

## SUBCUTANEOUS COMPARED WITH INTRAVENOUS EPOETIN IN PATIENTS RECEIVING HEMODIALYSIS

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### ABSTRACT

**Background** Several studies have suggested that if recombinant human erythropoietin (epoetin) is administered subcutaneously rather than intravenously, a lower dose may be sufficient to maintain the hematocrit at a given level.

**Methods** In a randomized, unblinded trial conducted at 24 hemodialysis units at Veterans Affairs medical centers, we assigned 208 patients who were receiving long-term hemodialysis and epoetin therapy to treatment with either subcutaneous or intravenous epoetin. The dose was initially reduced until the hematocrit was below 30 percent and then was gradually increased to a level that would maintain the hematocrit in the range of 30 to 33 percent for 26 weeks. We compared the average doses in the 26-week maintenance phase and the discomfort associated with the two routes of administration.

**Results** For the 107 patients treated by the subcutaneous route, the average weekly dose of epoetin during the maintenance phase was 32 percent less than that for the 101 patients treated by the intravenous route (mean  $\pm$ SD,  $95.1 \pm 75.0$  vs.  $140.3 \pm 88.5$  U per kilogram of body weight per week;  $P < 0.001$ ). Only one patient in the subcutaneous-therapy group withdrew from the study because of pain at the injection site, and 86 percent rated the pain associated with subcutaneous administration as ranging from absent to mild.

**Conclusions** In patients receiving hemodialysis, subcutaneous administration of epoetin can maintain the hematocrit in a desired target range, with an average weekly dose of epoetin that is lower than with intravenous administration. (N Engl J Med 1998; 339:578-83.)

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**I**N patients with end-stage renal disease, treatment of anemia with recombinant human erythropoietin (epoetin) has improved cardiovascular function and the quality of life.<sup>1,2</sup> However, these benefits come at substantial economic cost, with 1994 Medicare expenditures for epoetin therapy exceeding \$700 million. Efforts to optimize the use of epoetin have been aimed at increasing the efficiency of administration and addressing factors that may cause resistance to the hormone, such as iron deficiency, hyperparathyroidism, and inadequate hemodialysis.<sup>3-5</sup>

The initial clinical trials of epoetin were performed

in patients undergoing hemodialysis, with the drug administered intravenously during hemodialysis. Pharmacokinetic studies indicating that the bioavailability of epoetin was lower but its half-life was longer after subcutaneous administration than after intravenous administration<sup>6-8</sup> led to clinical trials comparing the two routes of administration. Although the results suggested that lower doses could be used with subcutaneous administration, many of these studies used a nonrandomized crossover design or included small numbers of patients, and thus the evidence was not conclusive. A recent review concluded that there is no clear difference in doses between the two routes of administration.<sup>1</sup> Furthermore, subcutaneous administration may be associated with pain at the site of injection,<sup>9,10</sup> limiting its acceptability to patients. Therefore, the primary goal of the current study was to compare the intravenous route of administration of epoetin therapy with the subcutaneous route in terms of the dose required to maintain a target hematocrit value and of acceptance by patients who require long-term hemodialysis.

### METHODS

#### Study Subjects and Design

The study was a randomized, unblinded trial performed at 24 hemodialysis units at Veterans Affairs medical centers. The study population consisted of 208 patients (99 percent of whom were men) with end-stage renal disease treated by hemodialysis for at least six months who had received epoetin for at least three months before entry. All patients were required to have a hematocrit of 30 to 33 percent while receiving epoetin subcutaneously or intravenously thrice weekly during the week before randomization. If a patient's hematocrit value was outside the target range at the initial screening or the patient was receiving epoetin fewer than three times per week, the dose was adjusted before randomization. The patients were also required to have a serum

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ferritin concentration of more than 100 ng per milliliter and a transferrin-saturation value of more than 20 percent. We excluded patients in whom epoetin therapy might be unsafe (e.g., those with uncontrolled hypertension) and those who might not have a response to the usual doses (e.g., those with acute inflammatory disease or infection, a known hematologic disorder, or gastrointestinal bleeding and those who had received a transfusion in the previous eight weeks). We also excluded patients who were unusually sensitive or resistant to epoetin — those requiring a dose of less than 30 U per kilogram of body weight per week or more than 500 U per kilogram per week, respectively. The study was approved by the human-rights committee at the Hines Veterans Affairs Cooperative Studies Program Coordinating Center and the institutional review boards at the participating institutions, and all the patients gave informed consent.

