SYNOPSIS

A Double–Blind, Placebo–Controlled Study to Determine Whether r–HuEPO Can Facilitate Presurgical Autologous Blood Donation and to Determine its Safety for This Purpose (Protocols H87–017/H87–036)[1]

STUDY DATES: 9/87 - 5/88

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Protocol H87–017

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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 (i.v.) administration of r-HuEPO to facilitate presurgical autologous blood donation. Fifty–four patients scheduled for elective major orthopedic surgical procedures were randomly assigned to one of two treatment groups: one received 600 U/kg r–HuEPO and the other a comparable volume of placebo i.v. every three to four days for 21 days, for a total of six doses. All patients were to donate a unit of blood prior to dosing if their hematocrit was ≥ 34%.

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[1] The designs of protocols H87–017 and H87–036 were identical. Based on this and a request from the FDA (11/9/87) to stop the study at an enrollment of 50 patients (total for the two protocols), data from the two protocols were combined for analysis. Throughout this report, the letter A denotes subjects enrolled into Protocol H87–017 and the letter B subjects enrolled into Protocol H87–036.

Efficacy was primarily evaluated by comparing the number of autologous units of blood donated, the number of homologous units of blood transfused and the change in hemoglobin levels from prestudy to poststudy. Also examined were the volume of red blood cells per autologous unit donated, total red cell production and the number of substandard units donated.[1]

Safety was evaluated on the basis of reported adverse experiences, electrocardiograms, physical exams, clinical laboratory tests, vital signs measurements, r-HuEPO-specific antibody titers, and at selected sites, audiometric and ophthalmologic exams.

RESULTS

Patient Population: Fifty-four patients scheduled to undergo elective major orthopedic surgery were enrolled into the study. Twenty-five patients were treated with r-HuEPO 600 U/kg and 29 were treated with placebo. Patients completed the study if they made six visits to the donation center. Of the patients enrolled, 37 (18 r-HuEPO, 19 placebo) received six doses of r-HuEPO and had their scheduled surgical procedures performed within 35 days of receiving their first dose of study medication and were therefore evaluated for efficacy. Patients receiving fewer than six doses of study medication or who had their surgery more than 35 days after their first dose of study medication were not evaluated for efficacy. The 35 day time frame was chosen to insure usability of the first donated unit of blood. Analysis of key efficacy data (mean autologous units donated per patient and prestudy to poststudy [postdosing, prior to surgery] change in hemoglobin) using all patients (intent-to-treat) revealed that exclusion of the 17 non-evaluable patients did not have an effect on interpretation of the data. All enrolled patients were evaluated for safety. Seven patients discontinued therapy prematurely: three for adverse experiences, one for a non-therapy related concurrent illness, and three for protocol violations.

Roughly equal numbers of men (26) and women (28) with a mean age of 55.4 years were enrolled. The majority (64.6%) were scheduled to have hip surgery, the remainder having back (22.9%) or knee (12.5%) surgeries scheduled. The majority of patients (64.8%) were not iron deficient at baseline and appeared to be hematologically normal (mean hematocrit at baseline, 43.0%). When considering all patients, there were no significant between-treatment differences with regard to sex, ethnic origin, surgery type, age, weight, height, ferritin level, predicted normal blood volume, presence of iron deficiency, hematocrit, hemoglobin level or reticulocyte count. A significant ($p \leq 0.05$) between-treatment group difference in surgery type was noted for patients evaluable for efficacy; there were more back surgeries among placebo-treated patients (31.6%) than among r-HuEPO-treated patients (5.6%) and more knee surgeries among r-HuEPO-treated patients (22.2%) than among placebo (0.0%).

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[1] Red cell volume (RCV) = (Hematocrit) x (Volume of donated unit in mL)/100. Total RCV is the sum of the RCVs for all visits.

Total red cell production = (Presurgery RCV) – (Baseline RCV) + (Total RCV of Donated Units).

A substandard unit of blood is defined by the AABB as a unit with a red cell volume of less than 154 mL.

Efficacy

Treatment with r–HuEPO was associated with significant ($p \leq 0.05$) improvement in the following primary evaluations for efficacy:

- Mean units of autologous blood donated
- Mean total red cell production
- Mean total red cell volume of units donated
- Mean prestudy to poststudy (postdosing, prior to surgery) change in hemoglobin

r–HuEPO–treated patients had a smaller prestudy to poststudy decline in hemoglobin than placebo–treated patients in spite of the fact that they donated significantly more blood than placebo–treated patients. Transfusion requirements were also measured, and there was no notable difference in the amount of homologous blood transfused between the two groups (two placebo patients transfused versus one r–HuEPO–treated patient).

Blood Donation. Patients treated with r–HuEPO were able to donate more blood and were able to donate blood more frequently than those treated with placebo. r–HuEPO–treated patients donated a significantly ($p \leq 0.05$) greater mean number of units of autologous blood (5.56 ± 0.92 units) than placebo–treated patients (3.95 ± 1.08 units). r–HuEPO–treated patients donated 92.6% (100 of 108 units) of the maximum number of donatable units compared with placebo–treated patients who donated 65.8% (75 of 114 units). This difference supports the results indicating that r–HuEPO therapy was effective in improving the patient's ability to pre–deposit blood in preparation for surgery. Seventeen out of 18 r-HuEPO–treated patients (94%) compared with 12 out of 19 placebo–treated patients (63%) were able to donate four or more units of blood. Fourteen of the r–HuEPO–treated patients (78%) and only two of the placebo–treated patients (11%) were able to donate the maximum of six units of blood. TABLE A illustrates the distribution of autologous blood donation frequencies and the mean units donated per patient.

