ORIGINAL ARTICLE

Peginterferon Alfa-2a (Pegasys) and Ribavirin in the Treatment of Chronic Hepatitis C

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Abstract

BACKGROUND AND AIMS: Pegylation of interferon alfa-2a is a new modality for treatment of chronic hepatitis C. This clinical trial was conducted to evaluate the efficacy and safety of PEG IFN in combination with ribavirin in CHC patients.

METHODS: Fifty seven patients with HCV RNA in serum, persistently elevated ALT and chronic C hepatitis on liver biopsy enrolled to this study. The patients received PEG IFN 180 micg per week plus ribavirin 10-15 mg/kg per day.

RESULTS: HCV RNA was negative in 37 patients (74%) after three months of beginning of study (EVR) and SVR occurred in 50% of all patients.

CONCLUSION: Peginterferon alfa-2a plus ribavirin is safe and effective in treatment of naïve patients and relapsers.

KEY WORDS: Hepatitis C, Pegylated interferon alfa-2a, Ribavirin, Therapy

Introduction

HCV is an RNA virus that belongs to the family of flaviviruses; the most closely related human viruses are hepatitis G virus, yellow fever virus, and dengue virus.[1] The natural targets of HCV are hepatocytes and, possibly, B lymphocytes.[2,3] Nearly 170 million people worldwide are infected with hepatitis C virus (HCV).[4] Progression to chronic disease occurs in the majority of HCV-infected persons, and infection with the virus has become the main indication for liver transplantation.[5] Only a subgroup of infected persons will have a clear indication for therapy.[6] This is the case in patients with detectable levels of HCV RNA who have persistently elevated alanine aminotransferase (ALT) levels and a liver biopsy showing fibrosis or at least moderate necrosis and inflammation. Even before HCV was identified as the chief etiologic agent in non-B hepatitis, interferon alfa therapy was associated with normalization of ALT levels in some persons who were given this diagnosis. In 1989, the first cases of successful treatment of documented HCV infection with interferon alfa were reported.[7, 8]

The National Institutes of Health (NIH) Consensus Panel and the European Association for the Study of the Liver Consensus Conference recommended that antiviral therapy be indicated in Chronic Hepatitis C (CHC) patients of18 to 60 years old who had persistently abnormal ALT levels, HCV RNA in serum, and evidence of portal or bridging fibrosis and moderate to pronounced inflammation and necrosis.[9, 10] Although the introduction of combination therapy with interferon and ribavirin has markedly improved clinical outcomes, less than half of those with HCV infection can be expected to have a favorable response to the agents that are currently available.[11,12] Virologic response is considered a more accurate measurement of efficacy compared with biochemical response due to individual and temporal fluctuations in serum ALT concentrations, and the presence of HCV RNA in CHC patients with normal ALT levels.[13, 14]

Since responses to therapy may not be maintained after treatment is stopped, the success of clinical trials has been evaluated in terms of the response at the end of therapy (end-of-treatment response) and six months after the cessation of treatment (sustained treatment response). Persons with a sustained virologic response (SVR) have a high probability of having a durable biochemical, virologic, and histologic response.[15]

The attachment of polyethylene glycol to interferon alfa (peginterferon alfa-2a) extends the half-life and duration of therapeutic activity of interferon alfa. In contrast with conventional interferon alfa, peginterferon alfa-2a is given only once a week, and the individual dose is calculated according to the patient's weight.[5] Results from various clinical trials clearly demonstrate that peginterferon alfa-2a (40 kDa) provides a significant improvement over standard IFN alfa-2a therapy and confers even further benefit when administered with ribavirin.[16]

We studied the efficacy and safety of peginterferon alfa-2a (Pegasys) and ribavirin in the treatment of Patients with chronic hepatitis C.