Hematocrit and hemoglobin were measured weekly with electronic methods. Serum iron, serum total iron-binding capacity, serum ferritin, the urea-reduction ratio (defined as the percent reduction in the blood urea nitrogen concentration during a single hemodialysis treatment), and routine serum chemical variables were measured monthly with standard methods at the individual centers. At base line, serum parathyroid hormone was measured in each patient by immunoradiometric assay and serum aluminum was measured by atomic absorption spectrophotometry.

### Epoetin Regimen

The primary objective of the study was to compare the weekly doses of intravenous and subcutaneous epoetin needed to maintain a target hematocrit of 30 to 33 percent for 26 weeks. This range was selected because when the study was begun it was the range approved by the Food and Drug Administration, although the upper limit is now 36 percent. The patients were randomly assigned to receive epoetin (epoetin alfa, Epogen, Amgen, Thousand Oaks, Calif.) three times weekly either subcutaneously or intravenously. Randomization was stratified according to center and the route of epoetin administration before randomization. After randomization, all patients had their epoetin doses reduced by 50 percent, but by no more than 60 U per kilogram per week, every six weeks until the hematocrit was below 30 percent for two consecutive weeks. The dose was then increased by 30 U per kilogram per week every four weeks until the hematocrit was at least 30 percent for two consecutive weeks. The patients then entered the 26-week maintenance phase in which the dose of epoetin was adjusted according to a specific algorithm to maintain the hematocrit in the range of 30 to 33 percent.

### Dosing Algorithms for Epoetin and Parenteral Iron

Hematocrit was measured weekly before the mid-week hemodialysis treatment, and if two consecutive values were outside the target range, the dose of epoetin was modified by 30 U per kilogram per week, the dose being increased if the hematocrit was below 30 percent and decreased if it was above 33 percent. The dose of epoetin could not be changed more frequently than every four weeks. Epoetin (10,000 U per milliliter) was administered on a weight-adjusted basis with insulin syringes with small-gauge needles at the end of hemodialysis; all doses were rounded to the nearest 100 U. The patients in the intravenous-therapy group received the hormone through a port in the venous tubing before blood was flushed from the tubing, and the patients in the subcutaneous-therapy group received it at the end of hemodialysis in the arm that did not have the fistula.

All patients were encouraged to take oral iron supplements (polysaccharide-iron complex, Niferex-150, Schwarz Pharma, Milwaukee). Patients in whom iron deficiency developed, defined as a serum ferritin concentration of less than 100 ng per milliliter alone or a combination of a serum ferritin concentration of less than 400 ng per milliliter and transferrin saturation below 20 percent, received 100 mg of parenteral iron dextran (INFeD, Schein Pharmaceutical, Florham Park, N.J.) intravenously at 10 consecutive hemodialysis sessions.

### Assessment of Discomfort during Treatment

At base line all patients rated the level of discomfort associated with the entire hemodialysis procedure, including the administration of epoetin. This evaluation was repeated every 13 weeks in all patients in the intravenous-therapy group and half of those in the subcutaneous-therapy group; the other half of the subcutaneous-therapy group rated only the level of discomfort associated with the subcutaneous injection itself. The patients rated the level of discomfort using a visual-analogue scale consisting of a 100-mm line on which 0 mm indicated the absence of pain and 100 mm severe pain. The patients also rated the pain using a seven-category descriptive scale (no pain, very mild pain, mild pain, not very severe pain, quite severe pain, very severe pain, and almost unbearable pain).

