admin-

Table 2-6-Dose Response to Intravenous Recombinant erythropoietin

Dose used (units/kg)	Number of patients	Percent responding	Source
300/150	309	97	Eschbach, et al., 1989 (58).
200	43	>90	Sobota, 1989 (131).
120	2%	93	Kuhn, et al., 1988 (186).
100	44	>90	Sobota, 1989 (131).
80	2a	82	Kuhn, et al., 1988 (186).
50	116	71	Blagg, 1989 (17).
44	236	55	Roxas, 1989 (122).
40	29	28	Kuhn, et al., 1988 (186).
25	44	<25	Sobota, 1989 (131).

a Response was considered an increase in hematocrit to over 30 percent in 3 months.
Numbers in parentheses refer to list of references.

KEY: kg = kilogram.

SOURCE: Eschbach, and Adamson, forthcoming, 1990 (55).

Table 2-7-Studies of Subcutaneous Administration of Recombinant erythropoietin

Study design	Number of patients	Dose[a]	Results	Significance level (p value)	Source[b]
A	14 PD	SC doses of 100 units/kg or placebo	Average hematocrit increased for treated group from 2 35.8 percent over 12 weeks. Average hematocrit remained at 28 percent for placebo group.	0.004	Kleinman, et al., 1990 (83).
A	12 PD	SC doses of 100 units/kg or placebo	Hematocrit increased in 11 patients from 25 percent to 36 percent after 3 months.	0.001	Teehan, et al., 1989 (140).
A	93 PD	SC doses of 100 units/kg (45) or placebo (48)	Hematocrit of 38-40 percent attained by 58 percent of treated vs. 4 percent placebo in 12 weeks.	NA	US DHHS, FDA, 1989 (160).
A	117 PD	SC or IV doses of 75-150 units/kg in maintenance phase after target hematocrit of 35-40 percent reached.	Hematocrit maintained in 36-38 percent range for 6 months in 94 percent of patients.	NA	US DHHS, FDA, 1989 (160).
B	17 PD	IV doses of 50-100 units/kg and SC doses of 150 units/ kg in initial phase. Maintenance dose given SC at levels to sustain increase in hematocrit.	Hematocrit increased from 28 percent to 37 percent in 12 weeks by SC and 8 weeks by IV.	0.0001	Eschbach, et al., 1989 (58).
C	5 CAPD (Pediatric)	SC doses of 150 units/kg	Hematocrit increased from 22 percent to 33 percent.	0.001	Sinai-Trieman, et al. 1989 (130).
C	12 CAPD	Initial SC doses of 100 and 150 units/k& reduced to 50 units/kg.	Hemoglobin increased 2 g/dl over 26+ weeks, reaching 11 to 11 1/2 g/all in 11 patients.[c]	NA	Stevens, et al., 1989 (134).
C	86 HD[a]	IV doses averaged 101 units/kg in 55 patients and SC doses averaged 108 units/kg in 31 patients.	Patients treated IV maintained target HCT for 23 months; patients treated SC maintained HCT for 21 months.		Blagg, 1990 (17).
C	29[e]	Doses, routes, and frequency of administration were varied.	Hemoglobin was maintained in target (10.5 < Hb < 13) at doses of 80 units/kg SC weekly in 13 patients and 164 units/kg SC twice weekly in 16 patients.	NA	Besarab, et al., 1990 (13).

administered three times weekly, unless otherwise noted.

b Numbers in parentheses refer to list of references.

[c] Hemoglobin is the oxygen-carrying protein of red blood cells. Normal average hemoglobin levels in men are 14-18 g/all (grams/deciliter) and 12-16 g/all for women (12).

d study compared administration in home dialysis with ***in-center dialysis patients.***

'Abstract did not report the patients' methods of dialysis.

KEY: A = randomized clinical trial that employed placebo or untreated control; C = nonrandomized trial in which a before and after effect was examined; CAPD = continuous ambulatory peritoneal dialysis; HCT = hematocrit; HD = hemodialysis; IV = intravenous; kg = kilogram; NA = not available; PD = predialysis; SC = subcutaneous; TIW = three times **weekly.**

istered product is stored in the muscle tissues and released into the blood stream over a period of time, in contrast to intravenous product, which is released into the blood stream immediately upon injection. The benefit of very high peak serum levels after an intravenous injection seems to be questionable (105). The differences in the doses used maybe the primary reason for this phenomenon, however. In the final analysis, additional randomized trials with control groups in larger patient groups are needed to compare the relative efficacy of these two routes.

