SYNOPSIS (Continued)

SYNOPSIS

NAME OF SPONSOR/COMPANY: The R.W. Johnson Pharmaceutical Research Institute NAME OF FINISHED PRODUCT: PROCRIT®, EPREX™ NAME OF ACTIVE INGREDIENT(S): Epoetin alfa (r-HuEPO)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CR005905 **Title of Study**: The Effect of Subcutaneous r-HuEPO in Patients With Chronic Lymphocytic Leukemia: Results From North America Only.		
Investigators: Multicenter (see Appendix 3).		
Study Centre(s): Multicenter (see Appendix 3).		
Publication (Reference): None		
Studied Period (years): September 14, 1990 - January 31, 1994		**Phase of development**: 3
Objectives: The objective of this study was to determine the effect of subcutaneous r-HuEPO on hematocrit and quality of life in anemic, chronic lymphocytic leukemia (CLL) patients.		
Methodology: This was a multicenter study that consisted of two treatment phases: a 12-week, randomized, double-blind, placebo-controlled phase, followed by a 12-week, open-label phase. Patients with CLL whose prestudy hematocrit was <32% received either r-HuEPO 150 IU/kg or placebo three times weekly by subcutaneous injection. Patients were randomized to treatment groups in a 2:1 fashion (i.e., two patients received r-HuEPO for every one patient who received placebo). Patients who completed the double-blind phase of the study were eligible to enter the open-label phase, during which all patients received r-HuEPO at a dose titrated to maintain a hematocrit between the target of 38% to 40%. Patients were allowed to receive concomitant chemotherapy and/or prednisone for their underlying CLL; the protocol allowed for changes in their chemotherapy regimen if medically mandatory. In addition, the use of intravenous gamma globulin was allowed. All patients were to receive 1 mg folate per day and were allowed to receive supplemental iron as indicated.		
Number of Subjects (planned and analyzed): The study was planned for the enrollment of 216 patients randomized in a 2:1 fashion (144 patients in the r-HuEPO group and 72 patients in the placebo group). A total of 221 patients were enrolled across 50 study centers, including 142 patients in the r-HuEPO group and 79 patients in the placebo group.		
Diagnosis and Main Criteria for Inclusion: Male or female patients with CLL and a history of documented lymphocytosis were eligible to participate in this study. Patients could have received no treatment, prednisone, or a single agent or combination chemotherapy regimen for their CLL, were to be at least 18 years old, have a performance score of 0, 1, 2, or 3, and have a life expectancy of six months or greater. All female patients must have been postmenopausal for at least one year, surgically sterile, or practicing an acceptable method of birth control and have a negative serum pregnancy test prior to study entry. Patients must have been clinically stable with hematocrit <32%, corrected reticulocyte count <3%, platelets >25,000 cells/mm^3, and creatinine <2.0 mg/mL. In addition, patients were to have no occult blood in the stool, have a negative direct Coombs test or be Coombs positive with no evidence of active hemolysis, and have been able to administer self-injections.		
Test Product, Dose and Mode of Administration, Batch No.: Recombinant human erythropoietin (10,000 IU/mL Formula Designation [FD] no. 22512-C-45) was formulated as a sterile, buffered solution containing 2.5 mg/mL human serum albumin. Each single-use vial contained approximately 1.1 mL of study medication. During the double-blind phase of the study, patients randomized to the r-HuEPO group received r-HuEPO 150 IU/kg three times weekly by subcutaneous injection for 12 weeks.		
Duration of Treatment: The double-blind phase of this study lasted 12 weeks.		
Reference Therapy, Dose and Mode of Administration, Batch No.: The placebo (FD no. 22512-AX-45) was identical to the active study medication, except that it did not contain r-HuEPO, and was administered three times weekly by subcutaneous injection for 12 weeks.		

SYNOPSIS (Continued)

NAME OF SPONSOR/COMPANY: The R.W. Johnson Pharmaceutical Research Institute	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: PROCRIT®, EPREX™	Volume:	
NAME OF ACTIVE INGREDIENT(S): Epoetin alfa (r-HuEPO)	Page:	

Criteria for Evaluation:

Efficacy: The primary determination of efficacy was the effect of r-HuEPO on the change in hematocrit from baseline to the completion of the double-blind phase or to early withdrawal. Secondary evaluations included transfusion requirements (cumulative transfusion rate, the proportion of patients becoming transfusion-independent, and the proportion of patients transfused on-study), the proportion of patients achieving a hematocrit of 38% to 40% (correctors) at any time during the study (unrelated to transfusion), the proportion of patients achieving a six percentage point increase in hematocrit (responders) at any time during the study (unrelated to transfusion), and the change in quality-of-life parameters. Efficacy evaluations were performed for the intent-to-treat and efficacy evaluable populations. Depending on the efficacy parameter, efficacy evaluations were performed on three populations: the intent-to-treat population (all patients randomized to receive study medication); all patients who received at least 15 days of therapy; and all patients who received at least 71 days of therapy.

