ORIGINAL ARTICLE

Pegylated Interferon Alfa-2b (Peg-Intron) Plus Ribavirin (Rebetol) in the Treatment of Chronic Hepatitis C: A Local Experience

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Summary

This was an open-label, uncontrolled study with the aim of assessing the efficacy and safety of pegylated interferon alfa-2b plus ribavirin in the treatment of chronic hepatitis C. The study was conducted in Island Hospital, Penang between January 2002 and December 2003. Thirty-three patients were enrolled in this study with ten defaulters. The overall sustained virological response (SVR) (Intention To Treat analysis) in naive patients was 39.1%. However, when the study was adjusted to only include those who completed treatment and follow-up, overall SVR was 52.9%. Side-effects were tolerable in most patients with anaemia occurring in 22 patients (66.7%), leukopenia in 23 patients (69.7%) and thrombocytopenia in 15 patients (45.5%). This study showed that pegylated interferon alfa-2b 1.5 mcg/kg/week plus ribavirin >10.6mg/kg/day is efficacious and safe to be used in the treatment of chronic hepatitis C.

Key Words: Hepatitis C, Pegylated interferon, Sustained virological response, SVR

Introduction

Hepatitis C virus infection affects approximately 2.2% of the world's population with approximately 130 million chronic carriers in the world[1]. It is a common cause of cirrhosis and hepatocellular carcinoma (HCC), and by far the commonest reason for liver transplantation[2,3,4]. Until recently, the most effective initial therapy for patients with chronic hepatitis C (CHC) is the combination of interferon alfa plus ribavirin given for 24 or 48 weeks. With this combination regimen, about 40% of the patients achieved a sustained virological response (SVR) and hence long-term benefits[5,6].

Since 2001, the arrival of pegylated interferon further improved the SVR to 54%[7]. The addition of a polyethyleneglycol molecule to interferon produces a biologically active molecule with a longer half-life than the natural molecule and more favourable pharmacokinetics; allowing more convenient once a week dosing. Thus, since 2001, one of the most effective therapies in patients with chronic hepatitis C is the combination of pegylated interferon and ribavirin[7].

Materials and Methods

This was an open-label, uncontrolled study conducted in Island Hospital, Penang between January 2002 and December 2003. A total of thirty-three patients were enrolled in this study. The inclusion criteria was detectable serum HCV RNA by PCR including naïve and previously failed standard interferon plus ribavirin therapy. The exclusion criteria were patients with age less than 18 year-old and those with decompensated liver cirrhosis.

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All patients who fulfilled the above criteria were given pegylated interferon alfa-2b at a dose of 1.5mcg/kg/week and ribavirin > 10.6 mg/kg/day in two divided doses for a duration of 24 weeks for genotype 2 and 3 patients and 48 weeks for genotype 1 patients. All patients were reviewed 4 weekly and the adverse events were documented on each visit. Therapy was permanently discontinued for life-threatening events. For severe adverse events other than anaemia, the dose of pegylated interferon alfa-2b was decreased by 50% and the dose of ribavirin was lowered to 600mg/day. Full doses were restarted when the event abated. If the event persisted, both drugs were discontinued. For anaemia, the ribavirin dose was lowered to 600mg/day for falls in haemoglobin of less than 100g/L. The ribavirin was discontinued if haemoglobin concentrations fell to less than 85g/L.

The primary measure of efficacy was the SVR, defined as undetectable serum HCV RNA 24 weeks after stopping therapy. Early viral response (EVR) defined as > 2 log decrease or negative HCV RNA at 12 weeks of therapy. End of Treatment Response (ETR) was defined as negative HCV RNA at the end of treatment. In the case of genotype 1, therapy was discontinued after 12 weeks if patients failed to achieve EVR and they were considered as non-responders (NR). For those with EVR, therapy was continued for a total of 48 weeks in genotype 1 and 24 weeks in genotype 2 or 3. All results were analyzed using intention-to-treat analysis (ITT). A sub-analysis (per protocol analysis) was also done on those patients who completed treatment and follow-up.

Results

Of the 33 patients, 23 completed the study (Table I). One patient stopped treatment prematurely after 24 weeks due to excessive lethargy. Nine patients failed to return for follow up. The overall SVR for all patients in this study using intention-to-treat (ITT) analysis was 33.3% (Table II). The SVR for treatment naïve and previously failed interferon plus ribavirin patients was 39.1% and 20% respectively. The SVR amongst genotype 2 and 3 patients and those with genotype 1 were 50.0% and 26.1% respectively. The side-effect profiles observed with pegylated interferon alfa-2b plus ribavirin were similar to those encountered with interferon alfa-2b plus ribavirin. No new side-effect was observed with pegylated interferon alfa-2b plus ribavirin therapy (Table III). Side-effects were tolerable in most patients with anaemia occurring in 22 patients (66.7%), leukopenia in 23 patients (69.7%) and thrombocytopenia in 15 patients(45.5%). Average drop of haemoglobin, leukocyte and platelet count below lower limit of normal range was 1.6g/dL, $1.4x10^9$/L and $43x10^9$/L respectively. Commonly seen side-effects were flu-like symptoms which include fever, rigor, myalgia, headache, and fatigue.

