Treatment of Chronic Hepatitis C with High Dose Interferon Therapy Experience from Pertamina Central Hospital Jakarta

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ABSTRACT

Background

Until several years ago, interferon alfa was the only drug with proven benefit for the treatment of chronic Hepatitis C. Several therapy categories such as fixed-dose regimens, induction-dose regimens and escalation-dose regimens are already known. With standard dose interferon therapy of 3 MU, TIW for 6 months, a sustained response rate can ve achieved in only 10-20% of patients. This study reports the results of treatment of chronic Hepatitis C with high dose interferon therapy of 6 MU, TIW for 6 months.

Patients and Methods

From February 1996 to February 1998, 15 patients with Hepatitis C were treated with interferon alfa-2b 6 MU, TIW for 6 months. Ultrasound-guided liver-biopsy was performed using the Menghini-Technique (Hepafix). Virological and biochemical responses were assessed at the end of the treatment period at week 24 and at the end of follow-up period at week 48 and up to 2 years later. Virological and biochemical sustained responses were defined as the absence of HCV-RNA, and SGPT concentration within the normal range at both weeks 24 and 48. Histological response was assessed after the end of treatment. Side-effects were observed and noted.

Results

Ten out of 15 patients (66.7%) were HCV-RNA negative and 11 out of 15 patients (73.3%) demonstrated ALT within the normal range at week 24. At the end of the follow-up, from week 48 until 2 years later, HCV-RNA negative and normal ALT were found in 6 patients (40%). Histological improvement was found in 4 out of 6 patients. Fever was the most common side-effect and was found in 13 patients, while fatigue was found in 12 patients, myalgia in 11, headache in 10, and anorexia in 11 patients.

Conclusion

High dose interferon alfa-2b therapy for the treatment of chronic Hepatitis C can improve the rate of sustained response, but is associated with more side-effects.

***Key Words**: Chronic hepatitis C, Interferon*

INTRODUCTION

Until several years ago Interferon alfa was the only drug with proven benefit for the treatment of chronic Hepatitis C.

After the first administration of Interferon for the treatment of Hepatitis NANB by Hoofnagle et al, in 1986[1], multicenter studies have been done to find out the optimal dose.

Since several years some therapy regimes with difference dose including high dose are already known such as: (1) fixed-dose regime with 3, 5 or 10 MU, TIW

or 3-5 MU, QD for 6 months; (2) induction-dose regime with 5-10 MU, QD or TIW for 2-8 weeks continued with the same or lower dose TIW for 8-22 weeks; (3) escalation-dose regime beginning with small dose of 1.5-9 MU, QD with increasing dose at monthly interval or 3-20 MU, TIW with increasing dose at 3 months interval, this regime usually administrated for nonresponse.[2] With standard-dose Interferon therapy of 3 MU, TIW for 6 months a sustained response rate can be achieved in only 10-20% of patients.[3, 4] High dose regime may increase the sustained response rate in some studies but were associated with more side-effects, higher cost and discontinuation of treatment.[5,7]

During the past 5 years the use of Ribavirin as a synthetic nucleoside analoque in combination with standard-dose Interferon can increase the sustained response rate.[8, 9]

This study reports the results of treatment of chronic Hepatitis C with high dose Interferon therapy of 6 MU, TIW for 6 months.

PATIENTS AND METHODS

From February 1996 to February 1998, 15 patients with chronic Hepatitis C were treated with Interferon alfa-2b 6 MU, TIW for 6 months. Patients were eligible if they fulfilled the inclusion criteria: persistently elevated alanine aminotransferase (ALT) 2 times the upper limit of the normal range for at least 6 months, positive anti-HCV and positive HCV-RNA. The exclusion criteria were decompensated cirrhosis, symptomatic heart disease, uncontrolled diabetes mellitus and hypertension, pregnancy and previous treatment with Interferon alfa-2b. The source of infection was blood transfusion in 3 patient and unknown in 12 patients. Ultrasound-guided liver biopsy was performed using the Menghini technique (Hepafix) before and after treatment. Histological changes were classified as chronic persistent hepatitis, chronic active hepatitis and cirrhosis. Activity of inflammation classified in 4 grades and fibrosis status in 5 stages. Grade 0: no activity, grade 1: minimal, grade 2: moderate and grade 3: severe activity.

Stage 0: no fibrosis, stage 1: portal fibrosis, stage 2: periportal, stage 3: bridging fibrosis and stage 4: cirrhosis.

Clinical and laboratory examinations were done every 4 weeks during the treatment and during the 6 months follow-up period, continued every 3-6 months for 1 and 2 years later.

Biochemical and virological responses were assessed at the end of treatment period week 24 and 48, continued with examination of ALT every 3-6 months and HCV-RNA at the end of week 24 and 48.

Patients with elevated ALT or positive HCV-RNA at the end of treatment were defined as non responders.

Side effects were observed and noted.

RESULTS

Fifteen patients (8 males and 7 females, ages 40 to 60 years) were treated with Interferon alfa-2b, 6 MU, no TIW for 6 months.

