RECOMBINANT HUMAN ERYTHROPOIETIN (R-HuEPO) IN NON-ANEMIC PATIENTS SCHEDULED FOR SELECTIVE ORTHOPEDIC AND VASCULAR SURGERY OR REDUCTIVE MAMMOPLASTY[1)] TO FACILITATE PRESURGICAL AUTOLOGOUS BLOOD DONATION COMBINED WITH NORMO-VOLEMIC HEMODILUTION (NVHD)

SUMMARY

STUDY DATES: May 15, 1990 - January 21, 1992

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STUDY DESIGN:

This was a double-blind, placebo-controlled, randomized, multicenter study to determine the safety and efficacy of intravenous administration of two different doses of r-HuEPO to facilitate presurgical autologous blood donation. A total of 112 patients scheduled for major elective orthopedic or vascular surgery or reductive mammoplasty were randomly assigned to one of three treatment groups: one group received 600 U/kg r-HuEPO, another 300 U/kg r-HuEPO and the third a volume of placebo comparable to one of the two dose levels. The doses were to be given intravenously three times before surgery (days 1, 4 and 7). Patients were to donate a unit of blood prior to dosing if their Hb was > 11.0 g/dl. On the day of surgery - but no later than day 11 after the first blood donation - normovolemic hemodilution (NVHD) was to be performed in order to achieve a Hct of 30% (Hb 10 g/dl). All patients received daily oral iron supplementation.

[1)] Added as per amendment of August 1990

Efficacy was evaluated by comparing the percentages of patients able to donate at least 4 units of blood (including the volume of blood obtained via the NVHD), the proportion of patients exposed to homologous red cell transfusion and the change in Hct/Hb levels and reticulocyte counts from baseline to pre-surgery. Also examined was the course of serum ferritin levels.

Safety was assessed on the basis of reported adverse experiences, physical examination, clinical laboratory tests and recording of vital signs.

RESULTS:

Efficacy: A total of 32 patients were excluded from the efficacy evaluation due to protocol violations; of the 80 remaining patients, each r-HuEPO-treated group had 27 patients and the placebo-treated group had 26 patients. Males were over-represented in the high-dose group (2:1) and in the placebo group (5:1); otherwise the groups were comparable. Due to a delay of the scheduled surgery in many patients, an extension of study duration from the originally planned 11 days (to 13 days) was accepted. The evaluation showed that although significantly more patients treated with r-HuEPO were able to donate 4 or more units of blood, as compared to placebo-treated patients, this favorable effect did not translate into differential requirements for subsequent homologous blood transfusions. In fact, 6 patients in each of the two r-HuEPO groups and 4 in the placebo group were exposed to homologous blood either intra- or postoperatively.

The dose-dependent increase of reticulocytes during the course of treatment, associated with a dose-related prevention of Hct and Hb decrease, provide indirect evidence of efficacy of r-HuEPO in the proposed indication. Based upon

the finding that approximately half of all patients were iron-depleted at the 4th clinical visit, iron supplementation is recommended in this population.

Safety: All 112 patients originally recruited for study participation were included in the evaluation of safety. Of the 31 patients reporting one or more adverse events, 7 were in the high-dose, 11 in the low-dose, and 13 in the placebo group. Most adverse events were related to the cardiovascular system (which had a 30% prevalence of abnormalities at baseline); of 7 patients with hypertension, 1 was in the high-dose-, 4 in the low-dose- and 2 in the placebo group. There is no reason to believe that r-HuEPO induces hypertensive events in a surgical population. Statistically significant increases of thrombocytes and neutrophils during the postoperative period were in the expected range, as was also the increase in serum ferritin. Other changes in laboratory parameters were consistent with performance of major surgery, with the exception of alkaline phosphatase which increased moderately in the two r-HuEPO-treated groups but not in the placebo-treated group for reasons that are unclear.

CONCLUSIONS:

This study shows that 3 doses of intravenously administered r-HuEPO, i.e., either 300 U/kg or 600 U/kg given within 1 week, enable the donation of 4 or more blood units during a time period of at most 13 days in significantly more patients as compared to placebo treatment. There was no difference between the r-HuEPO-treated groups, possibly because of incorrect performance of NVHD. R-HuEPO induces a dose-dependent increase in reticulocyte count, and has a statistically significant preventive effect on Hct and Hb decrease.

There were no gross differences between the 600 U/kg and 300 U/kg treatment groups based on the number of autologous units donated, however, subtle findings suggest there to be greater stimulation of erythropoiesis with 600 U/kg

than 300 U/kg. These findings include: (a) a larger increase in mean reticulocyte count (144 vs 109), (b) a smaller decrease in mean hematocrit (-5.6% vs -6.4%), and (c) a larger NVHD volume that could have been donated (965 vs 814 ml).

This study did not demonstrate a beneficial effect of r-HuEPO on reducing homologous transfusions. Homologous blood exposure might have been reduced by increasing the duration of the presurgical donation period and by providing more intensive iron support.

From a safety point of view, no findings in this study are suggestive of drug-specific adverse reactions. Thus r-HuEPO can be considered as a safe drug when used according to the cited dosing regimens.

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