Discussion

A significant number of our patients defaulted from this study. This was due to side effects in one patient and failure to return for follow up in nine patients. The majority of follow up defaulters were Indonesians (70%). The likely explaination for the high defaulters among the Indonesians are the long travel distance and high cost of treatment. This had resulted in the low SVR (33.3%) by ITT analysis. However, the SVR increased to 52.9% in the per protocol analysis group. This is comparable with results from other international trials.

Non-compliance towards treatment amongst patients was another possible factor that contributed to the low SVR in this study. This was particularly true amongst Indonesians who may have had difficulty in consulting their doctors whenever problems arosed. This resulted in temporary discontinuation of treatment and overall low SVR rate. McHutchison and colleagues had reported that overall SVR increased tremendously to 72% if patients adhere to at least 80% of both drugs for at least 80% of the duration[8].

The side-effect profiles observed with pegylated interferon alfa-2b plus ribavirin were similar to those encountered with interferon alfa-2b plus ribavirin. No new side-effects were observed with pegylated interferon alfa-2b plus ribavirin therapy.

Conclusion

Pegylated interferon alfa-2b (Peg-Intron) plus ribavirin (Rebetol) is an effective and safe therapy for Chronic Hepatitis C.

Patients' characteristics

Table I: Baseline characteristics of patients (ITT analysis)

Characteristics	Pegylated interferon alfa-2b 1.5 mcg/kg/week plus ribavirin > 10.6 mg/kg/day (n=33)
Demography	
Mean (range) age (years)	52.4 (24-75)
Male/Female (%)	13/20 (39/61)
Nationality (%)	
Malaysians	19 (58)
Indonesians	13 (39)
Others: Japanese	1 (3)
Treatment naïve	23 (70)
Previously failed interferon alfa or interferon alfa plus ribavirin	10 (30)
Mean (range) alanine aminotransferases (U/L)	139.4 (22.6 – 371.8)
Mean (range) alanine aminotransferase (x upper limit normal)	2.8 (0.5 – 7.4)
HCV RNA in serum	
Mean (range) (x 10^3 IU/ml)	490.2 (0.9 – 2,780)
High viral load* (> 600 x 10^3 IU/ml) (%)	10 (31.3)
Source of infection (%)	
Transfusion	9 (27.3)
Sporadic	24 (72.7)
Genotype (%)	
1	23 (70)
2 or 3	10 (30)
Histology**	6.4 (1-13)
Mean (range) baseline Knodell Inflammatory score	9 (27.2)
Cirrhosis (%)	

* High viral load is defined as > 2,000,000 copies/ml (2,000,000 copies/ml = 600,000 IU/ml)

** Liver biopsy was only obtained in 22 patients.

Efficacy Evaluation: Virological Responses

Table II: Virological response at the end of follow-up

Endpoint	SVR (number responding/ number treated) (ITT analysis) n=33)	SVR (number responding/ number completed treatment) (per protocol analysis) n=23
Overall (%)		
EVR	23 (69.7)	17 (73.9)
ETR	20 (60.6)	16 (69.6)
SVR	11 (33.3)	11 (47.8)
SVR by naïve/previously treated (%)		
Treatment Naïve	9 (39.1)	9 (52.9)
Previously failed interferon alfa or interferon alfa plus ribavirin treatment	2 (20)	2 (33.3)
SVR by genotype (%)		
1	6 (26.1)	6 (40.0)
2/3	5 (50)	5 (71.4)
SVR by baseline HCV (%)		
High viral load* (> 600 x10^3 IU/ml)	4 (40)	4 (44.4)
Low viral load (< 600 x 10^3 IU/ml)	7 (30.4)	7 (50)
SVR by degree of fibrosis (%)		
No/minimal fibrosis	10 (43.5)	10 (58.8)
Cirrhosis	1 (10)	1 (16.7)
SVR by nationality (%)		
Malaysian	9 (47.4)	9 (56.3)
Indonesian	1 (7.6)	1 (16.7)
Others (Japanese)	1 (100)	1 (100)

* High viral load is defined as > 2,000,000 copies/ml (2,000,000 copies/ml = 600,000 IU/ml)

Table III: Adverse event during treatment

Adverse event	Proportion of patients (%)
Anaemia	22 (66.7)
Leukopenia	23 (69.7)
Thrombocytopenia	15 (45.5)
Influenza-like symptoms	
Fatigue	18 (54.5)
Fever	16 (48.5)
Headache	15 (45.5)
Rigors	9 (27.3)
Weight decrease	5 (15.2)
Arthralgia	9 (27.3)
Myalgia	14 (42.4)
Gastrointestinal symptoms	
Anorexia	11 (33.3)
Diarrhoea	3 (9.1)
Nausea	9 (27.3)
Psychiatric symptoms	
Giddiness	7 (21.2)
Dermatological symptoms	
Alopecia	11 (33.3)
Pruritus	6 (18.2)
Rash	3 (9.1)

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