

Combination of interferon alfa-2b and ribavirin in relapsed or non-responding chronic hepatitis C patients following interferon therapy

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Abstrak

Dua puluh enam penderita dengan hepatitis kronik C (HKC) yang kambuh atau tidak berespons setelah terapi interferon (IFN) telah diberikan terapi kombinasi IFN alfa-2b 3 juta unit tiga kali seminggu dengan ribavirin (RIB) 800-1000 mg sehari selama 48 minggu. Dua puluh satu (81%) dari 26 pasien dapat menyelesaikan studi ini terdiri dari 12 pasien kambuh dan 9 tidak berespon sedangkan 5 pasien keluar dari studi karena efek samping pada 3 pasien dan 2 lainnya tidak berhubungan dengan terapi. Pada kelompok kambuh respon lengkap, kambuh dan respons permanen masing-masing didapatkan pada 9/12 (75%), 2/12 (17%) dan 7/12 (58%) pasien. Sedangkan di kelompok tidak berespons perhitungan tersebut masing-masing didapatkan pada 3/9 (33%), 1/9 (11%), dan 2/9 (22%). Efek samping yang tersering ditemukan adalah gejala seperti flu didapatkan pada 18 pasien (86%). Terapi kombinasi IFN dan RIB dapat memberikan respons permanen pada penderita HKC yang kambuh dan tidak berespon sementara terapi kombinasi ini lebih efektif untuk yang kambuh daripada yang tidak berespons. (*Med J Indones* 2001; 10: 214-8)

Abstract

Twenty six patients (pts) with chronic hepatitis C (CHC) who relapsed or non-responded following interferon (IFN) therapy were given IFN alfa-2b 3 MIU three times a week for 48 weeks in combination with Ribavirin 800-1000 mg daily 21 (80,8%) of the 26 pts completed the study consisted of 12 relapsers and 9 non-responders. Five pts dropped out due to drug adverse events in three pts and non-drug related reason in the other two. In the relapsed group complete response, relapse and sustained response rates were obtained in 9/12(75%), 2/12 (16,5%) and 7/12(58,3%) pts respectively. In the non-responding group, these figures were 3/9 (33,3%), 1/9(11,1%), and 2/9(22,2%) pts, respectively. The most frequent adverse event was flu-like syndrome, which was found in 18 pts (85,7%). Combination therapy of IFN alfa-2b and ribavirin may induce sustained virological response in relapsed and non-responding CHC patients. This combination therapy is more effective for relapsers compared to for non-responders. (*Med J Indones* 2001; 10: 214-8)

Keywords : Chronic hepatitis C, combination therapy, interferon, ribavirin

Hepatitis C virus (HCV) is the most common cause of post transfusion hepatitis and still the most important etiology of sporadic chronic hepatitis in the world.¹ Although this disease is insidious and the majority of patients do not develop jaundice at its onset, about 80% of patients will progress to chronic hepatitis and 25% of this lead to cirrhosis and hepatocellular carcinoma.²

Interferon (IFN) alfa is the most widely used antiviral agent for chronic hepatitis C (CHC) infection. Therapy with IFN alfa will lead to inhibition of HCV replication and amelioration of hepatic necro-inflammatory activity in about 50% of patients with chronic hepatitis C. Unfortunately, 50% of these responders will relapse within 6 months of discontinuing therapy. Thus, the overall sustained alanine transaminase (ALT) response rate to alfa-IFN therapy is approximately 20%.³

Ribavirin (RIB) is a synthetic nucleoside analogue and has a broad spectrum of in vitro activity against both DNA and RNA viruses. Its mechanism of action is not entirely clear, but it may act through depletion of intracellular phosphate pools, inhibition of viral polymerase, or shifting of the cytokine profile.⁴

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Treatment with ribavirin alone reduces serum ALT, but not serum HCV-RNA levels in patients with chronic hepatitis C.^{5,6} Pilot studies suggested that combination IFN and RIB reduced relapse, as compared to IFN alone, thereby increasing the likelihood of sustained response.^{7,8,9} Recently, two large randomized trials have shown that combination therapy achieved higher sustained response compared to IFN monotherapy.^{10,11} Improvement was also observed in terms of biochemical and histological endpoints in those receiving combination therapy.

Several investigators have examined this combination therapy for 6 months for those patients who relapsed after responding to IFN treatment or for those who did not respond to IFN.^{12,13,14}

In this open clinical study, we evaluate the efficacy and safety of IFN alfa – 2b and Rib for 12 months in relapsed or non-responding CHC patients following IFN therapy.