Ten out of 15 patients (66.7%) were HCV-RNA negative at the end of treatment (at week 24). In 1 patient, the HCV-RNA was negative 3 months later, while ALT levels were normal at the end of treatment. In 11 of 15 patients (73.3%) ALT levels were normal at the end of treatment (week 24).

During the 6 months, follow-up virological relapse was observed in 5 out of 10 patients (50.0%), and biochemical relapse in 5 out of 11 patients (45.5%). Thus at the end of the 6 months follow-up virological sustained response was found in 5 patients (33.3%), and biochemical sustained response in 6 patients (40.0%). After 2 years follow-up, no relapse was found.

If the patient with negative HCV-RNA at 3 months after the end of treatment is included, the virological sustained response rate increased from 33.3% to 40.0% (6 out of 15 patients), and the relapse rate decreased from 50.0% to 45.5% (5 out of 11 patients), thus achieving a virological response rate similar to biochemical response rate (Table 1).

Table 1. Virological and Biochemical Responses at The End of Treatment Week 24 and at The End of Follow-up 24 Weeks up to 2 Years

N	Virological response			Biochemical response		
	EOT	EOF		EOT	EOF	
	24 weeks	24 weeks	2 years	24 weeks	24 weeks	2 years
15	10 (66.7%)	6 (40.0%)	6 (40.0%)	11 (73.3%)	6 (40.0%)	6 (40.0%)

EOT = End of Treatment
EOF = End of Follow-up

Histological changes of 14 patients who underwent liver biopsy before treatment showed inflammation activity grade 1 in 4 patients and grade 2 in 10 patients. Fibrosis stage 1 in 4 patients, stage 2 in 4 patients, stage 3 in 3 patients and stage 4 (cirrhosis) in 3 patients. Histological improvement was found in 4 of 6 patients who underwent liver biopsy 1-7 months after treatment, 8 patients refused a second biopsy. This histological improvement was seen mostly in the patients with a sustained response. There was no improvement in 2 patients (Table 2).

Table 2. Histopathological Responses in 6 Patients at 1-7 Months After Treatment

N	Before treatment		After treatment	
	Grade	Stage	Grade	Stage
2	II	II	I	I
1	II	I	I	I
1	II	IV	I	IV
1	II	II	II	II
1	I	III	I	III

Flu-like symptoms were the most common side effect, followed by gastrointestinal, dermatological, and psychiatic symptoms (Table 3)

Table 3. Side-Effect of Using High Dose Interferon Therapy

• Flu-like symptoms	
Fever	: 13 patients
Fatique	: 12 patients
Malaise	: 10 patients
Myalgia	: 11 patients
Headache	: 10 patients
• Gastrointestinal symptoms	
Anorexia	: 11 patients
Nausea	: 7 patients
Weight loss	: 8 patients
• Dermatological symptoms	
Pruritus	: 3 patients
Alopecia	: 7 patients
Dry skin	: 4 patients
• Psychiatric symptoms	
Depression	: 3 patients
Emotional lability	: 3 patients
Insomnia	: 4 patients

DISCUSSION

Treatment of chronic Hepatitis C with high dose Interferon alfa (4.5-10 MU, QD or TIW) as a fixed-dose regime has been reported in previous studies. The following authors reported an increase of virological sustained response rate with high dose Interferon alfa: Hakozaki et al (1995) used 6 MU, TIW for 6 months, and reported a sustained response rate of 40%. [10] Lino, et al (1993) reported a sustained response rate of 48% with an induction-dose of 10 MU, TIW for 12 weeks.[11] Yamakawa, et al (1998) reported a 50% sustained response rate using an induction-dose of 6 MU, QD for 2 weeks continued with 6 MU, TIW for 12 weeks.[12]

In contrast, Farell, et al (1997) reported a low virological sustained response rate of 14% with 4.5 MU, QD for 6 months[13], while Lindsay, et al (1996) reported a sustained response rate of 17% with 10 MU, TIW for 6 months.[14]

The difference in these results may be caused by the difference in methodology and sampling.

In this study, we achieved a virological and biochemical sustained responses rate of 40.0% if we include the patient with late negative HCV-RNA.

A similar case was found in the study by Reichard, et al.[6]

Histological improvement was observed among patients with a sustained response. This finding was also found in the study by Davis G. L., et al. in 1998.[15]

The histological response in non-responders cannot be evaluated due to refusal of a second biopsy.

In this study, the incidence of side-effects was higher compared to the study by Davis, et al (1998) using an Interferon standard dose of 3 MU, TIW for 6 months.[16] However the side-effects did not cause a dose reduction or discontinuation of the treatment.

CONCLUSION

According to the data reported above, high dose Interferon alfa-2b for the treatment of chronic Hepatitis C can improve the rate of sustained response.

The use of high dose Interferon is associated with a higher incidence of side-effect, but did not cause dose reduction or discontinuation of treatment.

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