SYNOPSIS

A Double-Blind, Placebo-Controlled Study to Determine the Safety and Efficacy of Multiple Doses of r-HuEPO in Facilitating Pre-Surgical Autologous Blood Donation (Protocol I88-058).

STUDY DATES: 06/05/89 - 09/25/90

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STUDY DESIGN:

This was a multicenter, parallel-group, placebo-controlled, double-blind, randomized study to determine the safety and efficacy of intravenous administration of recombinant-human erythropoietin (r-HuEPO) to facilitate pre-surgical autologous blood donation. One hundred sixteen patients scheduled for major elective orthopedic surgery were randomly assigned to one of the following treatment groups: r-HuEPO at 600 U/kg, r-HuEPO at 300 U/kg, r-HuEPO at 150 U/kg, or placebo. Patients were to receive six doses, one every three to four days over a three-week period. All patients were to donate a unit of blood prior to each dose if their hematocrit was $\geq$ 33%.

Efficacy was evaluated primarily by comparing the number of units of blood donated by patients in each treatment group. Also examined were the number of units of homologous blood transfused, the total red cell volume of the blood donated, the percent of patients who received homologous units, the total red cell production, and the percent of substandard units donated.

Safety was evaluated on the basis of reported adverse experiences, clinical laboratory tests, and measurements of vital signs.

PATIENT POPULATION:

One hundred sixteen patients were enrolled in the study. During the study, 28 patients received r-HuEPO at 600 U/kg, 30 patients received r-HuEPO at 300 U/kg, 29 patients received r-HuEPO at 150 U/kg, and 29 patients received placebo. All enrolled patients were included in the safety analysis; the efficacy analysis was based primarily on "evaluable patients," that is, patients who received all six doses of study medication and had surgery within 35 days of receipt of their first dose of study medication. However, intent-to-treat analyses were done to confirm the evaluable patient analysis. Of the 116 patients enrolled in the study, 91 (78.4%) were evaluable. Sixteen patients discontinued therapy: 11 (4 r-HuEPO 600 U/kg, 3 r-HuEPO 300 U/kg, 2 r-HuEPO 150 U/kg, and 2 placebo) because of adverse experiences, two for protocol violations, and three for personal reasons.

Patients were almost evenly distributed with respect to sex: 52.6% (61 of 116) were female, and 47.4% (55 of 116) were male. They ranged in age from 13 to 87 years, and the median age was 63. Endogenous EPO levels, predicted blood volumes, hemoglobin values, hematocrit values, and uncorrected reticulocyte counts were comparable among the treatment groups at baseline. Patients who received placebo had higher average baseline ferritin levels, but this result was influenced by one patient whose baseline ferritin level was 1774 ng/mL. Of the 116 patients enrolled, 25.9% had back surgery, 38.8% had hip surgery, 22.4% had knee surgery, and 12.9% did not have surgery at all. There were no statistically significant differences among the treatment groups for any of the demographic or baseline characteristics analyzed.

RESULTS

EFFICACY

Treatment with r-HuEPO was associated with significant ($p \leq 0.05$) improvement in the primary efficacy variable, the number of units of blood donated. Significant improvement was also found in the following secondary efficacy variables:

Total red cell volume donated
Total red cell production

There were no significant differences among the treatment groups in the number of homologous transfusions required or the percent of patients who required homologous transfusions.

Donations

Treatment with r-HuEPO enhanced autologous blood donation. Evaluable patients who received r-HuEPO at any of the three doses were able to donate more blood than patients who received placebo. Patients who received r-HuEPO at 600 U/kg donated a significantly ($p \leq 0.05$) greater average number of units (5.6 units, with a standard deviation of 0.8 units [hereafter, 5.6 ± 0.8 units]) than patients who received placebo (4.6 ± 1.1 units). Patients who received r-HuEPO at 300 U/kg and 150 U/kg were also able to donate a significantly greater average number of units (5.5 ± 0.8 units and 5.2 ± 0.8 units respectively) than patients who received placebo. The number of units of blood donated by patients in each treatment group is summarized in TABLE A.