Patients that perform dialysis at home are most likely to self-administer recombinant erythropoietin by the subcutaneous route. If the patient self-administers the product correctly, there is every reason to believe that the product will be efficacious. Training to perform self-administration will most likely come from the patient's physician and will include instructions on how to store the product (e.g., refrigeration), how to draw up the product from the vial using sterile technique, and how to inject the needle. In addition, it will be important for patients that self-administer the product to have their hematocrit and iron stores checked regularly (17).

Evidence of the efficacy of self-administration of recombinant erythropoietin by patients is limited to a few reports. In one before and after report, 5 hemodialysis patients (ages 18-55) who self-administered recombinant erythropoietin intravenously through the arteriovenous graft over a 3-month period had a mean rise in hematocrit from 18.4 percent to 32.6 percent (110). None of the patients required further blood transfusions. In another before and after report, 17 patients maintained their target hematocrit by administering recombinant erythropoietin subcutaneously at home (82). The dose used to maintain the target hematocrit was tailored to the individual patient's needs. Finally, in a study comparing 55 in-unit dialysis patients treated intravenously with an average of 101 units/kg with 31 home dialysis patients, the home patients were able to maintain for 21 months the hematocrit level attained in the dialysis center in a self-administration program with intravenous doses of 108 units/kg of recombinant erythropoietin (18).

Effect of Recombinant Erythropoietin on Quality-of-Life in Chronic Renal Failure Patients

The efficacy of recombinant erythropoietin therapy may be measured by its impact on an individual's quality of life, a multifaceted, multidimensional concept. The quality of life may be assessed by measures that relate to such aspects as ability to work, level of functional impairment, well-being, psychological attitude, and life satisfaction (59).

The quality of life of chronic renal failure patients may be affected by several factors, such as the severity and number of the patient's underlying illness or illnesses, the treatment approach (dialysis vs. transplantation), the symptoms associated with anemia of chronic renal failure, and the characteristics of the dialysis and transplant centers, since patients at certain centers seem to be better rehabilitated than those at other centers (59).

The symptoms of anemia may impair the well-being and functioning of dialysis patients. Hypoxia due to anemia associated with chronic renal failure often leads to persistent lethargy, decreased exercise tolerance, poor appetite, and decreased sexual performance. From a theoretical point of view, any increase in the hematocrit should result in increased central and peripheral oxygen availability and enhance exercise capabilities and the quality of life. Because of the many medical and social problems confronting dialysis patients, however, alleviating the symptoms of anemia may only partially contribute to an improved quality of life. Treatment for this anemia, generally consisting of blood transfusions, can produce adverse reactions that effect patients' quality of life. In addition, therapies used to treat other underlying medical conditions, such as drugs, may have debilitating side effects. For example, drug therapy for treating diabetes and hypertension may produce side effects such as lethargy or sexual impotence, which are also common symptoms of anemia.

The time involved in undergoing regular dialysis treatments at home or traveling to a center to receive such treatments may prevent dialysis patients from

developing and maintaining a regular work schedule. This can affect a patient's perception of self-worth and result in financial hardships that affect lifestyle. Thus, when the efficacy of recombinant erythropoietin is considered, it is important to recognize that multiple factors contribute to the quality of life of dialysis patients.

With one exception, the information on recombinant erythropoietin's impact on quality of life comes primarily from randomized or before and after studies of hemodialysis patients in which there was no control group. These quality-of-life studies suggest that correction of anemia associated with chronic renal failure with recombinant erythropoietin can improve the functional abilities of chronic renal failure patients (see table 2-8).

One randomized study examining the quality-of-life involved 118 hemodialysis patients. After 6 months of treatment with recombinant erythropoietin, clinically and statistically significant improvements in the sickness impact profile ($p< 0.02$), stress test ($p< 0.0018$), and other quality-of-life indicators were noted (physical symptoms, fatigue, relationship with others) as compared with the control group (26).

A randomized study evaluated quality-of-life changes in 17 predialysis patients (58). Investigators described subjective improvement in well-being and appetite in the patients. Predialysis patients continued to work and be active, even though their renal functions continued to deteriorate. The quality of life of patients who were not on therapy was not reported, however, making comparison to the treated group impossible.