Method and Materials

In a prospective case series study, 57 consecutive patients with chronic hepatitis C were enrolled between Feb and Oct 2002. Patients with no previous interferon therapy during 6 months before participation in our study, with detectable serum HCV RNA (greater than 100 Copies/ml), pathologic finding of chronic HCV in liver biopsies and serum ALT concentration above the upper limit of normal(on two occasions during the preceding 6 month) were enrolled in the study. Patients were excluded from study if they had anemia; neutropenia; thrombocytopenia; creatinine concentration greater than 1.5 times the upper limit of normal; liver cirrhosis; serum alpha-fetoprotein concentration above 25 ng/ml; coinfection with hepatitis A, hepatitis B, or HIV; neoplastic diseases; severe cardiac or chronic pulmonary disease; autoimmune disease; psychiatric disorder; seizure disorder; severe retinopathy; or unwillingness to practice contraception.

All patients were treated with combination therapy of peginterferon alfa-2a (40kD) (Pegasys®–Roche) 180 micg subcutaneously once weekly and oral ribavirin 1000mg daily for 48 weeks. Peginterferon alfa-2a was the only prescribed drug for those who had hemoglobinopathies (such as thallassemia). Any adverse events or patient preference decreased the therapeutic period to 24 weeks, and the patients with less than 24 weeks treatment period were eliminated from the study. ALT level and side effects Such as anemia, neutropenia, thrombocytopenia, and physical side effects were evaluated at 2, 4, and 8 weeks and after that per 8 weeks until the end of treatment. Detection of HCV RNA by RT-PCR before week 24 and on week 48 was used to evaluate early response (EVR) and end treatment response (ETR). Virologic response was defined as undetectable levels of HCV RNA with a lower limit of detection of 100 copies/ ml. SVR was evaluated by detecting HCV-RNA 6 months after therapy cessation. When polymorph nuclear cells (PMNs) count appeared 500-750 per mm^2 or platelet count 20,000-50,000 per mm^2, the pegasys dosage was switched to half , 90 micg once weekly, and again was returned to normal value when those laboratory findings were repaired. But in below 500 for PMN and 20,000 for platelet, we stopped the treatment and excluded the patients. In some situations when the hemoglobin (Hb) dropped below 10 gr/dl, we decreased the ribavirin dose to 500mg per day, and if we didn't have improvement in Hb concentration, the ribaverin was eliminated from regimen.

We followed serum ALT, PMN count, platelet count and Hb concentration at 2 and 6 months after therapy cessation. Descriptive statistics for patients were reported. The chi-square test was used to compare categorical variables. The study was designed at a 5 percent level of significance. All reported P-values are two-sided.

Results

57 patients were enrolled in our study. There were 45 males and 12 females (male to female ratio: 3.75). The mean age of patients was 41±12, ranging between 19 to 73 years. 4 patients had thallassemia (3 thallassemia major, 1 thallassemia intermedia associated with Fanconi's anemia) and 4 patients had hemophilia A. Table 1 demonstrates characteristics of the patients at the beginning of treatment. 44 patients didn't have previous history of anti HCV therapy with interferon (naive). Among 51 patients with complete treatment period, 40 patients received 48week treatment, and the others were on 24week treatment. In spite of completing treatment period, one patient denied having RT-PCR to detect the HCV RNA in the end of treatment. 37 patients (74%) had early virologic response (EVR). HCV RNA wasn't detected in 10 patients (20%) between 24 and 48 weeks of treatment period. 3 patients (6%) did not response to this regimen, and HCV RNA was still positive in serum after 48 weeks.

SVR occurred in 50 % of all patients. SVR in patients with previous history of interferon alfa was 66.7%. There weren't statistical differences between men and women. SVR rate in early responders wasn't any different from that of the rest. Therapeutic period (24 or 48 weeks) did not have influence on SVR. In patients who had dose reduction of peginterferon due to adverse events, SVR was not significantly different from that of other patients.

The most frequent adverse events were flu-like symptoms, weight loss, mood disorders, hair loss, and pruritus with incidence of 22 (43.1%), 19 (37.3%), 15 (29.4%), and 10 (19.6%), respectively. 18 (35.2%) patients in laboratory evaluation had adverse events; anemia in 7 (13.7%) patients; neutropenia in 9 (17.6%) patients, and thrombocytopenia in 5 (9.8%) patients. No evidence of thyroid disorder appeared in our patients. Two patients had pneumonia. So, we interrupted treatment and after improving was started again. Fortunately we did not have any mortality in our study.

