SYNOPSIS

EFFECTIVENESS AND SAFETY OF A RECOMBINANT HUMAN ERYTHROPOIETIN (r-HuEPO) IN PATIENTS WITH LOW HEMATOCRIT LEVELS TO FACILITATE PRESURGICAL AUTOLOGOUS BLOOD DONATION IN PATIENTS UNDERGOING ORTHOPEDIC SURGERY.

STUDY DATES: Start of Study: September 11, 1989
End of Study: March 19, 1991

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STUDY DESIGN:

This was a single-blind (patient was blinded but not the principal investigator, and also the surgeon and anesthesiologist didn't know what the patient had received), placebo-controlled randomized study to determine the safety and efficacy of an intravenous administration of two different dose levels of r-HuEPO to facilitate presurgical autologous blood donation. Patients scheduled for hip replacement surgery were randomly assigned (2:2:1) to one of three treatment groups (r-HuEPO 600 U/kg, r-HuEPO 300 U/kg, placebo). Patients enrolled into the study had "low hematocrits". Study medication or placebo was administered intravenously every three to four days for a total of six doses. All patients received

daily oral iron supplementation; one half of the patients received additional intravenous injections of iron saccharate. Prior to dosing the patients were to donate one unit of blood if their hematocrit level was ≥ 35%.

Efficacy was primarily evaluated by comparing the number of autologous units of blood and the total volume of red blood cells donated, the number of homologous blood units transfused during surgery, and the change in hematocrit/hemoglobin and reticulocyte levels from baseline to pre-surgery.

Safety was assessed by examining the incidence of adverse experiences, physical examinations, clinical laboratory tests, and vital sign measurements.

RESULTS:

Patient population: Fifty-five patients were enrolled into the study; fifty at the principal site (Prof. Mercuriali, Milano) and five at a second site (Dr. Gombotz, Graz). The latter five patients were only included in the safety evaluations.

Of the 50 patients (20 r-HuEPO 600 U/kg, 20 r-HuEPO 300 U/kg, 10 placebo) at the principal site, 47 (19 r-HuEPO 600 U/kg, 19 r-HuEPO 300 U/kg, 9 placebo) were evaluable for efficacy. Two of the three patients not evaluable for efficacy discontinued the therapy prematurely: one for adverse events and one for non-compliance, the third patient underwent a different surgical procedure.

Only females were enrolled at the principal Italian site. Their mean age was 54.4 years. There were no significant differences among treatment groups at baseline with respect to age, weight, height, hematocrit/hemoglobin, red blood cells, reticulocytes, serum iron, TIBC, transferrin, serum ferritin level, predicted normal blood volume, or presence of iron deficiency.

EFFICACY

Autologous blood donation: Patients treated with r-HuEPO 600 U/kg and 300 U/kg donated a significantly ($p < 0.05$) greater mean number of units of autologous blood (r-HuEPO 600 U/kg: 4.68 ± 1.2 units, r-HuEPO 300 U/kg: 4.42 ± 1.1 units) than did placebo-treated patients (2.89 ± 0.6 units). Of the maximum number of units possible to donate, patients treated with r-HuEPO 600 U/kg donated 78% (89 of 114 units) and patients on r-HuEPO 300 U/kg donated 74% (84 of 114 units), whereas the placebo-treated patients donated 48% (26 of 54 units). Additionally the mean total red blood cell volume donated was higher for the patients on r-HuEPO (r-HuEPO 600 U/kg: 570 ± 168 ml, r-HuEPO 300 U/kg: 547 ± 159 ml) than for the placebo-treated patients (363 ± 91 ml). Sixteen out of 19 patients (84%) on r-HuEPO 600 U/kg and 15 out of 19 patients (79%) on r-HuEPO 300 U/kg compared with one out of nine patients (11%) on placebo were able to donate four or more units of blood. Thirty-two percent of the patients on r-HuEPO 600 U/kg and 21% of the patients on r-HuEPO 300 U/kg were able to donate the maximum of six units of blood, while none of the placebo-treated patients achieved this. These results support the conclusion that r-HuEPO therapy at both dose levels (i.e. 600 U/kg and 300 U/kg) was approximately equally effective in improving the patient's ability to pre-deposit blood in preparation for surgery.

Homologous Transfusion requirements: Homologous transfusions were employed in 42% of the patients on r-HuEPO 600 U/kg, in 16% of the patients on r-HuEPO 300 U/kg, and in 56% of the placebo patients. There was no statistically significant difference among the treatment groups regarding the proportion of patients receiving homologous transfusions.

Hematology Parameters: The pre-surgery hematocrit/hemoglobin levels for all treatment groups were lower than those at baseline and decreased further during the surgical procedure. The mean baseline to pre-surgery decrease in hemato-

crit/hemoglobin was not significantly different among the three treatment groups (r-HuEPO 600 U/kg: -4.3 percentage points / -2.0 g/dL, r-HuEPO 300 U/kg: -4.1 percentage points / -1.7 g/dL, placebo: -4.3 percentage points / -1.4 g/dL).

Reticulocyte counts in all treatment groups rose throughout the treatment period until visit 6. Among r-HuEPO treated patients, reticulocyte counts were generally higher than those for placebo treated patients except at discharge(66.6×10^9/L, 41.3×10^9/L and 46.7×10^9/L in the r-HuEPO 600 U/kg group, r-HuEPO 300 U/kg group and placebo group, respectively). There were no statistically significant differences among the treatment groups at baseline, visit 1, pre-surgery, discharge, and changes from baseline to pre-surgery. However, there were statistically significant differences during visit 2 to visit 6.

SAFETY

Adverse Experiences: Thirty-three percent of all patients reported adverse experiences during the study and there were no clinically significant differences among treatment groups. The only adverse experience reported by at least 10% of the patients was fatigue (r-HuEPO 300 U/kg: 17%).

Discontinuation due to adverse experience: One patient at the principal Italian site (No. 33 on placebo) was withdrawn from the study because of an adverse event (syncope) and one of the Austrian patients (no. 103 on r-HuEPO 300 U/kg) was withdrawn due to a circulatory collapse. The circulatory collapse occurred approximately 20 minutes after consecutive injections of r-HuEPO and iron saccharate. The investigator classified the adverse event as possibly related to study medication, but did not specify between r-HuEPO and iron saccharate. Given the known safety profile of both of these drugs, it would be more likely an adverse event secondary to the iron preparation than to r-HuEPO.

CONCLUSIONS

Autologous blood donation was enhanced to a similar extent in patients treated with r-HuEPO at doses of 600 U/kg or 300 U/kg. The r-HuEPO treated patients donated more blood than the placebo treated patients with a similar baseline to pre-surgery decrease in hematocrit/hemoglobin levels. The total red cell volume donated was comparably increased. Although the proportion of patients receiving homologous blood transfusions was less in the r-HuEPO treated patients than in the placebo treated patients, there was no statistically significant difference among the treatment groups. The dosing regimen was well tolerated at either dose level with similar adverse experience incidence rates among the three treatment groups.

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