A recent before and after study examining the relationship between recombinant erythropoietin therapy and quality of life in 333 hemodialysis patients supports earlier findings. Statistically significant increases in hematocrit were noted in patients treated with recombinant erythropoietin over a 4.4 month period and sustained over an average of 10.3 months ($p < 0.001$). Improvements in the quality of life were measured by the Karnofsky index ($p < 0.01$) and subjective quality-of-life indicators, such as well-being ($p < 0.004$), psychological affect ($p < 0.03$), and life satisfaction (p c 0.017). The use of the Nottingham Health Profile produced mixed results, with statistically significant improvements in some measures (energy, emotional reaction) and not in others (pain, sleep, mobility). The number of patients who returned to work after the 10.3 months of treatment was not significantly different from those working at baseline (61).

After the first period, patients reported statistically significant improvements in activity and energy levels ($p<0.01$), which were correlated with statistically significant increases in hematocrit over baseline ($p< 0.01$). Patients reporting low energy levels at the beginning of the study dropped by half after the first period of the study. Improvements reported after the first period of the study were maintained through the entire study period of about 10 months.

A Nottingham profile index was used to measure patient energy levels. A measure of O indicated "no limits" on energy levels, while a measure of 100 indicated complete limits. The patients' average energy level limitation score at the beginning of the study was 47, fell to 31.5 after the first phase of the study, and measured 17.7 at the end of the study ($p< 0.01$). Information on the mean age and other underlying disease states in the patients was not reported. The increase in energy levels was not reported by age group.

A Karnofsky score index was used in another before and after to measure the rehabilitation of 29 dialysis patients (64). (A score of 91-100 indicates ability to engage in full activities without significant effort, while 81-90 indicates ability to engage in usual activities with some effort.) The mean score for the patients increased from 76 to 86.6. Although the significance level was not included, a statistically significant increase in the score was reported for all patients in age groups 20 to 69, but not for those patients aged 70 or over.

In summary, reports to date suggest that recombinant erythropoietin has the potential to improve dialysis patients' quality of life. Long-term studies in the chronic renal failure population are needed, and the relationship between recombinant erythropoietin

Table 2-8-Quality-of-Life Studies

Study design	Number of patients	Physiologic results	Quality-of-Life results	Significance level (p value)	Source[a]
A	118 HD	After 5 months hemoglobin averaged 7.4 g/all for the placebo group, 10.2 g/all for one treatment group (target 95-10.0 g/all), and 11.7 g/all for the other treatment group (target 11.5-13.0 g/all).	Sickness Impact Profile improved, stress test improved	0.02 0.018	Canadian EPO Study Group, 1989 (26).
c	333 HD	Hematocrit rose from less than 30 to 35 after 4.4 months and stayed at 34 after 10.3 months.	Karnoksfy score increased from 27 percent to 48 percent. Ability to work: -patient reported -staff reported Subjective quality of life -well-being -psychological affect -life satisfaction	0.01[b] 0.69 0.93 **0.004** **0.03** **0.017**	Evans, et al., 1990 (61).
C	68 HD	Hematocrit rose from 22.9 to 33.5.	Increase in energy, body temperature, appetite sleep, hair growth, sexual interest.	NA	Eschbach and Adamson, 1989 (54).
C	130 HD	Hematocrit rose from 23.7 to 34.2 (after 5.6 months) to 33.9 (after 9.7 months)	Increase in categories of no complaints, activity energy, and energy limit, as measured by Nottingham profile.	0.01	Evans, et al., 1989 (60)[c].
C	45 HD	Hematocrit rose from 19.3 to 39.8	Appetite, cold tolerance, sleep, sex function, skin color, hair growth increased.	NA	Delano, et al., 1989 (42)[c].
C	37 HD	Hematocrit rose from 19.3 to 31.5. 32 patients remained in study for 2 years.	Well-being appetite, sexual function increased. Karnofsky score used to measure increased range of activities.	NA	Gibilaro, et al., 1989 (64)[c],
C	8 HD	Hematocrit rose from 17.3 to 33.3.	Improvement in exercise capacity	**0.002**	Meyer, et al., 1988 (100).
C	17 HD	Hematocrit rose from 22.7 to 36.6.	Central nervous system functional status increased.	NA	Nissenson, et al., 1989 (106)[c].
C	17 HD	Statistically significant increase in hematocrit noted.	Conceptual and visual motor skills increased.	NA	Wolcott, et al., 1989 (173)[c].
C	17 PD	Statistically significant increase in hematocrit.	Well-being and appetite increased.	NA	Eschbach, et al., 1989 (58).

a Numbers in parentheses refer to list of references.
b P values from baseline to 10.3 months.
c This study reported on a subset of the 333 patients in Evans, et al., 1990 (61).
Nissenson, et al., 1989 (106) and Wolcott, et al., 1989 (173) report on the same 17 patients.

