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Efficacy and safety of peg-IFN alfa-2a with ribavirin for the treatment of HCV/HIV coinfected patients who failed previous IFN based therapy

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Abstract

Background: Interferon (IFN) regimens for HCV treatment are less effective in HCV/HIV-coinfected patients. There are no effective treatments for patients who fail IFN therapies. We examined the safety and efficacy of peginterferon alfa-2a (peg-IFNα-2a) plus ribavirin (RBV) in 41 HCV/HIV-coinfected patients non-responsive to prior IFN treatment.
Methods: Patients received peg-IFNα-2a (180 mg/week) plus RBV (800 mg/day) for 24 weeks ($n=41$). At week 24, patients with non-detectable HCV RNA or ≥2-log decrease from baseline, received peg-IFNα-2a (180 mg/week) plus RBV (800 mg/day) for 24 weeks further. Patients not responding to treatment at week 24 were discontinued.
Results: Intent to treat (ITT) sustained viral response (SVR) was 21.9%. Patients who received at least 24 weeks of peg-IFNα-2a plus RBV treatment ($n=35$), SVR rates were 25.7%. SVR was associated with significant improvements in liver histology grade ($p=0.02$), stage ($p=0.02$), and fibrosis progression rate (FPR) ($p=0.03$). Patients that failed to achieve SVR had statistically significant decreases in grade ($p=0.09$) and FPR ($p=0.01$).
Conclusion: peg-IFNα-2a plus RBV is effective and safe to achieve SVR in HCV/HIV coinfected patients non-responsive to prior IFN treatment. Patients that achieve SVR have significant improvements in liver histology parameters. In patients that do not achieve SVR there are histological benefits beyond virological response that suggest that peg-IFNα-2a + RBV therapy may decrease risk of progression to end stage liver disease.
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Keywords: HCV; HIV; Non-responders; Peginterferon alfa-2a; Ribavirin; Liver biopsy

1. Introduction

Infection with hepatitis C virus (HCV) is the most common form of chronic hepatitis and blood-borne infection in the United States (Alter et al., 1999). HCV is now considered the leading cause of chronic liver disease in the United States, affecting nearly 4 million Americans and about 170 million people worldwide (CDC, 2004; WHO, 1998; Zein, 2003). Infection with HCV is common in patients infected with the human immunodeficiency virus (HIV), with about 16–25% of HIV-infected individuals estimated to be coinfected with HCV (Brau et al., 2002; Klein et al., 2003; Sherman et al., 2002). Coinfection with HIV has an adverse effect on the outcome of HCV infection resulting in a faster progression of liver fibrosis, with higher incidences of cirrhosis and hepatocellular carcinoma (Benhamou et al., 1999, 2001; Di Martino et al., 2001; Martínez-Sierra et al., 2003). It has thus

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become of increasing importance to treat HCV in HCV/HIV-coinfected patients.

Treatment with pegylated interferons plus ribavirin (RBV) has become the standard of care for HCV infected patients including HIV/HCV coinfected patients (Alberti et al., 2005; Fried et al., 2002; Hadziyannis et al., 2004; Manns et al., 2001; Tien, 2005). Results of the APRICOT trial, the largest global study in HCV/HIV-coinfection, reported an overall SVR of 40% in patients treated with peg-IFN α-2a and RBV (Torriani et al., 2004). These results are lower than the 54–62% SVR rates observed in the HCV-monoinfected population (Fried et al., 2002; Hadziyannis et al., 2004; Manns et al., 2001). HCV-monoinfected patients who do not respond to treatment with interferon (IFN) or the combination of IFN plus RBV are particularly difficult to treat (Moskovitz et al., 2003; Poynard et al., 2003a; Thuluvath et al., 2003). HCV/HIV-coinfected population that are non-responders to prior IFN based therapy, have the added complications of HIV+ status: increased HCV viral load, increased prevalence of severe fibrosis and cirrhosis, and issues of drug toxicity (Bonacini et al., 1999; Cribier et al., 1995; Laskus et al., 1998; Sherman et al., 1993). There have been limited reports of clinical trials for treatment of HCV/HIV-coinfected patients who were non-responders to prior treatment with IFN or IFN plus RBV.