### Statistical Analysis

The groups were compared with the two-sample t-test for continuous data and Fisher's exact test for categorical data.<sup>11</sup> Intention-to-treat analysis was used in reporting results unless otherwise stated. To analyze the maintenance-phase doses of epoetin and hematocrit and hemoglobin values, we first calculated the average of each measure for all available maintenance-phase visits for each patient. For patients who did not enter the maintenance phase, we imputed an average value for each measurement using the last available measurement. If patients discontinued epoetin therapy during the dose-reduction phase because the target hematocrit was maintained at a dose of less than 3 U of epoetin per kilogram per week, their average dose was considered to be zero. Mean discomfort scores during the maintenance phase were computed with use of the average of the quarterly assessments during this phase. Fisher's exact test was used to assess the relation between a change in the route of administration from base line and a change in the dose. All statistical tests were two-sided.

## RESULTS

The base-line characteristics of the patients in the two groups were similar (Table 1). Of the 208 patients who underwent randomization, 157 entered the maintenance phase and 138 completed the 26-week maintenance phase. Seventy patients withdrew after randomization, including 12 patients who were able to discontinue epoetin therapy during the dose-reduction phase without having their hematocrit values decrease below 30 percent (Table 1). The average ( $\pm$ SD) length of time in the study was  $48 \pm 20$  weeks (range, 2 to 102) in the intravenous-therapy group and  $46 \pm 17$  weeks (range, 2 to 87) in the subcutaneous-therapy group ( $P=0.46$ ). When we compared base-line values with the average values during the maintenance phase in the study group as a whole, we found that there was little change in the urea-reduction ratio (mean change,  $0.3 \pm 6.9$  percent;  $P=0.61$ ) and diastolic blood pressure ( $1.7 \pm 12.2$  mm Hg,  $P=0.08$ ), but an increase in systolic blood pressure ( $4.6 \pm 19.8$  mm Hg,  $P=0.005$ ).

### Dose of Epoetin

During the maintenance phase, the average weekly dose of epoetin was 32 percent lower in the subcutaneous-therapy group than in the intravenous-therapy group (Table 2 and Fig. 1). When the analysis was restricted to the 138 patients who completed the 26-week maintenance phase, the average dose in the

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE PATIENTS AND REASONS FOR WITHDRAWAL FROM THE STUDY.\*

CHARACTERISTIC	SUBCUTANEOUS-THERAPY GROUP (N=107)	INTRAVENOUS-THERAPY GROUP (N=101)	P VALUE
Age (yr)	60±13	61±13	0.48
Male sex (no.)	105	100	1.00
Weight (kg)	78.6±15.4	73.5±15.6	0.02
Duration of dialysis (yr)	3.0±2.6	4.4±4.9	0.01
Duration of epoetin therapy (yr)	2.0±1.5	2.4±1.5	0.09
Subcutaneous epoetin therapy (%)	71	70	1.00
Dose of epoetin (U/kg/wk)	117±84	122±79	0.62
Hematocrit (%)	31.6±1.0	31.7±1.2	0.53
Serum transferrin saturation (%)	28.5±10.1	28.1±11.3	0.79
Serum ferritin (ng/ml)	297±196	305±250	0.78
Serum albumin (g/dl)	3.8±0.5	3.7±0.4	0.09
Urea-reduction ratio (%)†	66.3±6.0	66.0±8.6	0.80
Serum aluminum (μg/liter)‡	19.4±13.6	24.3±19.6	0.07
Serum parathyroid hormone (pg/ml)§	294±336	274±326	0.71
Level of discomfort			
Visual-analogue scale (mm)	26±21	28±19	0.31
“Quite severe” or worse on descriptive scale (%)	5.6	4.0	0.75
Reasons for withdrawal from the study (no.)			
Study terminated before patient completed maintenance phase	3	9	
Death	11	8	
Left participating hemodialysis unit	3	5	
Kidney transplantation	2	3	
Began peritoneal dialysis	0	2	
No further need for epoetin therapy	7	5	
Other¶	6	6	
Total	32	38	

\*Plus-minus values are means ±SD.

†The urea-reduction ratio is the percent reduction in blood urea nitrogen from the beginning to the end of a hemodialysis session and is a measure of the adequacy of hemodialysis.

‡To convert values for aluminum to nanomoles per liter, multiply by 37.06. The normal value for serum aluminum is 15 μg per milliliter (556 nmol per liter) or less.