KEY: A = randomized clinical trial that employed placebo or untreated control; B = randomized clinical trial that did not employ placebo or untreated control, but a before and after effect was examined; C = nonrandomized trial in which a before and after effect was examined; HD = hemodialysis; NA = not available; PD = predialysis.

therapy and the ability to work in the case of predialysis patients or ability to return to work in the case of dialysis patients needs to be explored. Determining the long-term effect of recombinant erythropoietin on the quality of life is important because a number of factors contribute to this dimension. Recombinant erythropoietin may produce initial short-term improvements in patients that may or may not persist in the long-term. Finally, future studies should report impact on quality of life by age group, particularly the elderly, since they will constitute a larger percentage of the dialysis population in the near future, and previous studies have presented little information on this age group.

The potential to undertake quality-of-life studies increases as the number of patients on long-term recombinant erythropoietin therapy increases. The ability to find patients that are not being treated with recombinant erythropoietin for the purpose of serving as a control group for such studies, however, may become difficult or impossible. Patients may have to serve as their own control group, or the results from past quality-of-life studies of dialysis patients may serve as potential controls.

Other Potential Uses of Recombinant erythropoietin

The literature suggests that recombinant erythropoietin may be effective in correcting anemias associated with other medical conditions. Because insufficient endogenous erythropoietin production may only partially contribute to these anemias, careful evaluation of the efficacy of recombinant erythropoietin must be made for each condition.

Studies of the safety and efficacy of recombinant erythropoietin in other medical conditions are in various stages. Furthest along in the process are studies in anemia: associated with HIV, which is responsible for acquired immunodeficiency syndrome (AIDS). Ortho Pharmaceutical Corporation submitted a Product Licensing Application (PLA) to FDA for this indication in February 1989 (l).

Anemias Associated With the Human Immunodeficiency Virus (HIV)

Anemia associated with HIV appears to be prevalent among infected people. Recent data indicate that up to 71 percent of patients with AIDS are anemic (hemoglobin value of less than 14 g/dl).[10] In addition, patients with other HIV-related symptoms also have some level of anemia. For example, about 63 percent of AIDS patients with Kaposi's sarcoma,[11] 20 percent of patients with AIDS-related complex (ARC),[12] and 8 percent of patients who are infected with the HIV virus and asymptomatic, are also anemic (175).

In contrast to anemia associated with chronic renal failure, multiple factors are responsible for anemia in people infected with HIV. These include insufficient bone marrow stores as an adverse effects of drug treatment. For example, anemia is a common complication of therapy with zidovudine (37), the only drug currently approved as effective against HIV.[13] FDA has approved zidovudine for treating AIDS and ARC and, more recently for retarding progression of the disease in certain infected people who have not yet developed symptoms (163).

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10 Hemoglobin is the oxygen-carrying protein of red blood cells and can also be used as a measure of anemia. Normal hemoglobin values in men are 14-18 g/all (grams/deciliter) and 12-16 g/all for women (12).

11 Kaposi's sarcoma is a multifocal, spreading cancer of connective tissue, principally involving the skin; it usually begins on the toes or the feet as reddish blue or brownish soft nodules and tumors. Previously seen in older men of Jewish or Mediterranean descent, Kaposi's sarcoma is now one of the opportunistic diseases occurring in AIDS patients.

12 AIDS-related complex is a variety of chronic but nonspecific symptoms and physical findings that appear related to AIDS and that may consist of chronic generalized lymphadenopathy, recurrent fevers, weight loss, minor alterations in the immune system, and minor infections.

13 Zidovudine is the generic name for Retrovir, also known as AZT.

A randomized study of AIDS patients treated with AZT (1,500 mg/day) or placebo for up to 24 weeks indicates the extent to which AZT can cause anemia. More than half of the 83 AZT-treated patients (46) required transfusions during the treatment period vs. only 15 of the 74 placebo-treated patients (119).

One randomized study with a control group has evaluated the efficacy of subcutaneously administered recombinant erythropoietin in 63 AIDS patients taking zidovudine. The trial produced mixed results; as one would expect, those patients with low levels of endogenous erythropoietin responded better than those patients with high levels. At the beginning of the study, 23 of 29 patients receiving recombinant erythropoietin required blood transfusions. At the end of the study, 11 of these patients still needed transfusions. In the control group of 34 patients, 27 required transfusions before the study and 21 still required them after the study. Some patients in the treated group reported improvement in energy level, work capacity, and quality of life (108).