In contrast to the analysis of evaluable patients, the analysis of all patients who entered the study did not yield a statistically significant difference among the treatment groups for the number of units donated. This result was influenced by the fact that more patients who received r-HuEPO withdrew from the study before they completed six visits than did patients who received placebo, so they had fewer opportunities to donate a unit. In the secondary intent-to-treat analysis of the proportion of successful donation visits made, there was a statistically significant difference ($p \leq 0.05$) among the treatment groups, which supports the efficacy of treatment with r-HuEPO.

TABLE A

Units of Blood Donated
(Evaluable Patients)

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Variable		600 U/kg (N=18)	300 U/kg (N=26)	150 U/kg (N=24)	Placebo (N=23)
Number of Units Donated	Mean	5.6	5.5	5.2	4.6
	Std Dev	0.8	0.8	0.8	1.1

Patients who received r-HuEPO at any of the three doses were able to donate blood more frequently than patients who received placebo. The percent of patients who were able to donate units of blood at all six visits decreased as the dose of r-HuEPO taken decreased -- from 78% (14 out of 18) of the patients who received 600 U/kg, to 65% (17 out of 26) of the patients who received 300 U/kg, to 46% (11 out of 24) of the patients who received 150 U/kg. By comparison, only 26% (six out of 23) of the patients who received placebo were able to donate units of blood at all six of their visits. The number of patients who donated a specified number of units of blood is summarized by treatment group in TABLE B.

TABLE B

Number of Patients Donating Units
(Evaluable Patients)

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Number of Units	Number (Percent) of Patients			
	600 U/kg (N=18)	300 U/kg (N=26)	150 U/kg (N=24)	Placebo (N=23)
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.7%)
4	3 (16.7%)	5 (19.2%)	6 (25.0%)	8 (34.8%)
5	1 (5.6%)	4 (15.4%)	7 (29.2%)	6 (26.1%)
6	14 (77.8%)	17 (65.4%)	11 (45.8%)	6 (26.1%)

Red Cell Volume

At every visit, patients in each of the three groups who received r-HuEPO had higher average red cell volumes per unit of blood donated than patients who received placebo. Patients who received r-HuEPO at 600 or 300 U/kg donated significantly ($p \leq 0.05$) higher total red cell productions than patients who received placebo, and patients in each of the three groups who received r-HuEPO had significantly higher total red cell productions on average than patients who received placebo.

Patients who received r-HuEPO at 600 U/kg had the highest total red cell production on average (971.6 ± 206.8 mL), and patients who received placebo had the lowest total red cell production on average (756.8 ± 218.4 mL). Patients who received r-HuEPO at 300 U/kg and 150 U/kg had intermediate total red cell productions on average (917.0 ± 178.8 mL and 864.4 ± 164.3 mL, respectively).

Transfusions

There were no significant differences among the treatment groups in either the number of homologous transfusions required or the percent of patients who required homologous transfusions. This result is in part influenced by the fact that no more than four patients in any treatment group required homologous transfusions at all. There were also no significant differences among the treatment groups in the number of autologous transfusions required or the percent of patients who required autologous transfusions.

Hematologic Variables

The benefits of r-HuEPO treatment were also reflected in the changes from baseline to the post-study time period for hemoglobin, hematocrit and reticulocyte levels, although differences among the groups were not statistically significant. Patients who received r-HuEPO at 600 U/kg had the smallest average decrease in hemoglobin (-2.1 ± 0.8 g/dL), whereas patients who received placebo had the largest average decrease (-2.9 ± 1.4 g/dL). Patients who received r-HuEPO at 600 U/kg had the smallest average decrease in hematocrit (-4.3 ± 2.9 percentage points), whereas patients who received placebo had the largest average decrease (-8.4 ± 4.5 percentage points). Patients who received r-HuEPO at 300 U/kg had the largest average increase in uncorrected reticulocyte count (4.8 ± 2.6 percentage points), whereas patients who received placebo had the smallest average increase (3.0 ± 1.8 percentage points).