§To convert values for parathyroid hormone to picomoles per liter, multiply by 0.105. The normal range for serum parathyroid hormone is 10 to 65 pg per milliliter (1.05 to 6.85 pmol per liter).

¶Other reasons for withdrawal from the study in the subcutaneous-therapy group included pain at the injection site (one patient), requirement for a higher hematocrit because of cardiac disease (three), metastatic cancer (one), and no further need for thrice-weekly hemodialysis (one). Other reasons in the intravenous-therapy group included requirement for a higher hematocrit because of cardiac disease (two patients), metastatic cancer (two), the development of allergy to parenteral iron (one), and active ulcerative colitis (one).

subcutaneous-therapy group (104±60 U per kilogram per week; 75 patients) was 27 percent less ( $P<0.001$ ) than that in the intravenous-therapy group (142±72 U per kilogram per week; 63 patients). During the maintenance phase, nine patients in the intravenous-therapy group (12 percent) received a total of 78 units of packed red cells and seven patients in the subcutaneous-therapy group (9 percent) received a total of 79 units ( $P=0.61$ ). Eighty-four percent of the patients in the intravenous-therapy group and 83 percent of those in the subcutaneous-therapy group received at least one course (1000 mg) of intravenous iron dextran. The average total amounts of iron administered during all phases of the study were

not significantly different between the two groups (1683±1280 mg per patient in the intravenous-therapy group and 1765±1342 mg per patient in the subcutaneous-therapy group,  $P=0.65$ ).

To compare the dose requirements at similar hematocrit values in the patients in whom the route of administration of epoetin was not changed from that at base line and the patients in whom the route of administration was changed, we compared the dose in the week before randomization to the average dose during the maintenance phase. We defined a meaningful change in the dose as an increase or a decrease of more than 30 U per kilogram per week because this value corresponded to one dose change in our dosing

**TABLE 2.** RESULTS DURING THE MAINTENANCE PHASE OF SUBCUTANEOUS AND INTRAVENOUS EPOETIN THERAPY.\*

VARIABLE	SUBCUTANEOUS-THERAPY GROUP (N=107)	INTRAVENOUS-THERAPY GROUP (N=101)	P VALUE
Weekly maintenance dose of epoetin			
Average (U/kg/wk)	95.1±75.0	140.3±88.5	<0.001
Average (U/wk)	7397±6139	10,068±6334	0.002
Average hematocrit (%)	31.3±2.9	31.1±2.5	0.60
Average hemoglobin (g/dl)	10.4±1.0	10.3±0.9	0.21

\*Plus-minus values are means ±SD.

algorithm. Of the patients who switched from intravenous to subcutaneous therapy, 58 percent had a reduction in the dose during the study and 23 percent an increase. The corresponding values for the patients who switched from subcutaneous to intravenous therapy were 28 percent and 49 percent. Of the patients who received epoetin subcutaneously before and during the study, 34 percent had a reduction in the dose during the study and 20 percent an increase. The respective numbers for the patients who received epoetin intravenously before and during the study were 30 percent and 23 percent. These results confirm the greater efficiency of subcutaneous administration but suggest that the subcutaneous route may not be more efficient in all patients.

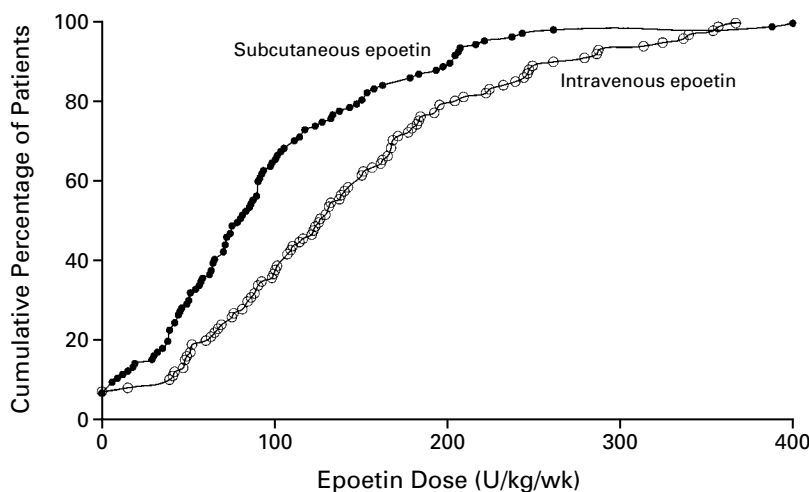
The base-line dose and a change in the route of administration had independent effects on the change