The results of another randomized trial support the notion that recombinant erythropoietin corrects anemia associated with zidovudine treatment in only a subset of the population, primarily those individuals with low endogenous stores of erythropoietin. There were statistically significant changes in the hematocrit level ($p=0.0002$) from baseline for patients with low circulating erythropoietin levels (less than 500 milliunits/milliliter) vs. placebo-treated patients. Alternatively, patients with high levels (greater than 500 milliunits/milliliter) did not have a statistically significant increase in hematocrit, nor was the increase in hematocrit statistically different from the placebo-treated patients in the same group (174).

In contrast to chronic renal failure patients treated with recombinant erythropoietin, there was little relationship between hypertension, seizures, and the use of recombinant erythropoietin in HIV-infected patients (174).

Anemia Associated With Rheumatoid Arthritis

Another potential use of recombinant erythropoietin is to treat anemia associated with rheumatoid arthritis, a progressive, chronic, inflammatory disease that can lead to irreversible joint damage. Anemia associated with arthritis usually results from the bone marrow's inability to respond to endogenous erythropoietin ***(23).*** Therefore, exogenous erythropoietin may have limited therapeutic use in this condition. In one observational study, 2 patients with rheumatoid arthritis treated over a 5-month period (with 100-200 units/kg intravenously three times a week) experienced an increase in hematocrit level from 32 and 30 percent to 43 and 39 percent, respectively, during the treatment period (98).

Autologous Blood Transfusions

Recombinant erythropoietin may be used for patients who want to donate their own blood for potential transfusions during elective surgery, commonly referred to as autologous blood transfusion. The transfusion of homologous blood, or blood from another person, may be associated with various adverse effects, including rejection of the blood if improperly matched and risk of transmission of certain viral infections. The use of autologous blood also reduces the demand on the nation's blood supply.

Current autologous blood donation averages only 2.2 units of blood over a 2-to 5-week period (141). In addition, there is usually a significant time lag between donations, which could delay surgical procedures. The American Association of Blood Banks recommends a minimum hematocrit value of 34 percent and a 7-day period between donations of blood from autologous donors (72). In a randomized controlled study of 47 adults scheduled for elective orthopedic surgery, either recombinant erythropoietin (600 units/kg 2 times a week intravenously) or placebo was administered for 21 days. The mean number of units of blood collected was 5.4 for the group treated with erythropoietin and 4.1 for the placebo group ($p<0.05$) (66).

Other Anemias

The use of recombinant erythropoietin in correcting cancer-related anemias is currently under investigation. Cancer-related anemia usually results from increased destruction of red blood cells and decreased erythropoiesis due to kidney damage from cancer treatments, such as radiation and chemotherapy. A recent abstract suggested that anemia of cancer may be due to the malignancy itself or may be caused by antineoplastic agents (101). The data suggested that both treated and untreated cancer patients may have low levels of endogenous erythropoietin.

Recombinant erythropoietin has also been used in treating anemia of Gaucher's Disease, an inherited disorder of lipid metabolism (121), and in treating anemia of preterm infancy (87). No studies on efficacy have been done in these conditions to date.

EVALUATION OF THE SAFETY OF RECOMBINANT erythropoietin

Adverse Effects of Recombinant erythropoietin

In evaluating the safety of recombinant erythropoietin, it is important to distinguish among those adverse effects that are attributable to the product itself versus those that result from the natural progression of chronic renal failure. For example, both hypertension and seizures, adverse effects attributable to recombinant erythropoietin,

Table 2-9-Adverse Reactions to Recombinant erythropoietin

Study design	Number of patients	Adverse reactions reported	Source[a]
A	375 HD[b]	The most frequently reported adverse reactions for all patients were nausea, fever, chest pain, fatigue, pain, dizziness, dyspnea, vomiting, upper respiratory infection. 92 percent of treated patients in randomized phases had one or more adverse reactions vs. 83 percent untreated patients.[c] The incidence of headache and clotting of placebo of the access site appeared to be related to treatment.	Sobota, 1989 (131).
A	14 PD	An increase in antihypertensive medication was needed in 3 treated patients.	Lim, et al., 1989 (92).
B	17 PD	14 of 17 patients were taking antihypertensives. 9 had an increase in blood pressure with additional antihypertensives needed. 2 originally normotensive patients needed antihypertensives.	Eschbach, et al., 1989 (58).
C	333 HD[d]	44 percent of normotensive patients (n = 71) developed hypertension and 32 percent of the 71 patients needed antihypertensives. 72 percent of hypertensive patients (n= 180) had an increase in blood pressure, and 32 percent of the 180 patients needed additional antihypertensives. 43 percent developed iron deficiency (would have been 20 percent greater if some patients were not iron overloaded from blood transfusions). 5.4 percent had seizures (in 18 of 333 patients; 10 of 18 occurred in first 3 months of therapy).	Eschbach, et al., 1989 (56).

a Numbers in parentheses refer to list of references.
b The trial consisted of an initial randomized dose-response phase (n=131) without placebo control. Two later phases were randomized, placebo-controlled (n=244). The total number of patients in study was 375.
[c] An adversereactionwas defined as any event that occurred to patients,whether relatedor unrelated to the intervention.
Of 333 patients in the study, data for 251 patients were sufficient to evaluate changes in blood pressure.

