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SYNOPSIS

A Double-Blind, Placebo-Controlled Study to Determine Whether r-HuEPO Can Facilitate Presurgical Autologous Blood Donation in Patients with Low Hematocrit Levels (Protocol I88-027).

STUDY DATES: 03/02/89 - 07/29/91

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STUDY DESIGN

This multicenter, parallel-group, placebo-controlled, double-blind, randomized study was designed to determine the efficacy and safety of intravenous administration of r-HuEPO to facilitate pre-surgical autologous blood donation in patients with low hematocrit levels (≤ 39%)

and thus reduce the need for homologous transfusion. Two hundred four patients scheduled for major elective orthopedic surgery were randomly assigned to receive either r-HuEPO at 600 IU/kg or placebo. Patients received six doses, one every three to four days over a three-week period. All patients were to donate a unit of blood before dosing if their hematocrit was ≥33%.

Efficacy was evaluated primarily by comparing the percent of patients in each treatment group who received homologous blood. Also examined were the number of units of blood donated, the proportion of successful donation visits, the total red cell volume of the blood donated, the total red cell production, the proportion of substandard units donated, the number of units of homologous blood received, and the change in hemoglobin level from baseline to the post-study period (after the final dose of medication and before surgery).

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

PATIENT POPULATION

Two hundred four patients were enrolled in the study. During the study, 102 patients received r-HuEPO and 102 patients received placebo. All enrolled patients were included in the safety analysis; the efficacy analysis was based primarily on "evaluable patients," that is, those patients who received all six doses 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 analyses. Of the 204 patients enrolled in the study, 173 (84.8%) were evaluable, of which 49.7% (86) received r-HuEPO and 50.3% (87) received placebo. Thirteen patients discontinued treatment prematurely: seven (four r-HuEPO and three placebo) because of adverse experiences, two for protocol violations, and four for personal reasons. Of the 204 patients enrolled, 17.2% had back surgery, 44.6% had hip surgery, 27.9% had knee surgery, 1.5% had other surgery, and 8.8% (18 patients) did not have surgery at all.

Most of the patients were female; 87.3% were women and 12.7% were men. They ranged in age from 13 to 87 years, and the median age was 66. The treatment groups were comparable at baseline with respect to age, sex, endogenous EPO levels, predicted blood volumes, hemoglobin values, hematocrit values, uncorrected reticulocyte counts, iron deficiency, ferritin levels, presence of arthritis, and type of arthritis. Among the demographic and baseline characteristics analyzed, the only statistically significant difference between the treatment groups occurred for ethnic origin; more black patients received r-HuEPO than placebo.

RESULTS

Efficacy

Among evaluable patients, 19.8% (17 of 86) of patients who received r-HuEPO and 31.0% (27 of 87) of patients who received placebo required homologous transfusions (p=0.062). Significant differences (p≤0.05) in favor of r-HuEPO were found in the following secondary efficacy variables:

Number of units of blood donated
Proportion of successful donation visits
Total red cell volume
Total red cell production
Change in hemoglobin from baseline to post-study (after the final dose of study medication, but before surgery)

Donations

Evaluable patients who received r-HuEPO donated significantly (p≤0.05) more units on average (4.5 units, with a standard deviation of 1.0 units [hereafter, 4.5±1.0 units]) than patients who received placebo (3.0±1.1 units). A similar, statistically significant difference in the number of units donated was seen in the intent-to-treat analysis based on all patients.

In the secondary analysis of the proportion of visits at which a donation was made, there was again a significant (p≤0.05) difference between the treatment groups. This result also supports the efficacy of treatment with r-HuEPO.

A total of 17.4% (15 of 86) of the evaluable r-HuEPO-treated patients were able to donate units of blood at all six visits, compared with none of the evaluable placebo patients. Also, 81.4% (70 of 86) of the evaluable patients who received r-HuEPO were able to donate four or more units of blood, compared with 36.8% (32 of 87) of the evaluable patients who received placebo.

Red Cell Volume

The mean red cell volume of the blood donated by evaluable patients who received r-HuEPO was higher at each visit than that of the blood donated by evaluable patients who received placebo. There was a statistically significant (p≤0.05) difference between the treatment groups for the total red cell volume in the donated blood. Patients who received r-HuEPO donated 683.8±180.2 mL on average, and patients who received placebo donated 448.9±176.2 mL on average.

