RECOMBINANT HUMAN ERYTHROPOIETIN (R-HuEPO) IN NON-ANEMIC PATIENTS SCHEDULED FOR ORTHOPEDIC OR CARDIOVASCULAR SURGERY, TO FACILITATE PRESURGICAL AUTOLOGOUS BLOOD DONATION

SUMMARY

STUDY DATES: Start of Study: January 9, 1990
End of Study: May 30, 1992

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STUDY DESIGN:

This was a double-blind, randomized, placebo-controlled, parallel group, multicenter study in 103 patients with an expected transfusion need of at least 3 units of blood for elective orthopedic or cardiovascular surgery. The study included only patients whose baseline Hb was within the normal range (12.0 - 18.0 g/dl). It was planned to administer study medication (r-HuEPO or placebo) three times: on days 1, 4 and 7. If Hb was ≥ 11 g/dl, one unit of blood was to be collected just prior to each dosing. An additional unit of blood was to be collected on days 11

and 14, provided that Hb was still ≥ 11g/dl. Oral iron supplementation was to be given from days 1 through 14. Surgery was planned to take place between days 18 and 21, i.e., 4-7 days after the last autologous blood donation (ABD) procedure. The study ended with the day that the patient was discharged from the hospital. Treatment with r-HuEPO was defined as being efficacious if a) a higher percentage of patients on r-HuEPO had predeposited at least 4 units of autologous blood as compared with placebo-treated patients, or if b) less r-HuEPO-treated patients were exposed to homologous blood transfusions than patients treated with placebo.

RESULTS:

Of the 103 patients recruited for study participation, 34 were randomly assigned to receive r-HuEPO 600 U/kg, 35 patients received r-HuEPO 300 U/kg, and 34 patients received placebo. For various reasons 23 patients were excluded from the efficacy analysis; all patients were analyzed for safety.

EFFICACY:

Patients were defined as evaluable for efficacy if they had made 4 clinical visits to the blood donation center in the course of two weeks (deviation of + 2 days accepted) and had received study drug 3 times.

The high-dose group comprised 27 evaluable patients, the low-dose group 30 patients and the placebo group 23 patients. The demographic characteristics and baseline values for key variables were comparable among groups. Significantly more patients in either r-HuEPO-treated group (100% in the high-dose group and 97% in the low-dose group) were able to donate ≥ 4 units of blood within two

weeks as compared to placebo-treated patients (78%). This difference was also significant in an "intent-to-treat" analysis (all patients enrolled).

Among the 80 patients eligible for efficacy analysis, 3 of 57 r-HuEPO-treated patients were in need of homologous blood vs 4 of 23 patients in the placebo group. No significant difference among treatment groups could be detected. An "intent-to-treat" analysis (all patients enrolled who had surgery) found a significant difference in transfusion rates among treatment groups. Two of 33 high-dose and 1 of 35 low-dose r-HuEPO-treated patients vs 9 of 34 placebo-treated patients required homologous blood; inter-group comparisons revealed that both r-HuEPO-treated groups had a significantly better preventive effect against homologous blood transfusions as compared to placebo-treated patients. In analysing the results, it should be noted that intra-operative blood losses were up to 4000 ml in individual patients, whereas the maximal amount of collected autologous blood could be 5 units (according to the study protocol).

The changes in Hb/Hct and reticulocytes confirmed the capacity of r-HuEPO to accelerate erythropoiesis in the presented clinical setting. The monitoring of patients' iron state showed that some r-HuEPO- and placebo-treated patients became iron-deficient in the course of an aggressive, 2-week ABD program, thus indicating that iron administration was insufficient to maintain adequate iron supply for the accelerated Hb synthesis in all patients.

SAFETY:

Most reported adverse events corresponded to the expected pattern of symptoms/signs in this category of patients. No problems were encountered with regard to blood pressure regulation.

Although as many as 21% of all patients had a history of allergy, no clear-cut allergic reactions were seen during treatment with r-HuEPO. Five r-HuEPO-treated and 1 placebo-treated patient presented with symptoms compatible with the "flu-like syndrome". Safety monitoring by means of a battery of hematologic and blood chemistry parameters revealed only one inter-group difference (chloride), suggesting that no abnormalities were related to r-HuEPO therapy. The overall impression is that r-HuEPO is a safe drug when used according to the guidelines established for this study.

CONCLUSIONS:

The present study in surgical patients with normal baseline Hb demonstrates that dosage regimens of 300 U/kg and 600 U/kg r-HuEPO administered i.v. three times during one week, will result in an autologous blood procurement of ≥ 4 units during 2 weeks in statistically significantly more patients than in those treated with placebo.

Because intraoperative blood losses were excessive in individual patients, the need for homologous blood could not be totally abrogated. However, an "intent-to treat" analysis (all patients enrolled undergoing surgery) revealed a statistically significant overall treatment effect of r-HuEPO, and inter-group comparisons showed that both dosage regimens induced significantly better prevention of homologous blood transfusions than did placebo. No significant dose/effect-differences of the two r-HuEPO regimens in reducing the risk of homologous blood transfusions could be detected in this study.

Evaluation of other efficacy parameters in the study indicated differences between the 600 U/kg and 300 U/kg arms. Among evaluable patients, 67% of the patients in the 600 U/kg group donated 5 units versus 43% of the patients in the 300 U/kg

group. The change in reticulocyte count from baseline to presurgery was greater for the 600 U/kg group than for the 300 U/kg group. In addition, patients who received the 600 U/kg treatment donated a mean of 4.7 units with a decline in hematocrit of 6.1 percentage points compared to a mean donation of 4.4 units and a 6.7 percentage points decline in hematocrit for the patients in the 300 U/kg group. These data suggest that 600 U/kg gave a more intense stimulation of erythropoiesis than 300 U/kg, even though there were no differences between these groups in homologous transfusion rates.

Several patients in all treatment groups became iron depleted during the ABD-program; hence, optimal iron therapy needs to be given along with r-HuEPO in this setting.

From the safety point of view, r-HuEPO can be used without further restrictions in the population defined in the study protocol.

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