ORTHO BIOTECH

Clinical Study Synoptic Report

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

Protocol PR00-30-035; 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 HIV/ hepatitis C virus (HCV) co-infected patients receiving combination ribavirin/interferon therapy or ribavirin (RBV)/pegylated-interferon (PEG-IFN)

2. OBJECTIVES

In HIV/HCV co-infected patients receiving PEG-IFN/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 8-week, multi-center, observational study conducted at 23 sites in HIV/HCV-co-infected patients. Patients, 18-75 yr of age, on stable antiretroviral therapy, initiating PEG-IFN/RBV therapy were eligible to enroll if they were willing and able to sign an informed consent form. HIV infection was confirmed by plasma HIV-RNA or branched DNA, and HCV infection by polymerase chain reaction (PCR) or branched DNA (b-DNA). All patients were to be on a stable antiviral therapy regimen for HIV for $\geq$ 4 weeks, were scheduled to initiate PEG-IFN/RBV therapy for chronic HCV infection, had a life expectancy $\geq$ 6 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 HIV/HCV co-infected patients scheduled to receive their initial course of PEG-IFN/RBV therapy were to enter this study. 100 patients were enrolled, of which 91 who received PEG-IFN/RBV were eligble for analysis; 9 were not eligble, because they were not on stable antiretroviral therapy for at least 4 weeks prior to study entry.

6. EFFICACY/PHARMACODYNAMIC/SAFETY RESULTS

In the 91 evaluable patients of which 53 patients completed the study, (mean age 46 years, 71% on HAART) mean Hb decreased significantly (0.5 g/dL) within 1 week of initiating PEG-IFN/RBV therapy (p=0.0002); Hb nadir occurred at a median of 37 days. Maximum Hb decreases of $\geq$ 2.0 g/dL occurred in 56 (62%) patients and > 3.0 g/dL occurred in 45 (49%) patients. Reticulocyte count increased within the first 2 weeks and sEPO peaked at week 3. Means increase in baseline to week 2 in reticulocytes count and sEPO, respectively, was 1.3% (n=74) and 45.0 mIU/ml (n=80) ($p< 0.0001$ for each parameter), and from baseline to week 8 was 0.9% (n=48) and 41.0 mIU/ml (n=52) ($p\leq 0.0001$ for each parameter).

Adverse events were the most common reason for study discontinuation (66% of discontinuing patients). Among the 25 patients who discontinued due to AEs, 84% discontinued due to anemia (n=21).

7. CONCLUSIONS

In this natural history study significant decreases in hemoglobin were observed in HIV/HCV co-infected patients within 1 week of initiating PEG-IFN/RBV therapy. Serum Erythropoietin levels and reticulocytes increases were blunted in response to anemia; Hb levels did not return to baseline values and anemia was a frequent reason for discontinuing the study.

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