TABLE A

Distribution of Autologous Units of Blood Donated
and Mean Units Donated Per Patient
(Patients Evaluated for Efficacy in Protocols H87-017/H87-036)

Number of Units Donated	r-HuEPO 600 U/kg (N = 18)		Placebo (N = 19)	
	N	%	N	%
2	0	0.0	1	5.3
3	1	5.6	6	31.6
4	2	11.1	7	36.8
5	1	5.6	3	15.8
6	14	77.8	2	10.5
Mean Units Donated Per Patient	5.56[a]		3.95[a]	
Std Dev of Mean Units Donated	0.92		1.08	

[a] Significant between-treatment group difference ($p \leq 0.0001$).

Red Cell Volume: The mean total red cell volume donated was significantly ($p \leq 0.05$) higher for the r–HuEPO–treated (970.6 ± 214.2 mL) than for the placebo–treated patients (662.7 ± 209.0 mL). Total red cell production was also significantly ($p \leq 0.05$) higher for r–HuEPO–treated (776.1 ± 330.3 mL) than for placebo–treated (357.9 ± 170.8 mL) patients.

Blood Transfusion: There was no apparent difference noted in transfusion requirements between the two treatment groups. Patients in the r–HuEPO–treated group received an average of 3.9 units of autologous blood and the placebo–treated group received an average of 3.5 autologous units. Three patients (one r–HuEPO, two placebo) received homologous transfusions, but two of these patients (one r–HuEPO, one placebo) were not evaluable for efficacy.

Hematology Parameters: A linear model analysis with treatment and investigator as factors was done to examine the mean prestudy to poststudy change in hemoglobin. The changes presented are least–squares (LS) means obtained from this linear model analysis. Hemoglobin levels for both r–HuEPO– and placebo–treated patients were significantly lower at poststudy (postdosing, prior to surgery) than at prestudy ($p \leq 0.05$) regardless of whether all patients or patients evaluable for efficacy were used for the analysis. For evaluable patients, the mean prestudy to poststudy decrease in hemoglobin was significantly ($p \leq 0.05$) smaller for r–HuEPO–treated patients (LS mean ± std err: 2.54 ± 0.34 g/dL) than for placebo–treated patients (3.44 ± 0.34 g/dL). The intent–to–treat analysis using all patients yielded similar results showing a significant between–treatment group difference in the prestudy to poststudy decrease in hemoglobin (r–HuEPO, 2.20 ± 0.26 g/dL; placebo, 3.24 ± 0.27 g/dL; $p \leq 0.05$). There was no significant investigator effect observed for the prestudy to poststudy change in hemoglobin ($p > 0.05$).

At the presurgery visit, the mean hemoglobin for r-HuEPO–treated patients was 12.3 g/dL, compared to 11.3 g/dL for the placebo–treated patients. The corresponding mean hematocrit levels were 38.0% and 34.4%, respectively. At the time of the postsurgery (hospital discharge) measurement, the mean hemoglobin for the r-HuEPO–treated patients was 10.8 g/dL, compared to 10.4 g/dL for the placebo–treated patients. The corresponding mean hematocrit levels were 33.2% and 31.2%, respectively. Reticulocyte counts in both treatment groups rose throughout the study after Visit 1 and those for r–HuEPO–treated patients were generally higher than for placebo–treated patients. By the presurgery (r–HuEPO, 4.09%; placebo, 5.90%) and postsurgery (r–HuEPO, 3.10%; placebo, 4.90%) assessments, r–HuEPO–treated patients had lower reticulocyte counts than placebo–treated patients, possibly due to enhanced erythropoiesis (and higher hemoglobin and hematocrit) in the r–HuEPO treatment group.

Safety

Adverse experiences: Forty–one (76%) patients (20 [80%] r–HuEPO and 21 [72%] placebo) reported adverse experiences during the study (during dosing and prior to surgery). There were no statistically significant differences between treatment groups in the proportion of patients reporting any given adverse experience when classified by primary term. Adverse experiences reported by at least ten percent of r–HuEPO patients were: fatigue (20.0%), headache (20.0%), pain, extremities (16.0%), vomiting (16.0%), diarrhea (12.0%), dizziness (12.0%), nausea (12.0%), trunk pain (12.0%).

Discontinuation due to adverse experiences: Three patients (#305B r–HuEPO, #501B placebo, #708B r–HuEPO) discontinued treatment as a result of adverse experiences (peripheral artery occlusion, myocardial infarction, flu–like syndrome). The blind was broken for all three patients, and for those two treated with r–HuEPO the investigators had classified the relationship to study medication as unknown. However, it is possible that the two thrombotic events (myocardial infarction and peripheral artery occlusion) may have been related to hypovolemia induced by repeated phlebotomy.

Safety Reports: Two IND Safety Reports were filed during this study. One was filed for each of two patients who discontinued due to adverse experiences (#305B, r–HuEPO; #708B, r–HuEPO). No patients were reported to have died while on study.

Antibody Titers: Fifty–two patients enrolled in the study had tests for r-HuEPO–specific antibodies. Of these, 46 had both pre– and poststudy tests done, four had only poststudy tests and two had only prestudy tests. None of these patients had confirmed positive titers for r–HuEPO antibodies.

CONCLUSIONS

Autologous blood donation was enhanced in patients treated with r–HuEPO. The r–HuEPO–treated patients donated more blood with a smaller prestudy to poststudy (postdosing, prior to surgery) decrease in hemoglobin levels, and the blood contained a higher red cell volume compared with placebo–treated patients. This dosing regimen was well tolerated with there being no increase in adverse experiences over that seen with placebo therapy.

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