KEY: A = randomized clinical trial that employed placebo or untreated control; B = randomized clinical trial that did not employ placebo or untreated control and a before and after effect were examined; C = nonrandomized trial in which a before and after effect were examined; HD = hemodialysis; PD = predialysis.

Table 2-10-Percent of Patients Reporting Adverse Reactions from Recombinant erythropoietina

Adverse reaction	Treated patients (n=200)	Placebo patients (n= 135)
Hypertension	24.0	18.5
Headache	16.0	11.9
Muscle aches	11.0	5.9
Nausea	10.5	8.9
Swelling	9.0	10.4
Access to graft clotted	6.8	2.3
Seizure	1.1	1.1
Cerebrovascular accident	0.4	0.6

a Based on events reported in placebo-controlled studies in patients with chronic renal failure. Levels of statistical significance are unavailable.

SOURCE: Amgen, Inc., 1989 (5); US DHHS, FDA, 1989 (160).

Table 2-1 l-Adverse Reactions to Recombinant erythropoietin Per Patient Year[a]

Reaction	Total treated[b]	Placebo
Hypertension		
Dialysis patients	0.69	0.33
Predialysis patients	1.70	3.28
seizure	0.0473	0.037
Clotting of arteriovenous graft	0.249-0.273	0.59

a In U.S. and non-U.S. trials.
Levels of statistical significance are unavailable.

SOURCE: US DHHS, FDA, 1989 (160).

are common complications of chronic renal failure.[14] In addition, it is important to detect any differences in adverse reactions between predialysis patients and dialysis patients, and differences in adverse reaction between patients receiving recombinant erythropoietin by the intravenous route as compared with the subcutaneous route.

Adverse reactions from recombinant erythropoietin therapy are reported in table 2-9. In chronic renal failure patients using recombinant erythropoietin, hypertension is the most prevalent adverse effect and seizures are the most serious adverse effect. Iron deficiency also occurs frequently .15 Other side effects that have been reported include headache, muscular pain, nausea, hyperkalemia,[16] and clotted access to the arteriovenous graft (160).

The potential for the development of hypertension with recombinant erythropoietin is important because of the high rate of cardiovascular morbidity and mortality in chronic renal failure patients. Although data in FDA's Summary Basis of Approval seem to indicate that there is a higher absolute incidence of hypertension in treated than untreated patients, it did not specify whether the difference is statistically significant (see table 2-10). In addition, table 2-11 indicates the incidence of adverse reactions per patient year among total U.S. and non-U.S. treated patients vs. placebo. The incidence of hypertension per patient year was twice the rate in dialysis patients as compared to placebo, but only half the rate in predialysis patients.

The literature suggests that an increase in hypertension is most likely to occur in those patients who are already hypertensive (28). Whether the development of hypertension is also related to the rate of increase in hematocrit is inconclusive (40).[17,18] Since

14Up to 90 percent of patients in renal failure are hypertensive (38). Overall, deaths from cardiovascular disease account for more than half of all mortality in renal failure patients, whether treated by dialysis or transplantation (113). Seizures occur in approximately 5-10 percent of chronic renal failure patients (160).

15Chronic renal failure patients become iron deficient because effective erythropoiesis with recombinant erythropoietin requires iron.

16Patients on recombinant erythropoietin generally experience an increase in appetite. Hyperkalemia, an increase in serum potassium, results primarily from an increase in foods that are potassium-rich. The condition, left untreated may cause cardiac problems and muscular problems (91).

17Issues of dosing of recombinant erythropoietin are important because the adverse reactions may be dose-related and the product is expensive. The target hematocrit in the FDA-approved labeling is 30-33 percent, which is lower than the hematocrit targets of most of the clinical studies, The FDA Blood Products Advisory Committee decided that the 30-33 percent range was a more appropriate hematocrit range for chronic renal failure patients because of potential side effects (62). Based on clinical studies, Amgen, Inc. initially proposed a dose of 150 units/kg 3 times weekly intravenously. FDA proposed a 50 units/kg starting dose. The committee thought the FDA-proposed initial dose was too conservative, but thought Amgen's recommended dose was too high. The committee decided on a dose of 50-100 units/kg (62).

