ORTHO BIOTECH

Clinical Study Synoptic Report

A STUDY TO EVALUATE THE ERYTHROPOIETIC RESPONSE IN HCV PATIENTS RECEIVING COMBINATION RIBAVIRIN/INTERFERON THERAPY OR RIBAVIRIN/PEG-INTERFERON

Protocol PR00-30-034; Phase II

(Observational Study)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

1. PROTOCOL TITLE

A Study to evaluate the erythropoietic response in HCV Patients receiving combination ribavirin/interferon therapy or ribavirin/Peg-interferon

2. OBJECTIVES

In hepatitis C virus (HCV)-Infected patients receiving pegylated interferon (PEG-IFN)/ribavirin (RBV) combination therapy, anemia is a well-known side effect. The purpose of this study was to describe the time course and extent of hemoglobin (Hb) changes and the erythropoietic response to PEG-IFN/RBV-induced anemia.

3. STUDY DESIGN

This was an observational, 8-week, multicenter study conducted at 16 sites. Patients 18-75 yr of age were eligible if there were willing and able to sign an informed consent from, were infected with HCV with a detectable viral load as confirmed by polymerase chain reaction (PCR) or branched DNA (b-DNA) within 3 months prior to enrollment, were scheduled to initiate PEG-IFN/RBV therapy for chronic HCV infection, had a life expectancy $\geq$ months, and had normal serum creatinine levels.

Baseline was defined as the start date of PEG-IFN/RBV combination therapy, and week 8 (or early withdrawal) was defined as the endpoint. Samples were to be collected weekly at specified times (baseline, days 8,15,22,29,36,43,50,and 57 [or early withdrawal]) during the initial 8 weeks of PEG-IFN/RBV therapy for the determination of parameters of erythropoietic response and red blood cell turnover: Hb, sEPO, hematocrit, red cell indices, and reticulocytes. Bilirubin (total and direct) was measured weekly as an index of liver function; in addition, transfusion use, iron supplementation, and concomitant medications were recorded.

Primary endpoints were change in Hb and sEPO from baseline to Week 8 (or early withdrawal). Other endpoints measured changes in reticulocytes, platelets, white blood cells (WBC's), total bilirubin, and RBV dose from baseline to week 8.

4. DOSAGE AND ADMINISTRATION

During the study, all patients were to initiate PEG-IFN/RBV therapy for chronic HCV infection..

5. STUDY POPULATION

100 HCV infected patients scheduled to receive their initial course of PEG-IFN/RBV therapy were to enter this study. 105 patients were enrolled, of which 97 who received PEG-IFN/RBV were eligible for analysis; 8 were not eligible, because they did not receive PEG-IFN/RBV.

6. EFFICACY/PHARMACODYNAMIC/SAFETY RESULTS

In the 97 evaluable patients, mean Hb decreased from 14.4 $\pm$ 1.4 g/dL (baseline) to 11.9 $\pm$ 1.3 g/dL (week 8). Twenty one percent of patients withdrew before week 8. The estimated erythropoietic response was lower than that seen in two historic control populations of iron deficiency anemia patients. Mean RBV dose decreased from 986 $\pm$ 190 mg/day (baseline) to 913 $\pm$ 228 mg/day (week8). Fifty-seven out of 77(74%) patients who completed the study maintained their initial prescribed RBV dose. Patients maintained on the initial dose of RBV who had a higher baseline Hb and viral load showed a trend toward larger HB declines. Platelets and white blood cells (WBCs) also declined during the study.

7. CONCLUSIONS

This observational study showed that HCV-infected patients receiving PER-IFN/RBV therapy have reductions in hemoglobin, platelets and white blood cell's, possibly due to bone marrow suppression. They also have diminished endogenous serum erythropoeitin production for their degree of anemia.

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