in the dose from base line to the maintenance phase. Regardless of the prior or randomly assigned route of administration, patients who were receiving at least 140 U of epoetin per kilogram per week at base line had a greater decrease in the dose than those who were receiving less than 140 U of epoetin per kilogram per week at base line ( $P<0.001$ ). Of the patients who were receiving at least 140 U of epoetin per kilogram per week at base line, 64 percent had a reduction in the dose of more than 30 U per kilogram per week, whereas among the patients who were receiving less than 140 U of epoetin per kilogram per week at base line, only 22 percent had such a reduction in the dose ( $P<0.001$ ).

**Assessment of Discomfort**

All the patients in the intravenous-therapy group and half the patients in the subcutaneous-therapy group assessed the level of discomfort during the entire dialysis procedure. The scores were similar in the two groups (visual-analogue score,  $25\pm21$  in the intravenous-therapy group and  $22\pm22$  in the subcutaneous-therapy group;  $P=0.20$ ; percentage with verbal descriptive score of “quite severe” or worse, 8 percent in each group;  $P=0.27$ ). Of the patients in the subcutaneous-therapy group who assessed the level of discomfort associated with subcutaneous injection, most (86 percent) gave a rating of no pain, very mild pain, or mild pain. Only one patient withdrew from the study because of discomfort from subcutaneous injection.

At the completion of the study we asked the 96 patients who had at some time received epoetin by both routes to state their preferences regarding the route of administration. Seventy-four percent pre-



**Figure 1.** Average Epoetin Doses during the Maintenance Phase in the Subcutaneous-Therapy and Intravenous-Therapy Groups.

Values represent the cumulative percentage of patients on the y axis requiring a dose of epoetin that was equal to or less than each value on the x axis.

ferred the intravenous route, and 26 percent had no preference or preferred the subcutaneous route. The patients assigned to the subcutaneous-therapy group were more likely than those assigned to the intravenous-therapy group to have no preference or to prefer the subcutaneous route (47 percent vs. 12 percent,  $P < 0.001$ ).

### DISCUSSION

Our results indicate that the average dose of epoetin needed to maintain a hematocrit of 30 to 33 percent is 32 percent lower with subcutaneous administration than with intravenous administration. This result was accomplished with the use of a specific dosing algorithm and may represent the maximal reduction achievable in routine clinical practice. Although nearly all the patients were men, there is no evidence that there is a sex difference in the response to epoetin. On the basis of the average difference in the dose in our patients of 2671 U per week, the average savings realized by administering epoetin by the subcutaneous route would exceed \$1,100 per patient-year. Since the vast majority of the more than 150,000 patients undergoing hemodialysis in the United States receive epoetin intravenously, the savings to the health care system would be substantial.

Many,<sup>12-21</sup> but not all,<sup>22-27</sup> previous trials also concluded that the doses of epoetin required to maintain the hematocrit at a given level were lower with a subcutaneous route of administration, but most of those studies were nonrandomized crossover studies in which the patients were switched from the intravenous to the subcutaneous route of administration. This design does not take into consideration the possibility of crossover effects that would, owing to the long half-life of red cells, delay the decrease in hematocrit resulting from an inadequate dose. Also, some studies have suggested that the requirement for epoetin may decrease with time.<sup>28</sup> These time-dependent effects of epoetin therapy could bias studies in which patients switched from intravenous to subcutaneous therapy in favor of subcutaneous therapy. Most of the studies in which the dose was not lower during subcutaneous administration were parallel-group studies of small numbers of patients.<sup>22,24-26</sup>