During therapeutic period, 6 patients were excluded from study. 4 patients interrupt the treatment due to noncompliance, and 2 patients due to severe neutropenia (<500 cell/mm^3).

Table 1

Characteristic of the patients at base line

Sex	Male	45 (78.9%)
	Female	12 (21.1%)
Age (years)		41±12
Naiive Patients		44(77.2%)
Associated Disease (n=8)	Hemophilia	4(7%)
	Thallassemia	4(7%)
ALT (unit)		88±57
Hemoglobin		14.6±1.5
PMN		3110±1454
Platelet		190450±111409
Dropout (n=6)	Incompliance	
	Severe	4(7%)
	Neutropenia	2(3.5%)

ALT: Alanine aminoteransferase; PMN: Polymorphonuclear cells

Discussion

In patients with HCV infection, improvements in therapy have resulted in higher response rates.[17, 18] Several studies have demonstrated that combination of peginterferon and ribavirin is significantly more effective in achieving SVR than is the combination interferon and ribavirin.[19] Zeuzem et al found that administration of interferon alone results in 28% for end treatment response and 19% for sustained virologic response. These figures were 69% and 39% for peginterferon alpha-2a alone, respectively.[20] In the study of Fried and colleagues in 2002, combination of peginterferon alfa-2a and ribavirin for 48 weeks increased the ETR and SVR to 69% and 56%, respectivdely.[17] Our data have shown similar response rates.

This improvement in therapeutic response could be attributed to PEG polymer, which increases interferon molecular size in compare with interferon. PEG-IFN alfa-2a is absorbed in a sustained manner and its clearance is reduced substantially compared with IFN alfa-2a resulting in sustained serum drug concentrations.[21]

The factors which may influence therapeutic response such as sex, EVR, therapeutic period (24 week vs 48 weeks) and dose reduction due to adverse events have been evaluated and there was no significant evidence that they have effect on SVR.

Response rates were similar in men and women, which is compatible with other studies.[22] In Davis GL et al. Study, EVR had better prognosis after therapy[23] but in our study SVR values in patients with EVR were similar to those of others. In our opinion, to find out this situation, we need a larger sample size.

As we did not find any differences between 24 week and 48 week therapeutic period groups, it seems that dominant hepatitis C virus genotype may be treated with shorter course (24 weeks). To confirm this hypothesis we must design a similar study with genotype detection. In nonresponders with previous Interferon therapy or in relapsers, SVR was 66%. This SVR value is higher than that of other patients but there is not significant evidence statistically. So we have shown that the combination of Pegasys and ribavirin has more therapeutic effects on nonresponder patients with previous combination therapy of Interferon and ribavirin. Treatment with peginterferon alfa-2a plus ribavirin was beneficial in patients with chronic hepatitis C who had not been cured with interferon alone or combination of ribavirin and interferon.[24, 25] The SVR in patients who has dose reduction due to neutropenia, thrombocytopenia and anemia was not statistically different from that of other patients. About 45% of treated patients experienced no troubles during treatment. The most common cause of interruption in therapeutic period was patient's preference. Only in two cases, we stopped the treatment after decrease in the count of neutrophil to bellow 500 cells/ mm^3 in the underlying hematological disease. Patient's compliance for using Pegasys and ribaverin combination was higher than for ribavirin and conventional interferon. Treatment with peginterferon alfa 2a (40KD) is associated with less disabiliting and less impairment in patient's functioning and well-being.[26] Pegylation of interferon has improved efficacy and similarly safety and tolerability compared with interferon alpha in patients with chronic hepatitis C even with underlying cirrhosis.[27]

Conclusion

Peginterferon alfa-2a (40 KD) plus ribavirin is significantly more effective versus interferon alfa plus ribavirin at inducing SVR in treatment of naïve and relapsers. The impact on health related quality of life may be an important consideration for physicians who select an optimal treatment regimen.

Acknowledgement

The medications used in this study were provided by Hoffmann-La Roche Inc. and the authors wish to acknowledge their support.

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