METHODS

This was an open study for adult CHC patients who had relapsed or had not responded following an initial course of any interferon alfa therapy using a minimum of 3 MIU for a minimum of 3 months. Response to a prior therapy is defined as normal serum ALT documented on one or more occasion during either 6 weeks prior to the end of treatment or 6 weeks following the end of treatment. A relapse is defined as serum ALT > 1.5 X upper limit normal (ULN) within 12 months following the end of the initial interferon therapy. The evidence of CHC was established by the seropositivity of HCV-RNA by Roche Amplicor – PCR with persistent abnormal liver function tests.⁵ Patients were excluded if they had a history of depression, HIV infection, drug abuse, evidence of decompensated liver disease and uncontrolled thyroid abnormality. The patients consenting the study were assigned to receive Intron alfa 2b (Schering-Plough) 3 MIU administered subcutaneously three times a week (TIW) for 48 weeks in combination with ribavirin (RIB) given concurrently at either 1000 mg daily (for patients < 75 kg of body weight) or 1200 mg daily (for patients > 75 kg of body weight) in divided doses, for 48 weeks as a re-treatment of previously relapsed or non-responding CHC patients following IFN therapy. Dose of RIB was reduced 50% if hemoglobin

level decreased below 10 g/dl and dose of IFN was also reduced 50% if white blood cell decreased below $1.5 \times 10^9/l$, granulocyte below $0.75 \times 10^9/l$ and platelet below $50 \times 10^9/l$. Adverse events and laboratory tests including hematology and blood chemistry were performed at study entry, monthly during treatment, at end of treatment, every 3 months during follow-up and at 6 months of follow-up.

Serum HCV-RNA was determined at study entry, at end of treatment, and at 6 months of follow-up in majority of patients and results were expressed as positive and negative. In some patients serum HCV-RNA was also examined every 3 months during treatment.

Overall response assessment to combination treatment was determined at the end of treatment and at 6 months following the end of treatment. Sustained virological responders were those with undetectable HCV-RNA at the end of 6 months observation period. For either ALT or HCV RNA response, the patient could either be a primary non-responder or have responded initially with breakthrough at the end of the treatment period.

RESULTS

There were twenty-six subjects who could be evaluated in this study twenty-one patients have completed the treatment whereas the other five discontinued therapy. Of the 21 subjects 12 were relapsers and 9 were non-responders.

The demographic data of 26 patients who received re-treatment therapy with IFN and RIB is given in Table 1. The majority of patients were males and Malay. In most patients the primary mode of transmission was unknown

Table 1. Demographic data of patients receiving re-treatment IFN and RIB.

Mean age (yrs)	49.9
Race (% of Malay)	77
Gender (% of male)	69
Primary route of transmission (%) :	
Blood transfusion	15
Unknown	85
Mean duration of previous IFN therapy (month)	7.7