Recently, Virot et al. suggested that patients who are receiving intravenous doses of more than 150 U of epoetin per kilogram per week are more likely than those receiving lower doses to have a reduction in the dose when the route of administration is switched to subcutaneous.<sup>21</sup> In our study, whatever the previous or post-randomization routes of administration, patients who were receiving higher doses of epoetin at base line (at least 140 U per kilogram per week) were more likely to need a lower dose in the maintenance phase. Furthermore, in some patients, epoetin could be discontinued without de-

creasing the hematocrit (data not shown). The clinical implication of this finding is that it may be worthwhile to consider a reduction in the dose in patients who have reached the target hematocrit value, especially those receiving high doses of epoetin. Our cutoff value of 140 U of epoetin per kilogram per week was based on a target hematocrit of 30 to 33 percent. The value is likely to be higher if the hematocrit is maintained at the currently recommended guideline of 33 to 36 percent.<sup>29</sup>

A concern with the subcutaneous administration of epoetin is the pain of injection.<sup>9,10,30,31</sup> However, the acceptance of subcutaneous administration in our study was good. We attempted to minimize the pain of subcutaneous administration by using an epoetin concentration of 10,000 U per milliliter and using insulin syringes with small-gauge needles for injection. Since the initiation of our trial, epoetin with benzyl alcohol as a preservative has become available, and this formulation appears to decrease the pain of subcutaneous injection without reducing the efficacy of the drug<sup>16</sup> and may thus further increase the acceptability of subcutaneous administration.

In conclusion, in patients with end-stage renal disease treated by hemodialysis, hematocrit values of 30 to 33 percent can be maintained with about one-third less epoetin when the drug is given subcutaneously than when it is given intravenously.

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### APPENDIX

In addition to the authors, the following centers, investigators, and support staff participated in the Department of Veterans Affairs Cooperative Study Group on Erythropoietin in Hemodialysis Patients: *Office of the Chairman, Boston* — R. Cxypolski (clinic coordinator), P. London (secretary); *Veterans Affairs Medical Centers* — Ann Arbor, Mich.: E. Young, P. Rose; Boston: G. Schmitt, K. Bold, J. Briggs, V. Lee; Bronx, N.Y.: D. Kaji, F. Ohsumi, H. Chen; Cleveland: M. Ganz, S. Nurko, D. Linn; Dallas: R. Cronin, V. Kemp; Dayton, Ohio: M. Saklayen, S. Adams, Y. Jenkins, M. Davis; East Orange, N.J.: S. Sastrasinh, K. Lordi; Hines, Ill.: Z. Nawab, B. Kepka; Houston: G. Dolson, R. Therappel, A. Bonner; Indianapolis: J. Hasbargen, S. Nielsen, A. Frame; Long Beach, Calif.: G. Shah, D. Lim; Miami: L. Cason, J. Edelstein, C. Serrano; Milwaukee: J. Schramm, E. Sheahan-Meyer, B. Jackson; New Orleans: V. Batuman, D. Archie; New York: R. Discipulo; Northport, N.Y.: T. Dixon, E. Lamonica; Oklahoma City: P. Pederson, T. Albert; Palo Alto, Calif.: R. Jamison, D. Usi; Pittsburgh: P. Palevsky, P. Baltz Salai; Portland, Oreg.: S. Anderson, M. Wolfson, M. Cummings-Cosgrove; Richmond, Va.: G. Feldman, M. Katz, J. Burns; San Diego, Calif.: S. Thomson, M. Meek; San Juan, P.R.: C. Rosado, E. Galindo, P. Carde, J. Bou; Tucson, Ariz.: U. Michael, L. Kirlin; *Biostatistics and Research Data Processing* — D. Semlow (assistant chief for operations), L. Anfinsen (programmer), B. Mackay; *Pharmacy Coordinating Center* — M. Sather (chief), F. Chacon, M. Drago, W. Gagne; *Data Monitoring Board* — T. Steinman (chairman), Harvard Medical School, Boston; A. Nissenson, University of California at Los Angeles School of Medicine, Los Angeles; R. Swartz, University of Michigan School of Medicine, Ann Arbor; M. Symons, University of North Carolina School of Public Health, Chapel

Hill; *Cooperative Studies Program Administration* — J. Feussner (chief research and development officer) and P. Huang (staff assistant), Department of Veterans Affairs, Washington, D.C.; D. Deykin (ex-chief) and J. Gold (administrative officer), Boston.

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