SAFETY

Adverse Experiences

Adverse experiences were reported by 78% of the patients (79% of the 600 U/kg r-HuEPO-treated patients, 83% of the 300 U/kg r-HuEPO-treated patients, 69% of the 150 U/kg r-HuEPO-treated patients, and 79% of the placebo-treated patients). The only statistically significant ($p \leq 0.05$) differences among the treatment groups in adverse experiences reported during the study occurred for asthenia (reported by 7.1% of the 600 U/kg r-HuEPO-treated patients, 26.7% of the 300 U/kg r-HuEPO-treated patients, 3.4% of the 150 U/kg r-HuEPO-treated patients, and 3.4% of the placebo-treated patients), dizziness (reported by 7.1% of the 600 U/kg r-HuEPO-treated patients, 20.0% of the 300 U/kg r-HuEPO-treated patients, 10.3% of the 150 U/kg r-HuEPO-treated patients, and 34.5% of the placebo-treated patients), and constipation (reported by 14.3% of the 600 U/kg r-HuEPO-treated patients, no 300 U/kg r-HuEPO-treated patients, 6.9% of the 150 U/kg r-HuEPO-treated patients, and no placebo-treated patients).

Adverse experiences that were reported by at least 10% of the patients in any of the treatment groups were asthenia, fatigue, chest pain, dizziness, headache, edema, respiratory congestion, nausea, constipation, and diarrhea.

Patients Who Discontinued Because of Adverse Experiences

Eleven patients (4 r-HuEPO 600 U/kg, 3 r-HuEPO 300 U/kg, 2 r-HuEPO 150 U/kg, and 2 placebo) discontinued therapy because of adverse experiences. IND Safety Reports were filed for two of these 11 patients; one r-HuEPO-treated patient had a cerebrovascular accident and one placebo-treated patient had an exacerbation of angina. These two patients did not receive volume replacement after each donation suggesting that repeated phlebotomy without volume replacement of the blood drawn may result in aggravation of underlying cardiovascular disease. No other IND Safety Reports were filed for patients in the study.

Clinical Laboratory Tests

There were no statistically significant differences among the treatment groups for any of the laboratory tests for which data were collected during the study. The changes from baseline to the last available result in laboratory test values within treatment groups were significantly different from zero for many of the laboratory tests performed. For all four treatment groups, blood urea nitrogen, total protein, red blood cell counts, hemoglobin values, hematocrit values, and lymphocyte values all decreased significantly. For all four treatment groups, platelet counts and reticulocyte counts increased significantly. In addition, uric acid values increased significantly for all three groups of patients who received r-HuEPO, but did not increase significantly for patients who received placebo. Alkaline phosphatase values decreased significantly for all three groups of patients who received r-HuEPO, but did not decrease significantly for patients who received placebo.

CONCLUSIONS

The results of this study indicate that six doses of r-HuEPO, given at dose levels of 600 U/kg, 300 U/kg, and 150 U/kg every three to four days for three weeks prior to surgery, facilitate autologous blood donation. Patients who received r-HuEPO donated more blood than patients who received placebo, and their average red cell volume per unit of blood donated was higher than that of patients who received placebo.

The fact that there was no difference in homologous blood requirements in patients who received r-HuEPO compared with patients who received placebo was probably due to the fact that patients who received placebo were able to donate more than four units of blood on average, which was usually enough to satisfy their surgical blood requirements. Consequently, r-HuEPO may be most useful in treating patients who are unable to provide enough blood to satisfy their needs during surgery because of factors such as a low baseline hematocrit.

Recombinant-human erythropoietin was well tolerated in this study.

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