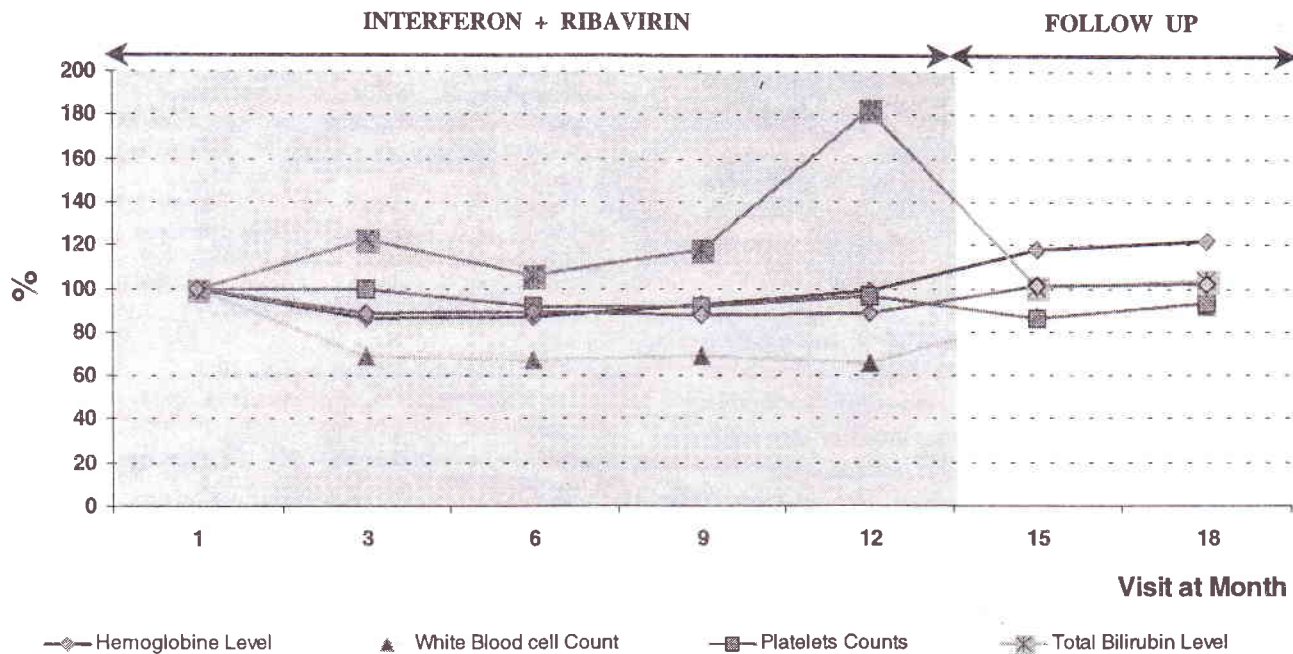


Figure 2. Hematological and serum bilirubin changes during treatment and follow-up. Values are expressed as means of percentage their initial levels.

Discontinuation of therapy occurred in 5 (19%) of 26 patients; three patients because of adverse events (severe weight loss, hyperthyroidism, and psychological disturbance) and non-drug related reason in the other two patients (pneumonia and loss of contact).

“Flu-like” symptoms (fatigue, fever, arthralgia, myalgia, and headache) were the most common adverse events and were observed in 69% of patients. Mental symptoms such as insomnia, sleepy, and psychiatric disturbance were recorded in 15% of patients. There were no signs of specific adverse events associated with longer re-treatment.

DISCUSSION

In about 40-50% patients with chronic hepatitis C, IFN therapy can induce normalization of serum alanine aminotransferase concentrations, loss of detectable HCV RNA in serum and histologic improvement, but the majority will relapse after cessation of treatment.^{15,16} Many of these patients will again response to re-treatment with IFN, but sustained response is uncommon.^{15,17} A second course of treatment with higher dose of IFN or for longer periods or both may

lead to sustained response in 20 to 50% of patients, but these regimens are costly and poorly tolerated.^{17,18}

Several initial reports have shown that combination IFN and RIB is more effective than re-treatment with IFN alone for chronic hepatitis patients who relapsed or non-responded to prior IFN therapy.^{12,13,14}

The present study confirms that combination therapy of Interferon alfa-2b and ribavirin can induce sustained virologic response in relapsers and in non-responders following IFN therapy. However, the virologic and biochemical responses in relapsers are greater than in non-responders. These results are in agreement with previous studies.^{13,14,19}

The sustained virologic response for relapsers and non-responders amounting 58.3% and 22.2%, respectively, in our study are higher than in previous studies using the same combination treatment for six months.^{13,14,20} These discrepancy is probably because of the difference in duration of treatment.

Using high dose of consensus interferon (15 microgram daily) Jenny et.al. have also reported the similar virologic response rate for relapsers but less

response rate for non-responders compared with our results.²⁰ However, the adverse events such as "flulike" and mental symptoms reported in 98% and 52% of their patients are greater than in our study.

Therefore, we are of the opinion that combination IFN and RIB for 12 months might be the re-treatment of choice for relapsed or non-responding chronic hepatitis C patients following IFN mono-therapy.

Some studies have shown that during combination IFN and RIB breakthrough rarely occurs compared to IFN mono-therapy.²¹ Since the interferon-antibodies and HCV genotypes were not measured in this study we can not postulate the probable mechanism of this phenomenon.

Our study has revealed that some patients developed decrease of hemoglobin levels during the combination treatment. Since the average body weight of our patients is less compared to that of patients in western countries, 600 to 800 mg ribavirin daily might be sufficient.

In conclusion, the present data show that combination IFN and RIB for 12 months is safe and effective in inducing sustained virologic response in relapsed or non-responding chronic hepatitis C patients. However, still low response rate in non-responders indicates a need for better therapeutic options.

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