18The increase in hypertension with recombinant erythropoietin may be attributable to two factors: the increase in blood viscosity resulting from an increase in red blood cells and an increase in peripheral vascular resistance (52).

most patients in the trials had their hypertension controlled by drugs, there is little clinical information to indicate the effect of recombinant erythropoietin on patients with uncontrolled hypertension. Nor have the studies reported the incidence of this side effect by racial or age groups.

A major unresolved issue in predialysis patients is whether exacerbation of hypertension from recombinant erythropoietin accelerates renal disease. The correction of the anemic condition in predialysis patients might result in better oxygen perfusion of organs, such as the kidney; alleviate symptoms of anemia; and increase the length of time the kidneys are able to function. Some investigators have observed that a further increase in blood pressure in hypertensive patients does not necessarily accelerate the progression of renal disease (58).

Although seizures clearly represent a significant adverse reaction to recombinant erythropoietin, it is not clear if the overall seizure rate in patients treated with recombinant erythropoietin is different from those treated with placebo or not treated at all. The rate of seizures in treated patients appears to be slightly higher in treated patients, as indicated in table 2-10; however, statistical significance data are unavailable. According to the FDA's Summary Basis of Approval, the seizure rate in treated vs. untreated or placebo-treated patients is the same; the rate is higher in the first 90 days of therapy compared with untreated or placebo-treated patients (160). There was no apparent relationship found, however, between the rate of rise of hematocrit and seizures for chronic renal failure patients experiencing a seizure during the first 90 days of treatment.

Finally, the rate of artervenous graft clotting was almost twice the rate in the placebo group as compared to the rate range in the treated group. According to the FDA's Summary Basis of Approval, the rate of graft clotting in patients treated with recombinant erythropoietin was no greater than that reported in two large independent surveys of untreated dialysis patients (160).

It is unlikely that different types of adverse reactions would occur based on the route of administration of recombinant erythropoietin. There may be some minor administration-related effects, such as pain and swelling at the site of injection after a dose of subcutaneous recombinant erythropoietin. There is some evidence to suggest that, if adverse reactions to recombinant erythropoietin are dose-related, then incidence of adverse reactions can be minimized if lower doses of recombinant erythropoietin can be given by the subcutaneous route. A slower, steadier increase in hematocrit by using low doses of the intravenous route or by using the subcutaneous route can allow clinicians to monitor response, adjust dose, and avert any cardiovascular crisis, such as seizures, if needed.

Based on clinical data available, and discussions with clinicians, it appears that self-administration of recombinant erythropoietin is relatively safe for home dialysis patients. A small number of patients successfully self-administered recombinant erythropoietin at home after only a brief explanatory session by their physician (110).

In another study of home patients whose target hematocrit level was attained and stabilized in the dialysis facility, a dose of 50 units/kg was used to maintain the hematocrit. Researchers in the study cautioned that blood pressure should be well-controlled and measured 3 times daily in patients that self-administer recombinant erythropoietin (171). The nature and extent of any adverse reactions were not reported, however. Another study compared the incidence of adverse reactions in 55 home hemodialysis patients who self-administered recombinant erythropoietin with 31 patients who received recombinant erythropoietin in a dialysis facility. At an average dose of 101 units/kg, 9 of the facility patients experienced seizures over 23 months, and at an average dose of 108 units/kg, 1 self-administration patient experienced a seizure. Data on differences among the patient groups, which may have accounted for different rates of adverse effects, were not given. In another study, 2 patients that self-administered recombinant erythropoietin subcutaneously had pain at the injection site (82). It thus appears that home use of recombinant erythropoietin is relatively safe, if a patient's hematocrit has been stabilized, and if patients are provided instructions on how to properly administer the product and monitor response.