In the analysis of total red cell production, there was a significant (p≤0.05) difference between the treatment groups. On average, patients who received r-HuEPO had a total red cell

production of 633.1±243.4 mL, and patients who received placebo had a total red cell production of 307.3±163.1 mL. There was no significant difference between the treatment groups in the proportion of substandard units donated per patient.

Transfusions

A total of 19.8% (17 of 86) of the evaluable patients who received r-HuEPO and 31.0% (27 of 87) of the evaluable patients who received placebo required homologous transfusions ($p=0.062$). Evaluable patients who received r-HuEPO required an average of 0.5±1.4 homologous transfusions, and evaluable patients who received placebo required an average of 0.7±1.4 homologous transfusions ($p>0.05$). The intent-to-treat analysis, based on all patients enrolled in the study who had surgery, yielded similar results. There were no significant differences between the treatment groups in either the number of homologous transfusions required or the percent of patients who required homologous transfusions.

Hematologic Variables

The benefits of r-HuEPO treatment were also reflected in the significant ($p\leq0.05$) difference between treatment groups in the change in hemoglobin from baseline to the post-study period. Patients who received r-HuEPO had a smaller average decrease in hemoglobin (-1.1±1.1 g/dL) than patients who received placebo (-1.5±1.0 g/dL) even though the patients who received r-HuEPO made more donations. Patients who received r-HuEPO also had a smaller average decrease in hematocrit (-1.8±3.5 percentage points) than patients who received placebo (-4.3±3.0 percentage points) and a larger average increase in uncorrected reticulocyte count (4.7±3.2 percentage points) than patients who received placebo (2.1±1.7 percentage points).

Safety

Adverse Experiences

During the study, 84.8% (173 of 204) of the patients reported adverse experiences. A total of 87.3% (89 of 102) of the patients who received r-HuEPO reported adverse experiences and 82.4% (84 of 102) of the patients who received placebo reported adverse experiences. The only statistically significant ($p\leq0.05$) differences between the treatment groups in adverse experiences reported during the study occurred for dizziness and nausea. Both dizziness (r-HuEPO, 31.4%; placebo, 14.7%) and nausea (r-HuEPO, 25.5%; placebo, 9.8%) were more prevalent among the patients who received r-HuEPO, but most of these reports were mild or moderate in intensity and only one occurrence was severe enough to result in discontinuation from the study.

Adverse experiences that were reported by at least 10% of the patients who received r-HuEPO were fatigue, dizziness, headache, and nausea. Adverse experiences that were reported by at least 10% of the patients who received placebo were fatigue, dizziness, and headache.

IND Safety Reports were filed for nine patients in the study (four r-HuEPO and five placebo).

Patients Who Discontinued Because of Adverse Experiences

Seven patients (four r-HuEPO and three placebo) discontinued therapy because of adverse experiences. IND Safety Reports were filed for two of these seven patients.

Clinical Laboratory Tests

There were statistically significant ($p \leq 0.05$) differences between the treatment groups with respect to the changes in test values for uric acid, total bilirubin, cholesterol, ferritin, red blood cell counts, and hematocrit values. On average, patients who received r-HuEPO had larger increases in uric acid and total bilirubin values, larger decreases in cholesterol and ferritin values, and smaller decreases in red blood cell and hematocrit values than did patients who received placebo.

CONCLUSIONS

The results of this study indicate that treatment with six doses of r-HuEPO, given at a dose level of 600 IU/kg every three to four days for three weeks prior to surgery, facilitates autologous blood donation in patients with low hematocrit levels. Patients who received r-HuEPO donated more blood than patients who received placebo (r-HuEPO mean, 4.5 units; placebo mean, 3.0 units; $p \leq 0.05$), and the red cell volume of their donated blood was higher ($p \leq 0.05$). Treatment with r-HuEPO significantly enhanced the production of red blood cells in these patients ($p \leq 0.05$). Among the evaluable patients, fewer patients who received r-HuEPO required homologous transfusions (19.8%; 17 of 86) than patients who received placebo (31.0%; 27 of 87), although the difference was not statistically significant ($p=0.062$).

Recombinant-human erythropoietin was well tolerated in this study.

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