In this study, we examined the safety and efficacy of treatment with peginterferon alfa-2a and RBV in HIV/HCV coinfected patients who were non-responders to treatment with IFN based therapies.

2. Methods

2.1. Patient selection

Adult patients (>21 years old) with chronic hepatitis C defined as, detectable plasma HCV RNA and stable HIV infection were enrolled in this study. Patients had to have a liver biopsy (unless contraindicated), within 6 months of enrollment consistent with chronic HCV infection. Cirrhotic patients were restricted to no more than 20% of enrolled patients. Patients had to have plasma HIV RNA < 25,000 copies/mL, CD4+ cell counts >200 cells/μL, and be in stable antiretroviral therapy for at least 4 weeks prior to enrollment. Patients with CD4 count ≤ 200 cells/μL but >100 cells/μL could participate if they had HIV RNA < 5000 copies/mL. All patients were non-responders to prior therapy with IFN or IFN plus RBV for a minimum period of 24 weeks, defined as showing no virological response (HCV RNA) at end of treatment, nor at any other point during treatment. (No relapsers or breakthrough relapsers were enrolled in the study.)

Patients were excluded from participation if they had active opportunistic diseases, other causes of chronic liver disease, absolute neutrophil count < 1250/μL, platelet count < 65,000/μL, Hgb < 10 mg/dL, serum albumin < 3.0 gm/dL, bilirubin > 2.5 g/dL, prolongation of prothrombin time greater than 4 s ULN, or uncontrolled thyroid disease. Other exclusion criteria included decompensated liver disease, defined as Child-Pugh other than Grade A; severe pulmonary, cardiac, psychiatric, or ophthalmic disease; history of transplantation; or active history of drug or alcohol abuse. Patients with incomplete or complete cirrhosis of the liver were excluded if their serum alpha-fetoprotein (AFP) levels were >200 ng/mL. For inclusion, cirrhotic patients with AFP > 50 μg/mL were required to have a CT scan, MRI or sonogram negative for hepatocellular carcinoma.

All patients gave written informed consent, and were required to use effective contraception throughout the study period. The Institutional Review Board of the Medical Sciences Campus, University of Puerto Rico, approved the study.

2.2. Study design

Patients received subcutaneous weekly injections of 180 μg peg-IFNα-2a plus RBV (800 mg/day) for 24 weeks. Patients who had virological response, defined as undetectable HCV RNA (<600 copies/mL) or a decrease of at least 2-log from baseline at week 24, were treated with peg-IFNα-2a (180 μg/week) plus RBV (800 mg/day) for an additional 24 weeks. Patients who did not achieve viral response at week 24 were discontinued from treatment.

2.3. Assessment of efficacy

The primary end point of the study was sustained viral response (SVR), defined as undetectable HCV RNA titer (<600 copies/mL, the Roche Amplicor HCV Monitor test v 2.0) at study week 72. Changes in HCV RNA were also assessed during the course of treatment at weeks 12, 24, and 48.

2.4. Assessment of liver histology

Histology activity indexes (HAI) was obtained using Ishak score necroinflamation, grade (0–18) and fibrosis stage (0–6) by a single experienced pathologist (AF). To be acceptable for interpretation, biopsies had to be ≥25 mm long and have no less than 15 portal spaces. Fibrosis progression rate (FPR) was calculated by the ratio of Ishak fibrosis stage score at baseline and the estimated duration of HCV infection in years and reported as IshakF/years. Post-treatment FPR was calculated by subtracting the Ishak fibrosis stage score at week 72 (post-treatment) biopsy from baseline (pre-treatment) and dividing between the interval of time (years) between biopsies. Ishak necroinflamation grade, fibrosis stage and FPR mean scores were determined at baseline and week 72. The percentage (%) of patients with Ishak stage score changes ≥2 points between baseline and week 72 was also obtained.

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