Recombinant erythropoietin and Blood Transfusions

The use of recombinant erythropoietin to treat anemia associated with chronic renal failure may substantially reduce or obviate the need for periodic blood transfusions. One nephrologist has estimated that 25 percent of dialysis patients require periodic or intermittent blood transfusions to maintain an acceptable hematocrit level (57). Use of recombinant erythropoietin instead of blood transfusions has multiple benefits. Although now relatively low, the risk of contracting blood-borne infections, such as HIV and various types of hepatitis, can be further minimized. Measures adopted in recent years to limit the spread of HIV through the nation's blood supply have minimized the risk of contracting these viruses. In 1989, screening procedures for HIV antibodies have lowered the risk of post-transfusion HIV infection to between 1 in 40,000 and 1 in 250,000 per transfusion. Post-transfusion hepatitis B infection occurs at the rate of 1 per 2,000 transfusions, and the risk associated with non-A, non-B hepatitis (NANBH, some of which is hepatitis C) is approximately 1 in 125 transfusions. The incidence of NANBH should further decrease in the near future with the development of a NANBH assay (4).

Eliminating or reducing blood transfusions may also increase the number of dialysis patients who can become candidates for successful renal transplantation. The development of transfusion-induced antibodies is a major factor limiting dialysis patients from receiving kidney transplants (27). Eliminating or reducing the need for blood transfusions could eliminate the development of these antibodies. In the long term, given a sufficient supply of transplantable organs and patient preference for this treatment, Medicare ESRD expenditures could decrease since expenditures for dialysis patients are about three times as much as transplantation (45). Despite the high -initial costs of transplantation, lower costs of maintaining patients with functioning transplants implies that Medicare recovers the costs of transplantation in about 3 years. In addition, transplant patients tend to have a better quality of life than do dialysis patients.

Finally, the use of recombinant erythropoietin could decrease Medicare's expenditures for blood and blood products. It is not evident, however, if the use of recombinant erythropoietin as a substitute for blood will ultimately reduce expenditures for the Medicare program. Recombinant erythropoietin may actually cost Medicare more than blood transfusions. Medicare covers 80 percent of the cost of blood transfusions after a beneficiary has met a 3-pint deductible under Part B of the program. That is, the patient has to replace or pay for 3 pints of blood before the program covers the cost of blood. The cost of blood does not count toward the annual Part B deductible, currently $75. In addition, blood provided under Part B does not meet the 3-pint Part A deductible (42 CFR 410.161).

SUMMARY OF SAFETY AND EFFICACY OF RECOMBINANT erythropoietin

Recombinant erythropoietin administered intravenously produces a dose-dependent rise in hematocrit level and can reduce or eliminate the need for blood transfusions in patients with anemia associated with chronic renal failure. The number of patient reaching a target hematocrit also depends upon the dose. Current information suggests that greater than 90 percent of patients will reach a target hematocrit of 30 percent with a dose of 100 units/kg. Some patients will reach the target with lower doses.

Further studies need to be done to evaluate long-term side effects and outcomes of therapy based on age (e.g., the pediatric and elderly population), race (outcomes among the various racial groups), and other underlying disease states in chronic renal failure patients. The effect of recombinant erythropoietin on predialysis patients also needs to be explored, that is, does the use of the product in this group of patients have the potential to delay the need for dialysis or does it accelerate the rate of renal injury?

Although evidence suggests that subcutaneously administered recombinant erythropoietin is efficacious, additional studies are needed to determine whether lower doses may be used in lieu of currently recommended doses, and whether lower doses can minimize the incidence of adverse reactions.

Initial studies seem to indicate that the quality of life of dialysis patients maybe improved with recom-

binant erythropoietin; however, additional studies are being conducted to evaluate the long-term impact of recombinant erythropoietin on the quality of life. Many factors contribute to the quality of life of dialysis patients, including the symptoms of anemia and treatment for underlying disease states. In addition, dialysis patients are generally taking drugs for many of these underlying disease states, which may have side effects that negate any positive impact that can be attributable to recombinant erythropoietin. For example, lethargy and impotence are common adverse reactions to antihypertensive mediations. Studies also need to be done on recombinant erythropoietin's ability to allow dialysis patients to return to work. This factor may depend more on current financial incentives for the patients not to return to work than on their ability to work.

A notable number of patients developed hypertension during the course of clinical trials, a relatively manageable adverse reaction to recombinant erythropoietin. Seizures appear to be the most serious side effect, but the relative risk appears to be no higher in treated patients than untreated patients. This event may be related to the hypertensive state of the patient and the rate of increase in hematocrit. Available information does not indicate whether the occurrence of adverse reactions in treated vs. non-treated patients, including hypertension and seizures, is statistically significant. Hypertension and seizures may also be associated with chronic renal failure.

Although recombinant erythropoietin has been studied in patients since 1986, there are still a number of outstanding issues that need to be addressed related to dosing, side effects, and long-term effect on the quality of life. As additional patients receive the product over a longer period of time, and additional information is collected, clinicians will be better able to address these and other identifiable issues that relate to patient care.