Safety: Safety determinations were based on the incidence and severity of adverse events, deaths, discontinuations, and changes in clinical laboratory tests and vital signs from baseline to final value.

Statistical Methods: The change in hematocrit from baseline to endpoint was analyzed using a linear model with treatment group as the main effect and with the following covariables: stage of disease, baseline chemotherapy usage, baseline splenomegaly, baseline transfusion status, baseline neutrophil count, baseline platelet count, and endogenous EPO level. Interactions were studied graphically. Cumulative 12-week on-study transfusion rates were compared between groups by using the two-sample t-test; Fisher's exact test was used to compare the proportion of patients transfused in each treatment group. In addition, a linear model analysis of the cumulative transfusion rates was performed. The proportion of patients who became transfusion-independent was determined (i.e., patients with at least one transfusion during the three months prior to study entry but with no transfusions during Months 2 and 3 of the study). The proportion of patients becoming transfusion-independent was compared between treatment groups using Fisher's exact test. The 0.05 level of significance was used for all statistical tests, except for tests of interaction in the linear models, where the 0.10 level of significance was used.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: Least squares mean estimates of change in hematocrit were significantly different between treatment groups overall and within two levels of baseline chemotherapy. In each case, the improvement in hematocrit was greater in the r-HuEPO group than in the placebo group. Treatment mean differences were significant at the level of cytotoxic chemotherapy without fludarabine subgroup (change from baseline: 7.4% r-HuEPO, 0.7% placebo) and at the level of no cytotoxic chemotherapy (5.8% r-HuEPO, 1.7% placebo). This effect is consistent across endogenous EPO levels for each of the groups: up to 1000 mU/mL in the cytotoxic chemotherapy without fludarabine and up to 450 mU/mL in the no cytotoxic chemotherapy group. No significant treatment difference was observed for the fludarabine subgroup.

There were no statistically significant differences between treatment groups in transfusion requirements or in quality-of-life variables. There were significant differences between treatment groups in the proportion of responders and in the proportion of correctors. Sixty-seven (47.2%) patients in the r-HuEPO group and 13 (16.5%) patients in the placebo group achieved at least a six percentage point increase in hematocrit (responders) at some point during the study, unrelated to transfusions ($p<0.0001$). Forty-six (32.4%) patients in the r-HuEPO group reached the target hematocrit of 38% (correctors), unrelated to transfusions, compared to six (7.6%) patients in the placebo group ($p<0.0001$).

SAFETY RESULTS: All 221 patients enrolled were evaluated for safety. One hundred twenty-three (87%) patients in the r-HuEPO treatment group and 70 (89%) patients in the placebo treatment group reported at least one adverse event during the double-blind phase of the study, including events considered by the investigator as related or unrelated to administration of the study drug. The most frequently reported adverse events were fever in the r-HuEPO group (23%) and the placebo group (25%), followed by diarrhea and fatigue (18% each) in the r-HuEPO group, and upper respiratory infection (19%) and diarrhea and nausea (18% each) in the placebo group. The majority of adverse events were assessed as mild or moderate in severity.

SYNOPSIS (Continued)

NAME OF SPONSOR/COMPANY: The R.W. Johnson Pharmaceutical Research Institute NAME OF FINISHED PRODUCT: PROCRIT®, EPREX™ NAME OF ACTIVE INGREDIENT(S): Epoetin alfa (r-HuEPO)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

SAFETY RESULTS (Continued)

Fifteen patients died during the double-blind phase of the study: 11 (8%) in the r-HuEPO group and 4 (5%) in the placebo group. The majority of deaths were related to CLL disease progression. Sixteen patients were discontinued due to an adverse event: 12 (8%) in the r-HuEPO group and 4 (5%) in the placebo group. Of these 16 patients, seven patients died due to these adverse events (six in the r-HuEPO group, one in the placebo group.) Most of the adverse events that caused discontinuation occurred in the cardiovascular and respiratory systems. A total of 47 patients experienced serious adverse events: 28 (20%) in the r-HuEPO group and 19 (24%) in the placebo group.

There were no clinically significant treatment-emergent mean changes from baseline to final value (value measured at completion of the double-blind phase or early discontinuation) for any laboratory analyte. There were no clinically significant changes in vital signs from baseline to final value.

CONCLUSIONS: r-HuEPO, administered subvcutaneously in doses of 150 IU/kg, three times weekly for 12 weeks, was safe and significantly more effective than placebo treatment in increasing hematocrit in anemic patients with CLL.

Date of the report: 12 March 1999

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.