

# Treatment of Chronic Hepatitis C in Patients with End-Stage Renal Disease and Hemophilia – The Singapore Experience

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## Key Words

Hemophilia · Hepatitis C virus · Interferon · Renal failure · Thyroid dysfunction

## Abstract

**Objective:** The aim of this study was to determine the response to treatment with interferon-alpha (IFN- $\alpha$ ) in patients with chronic hepatitis C who had end-stage renal disease (ESRD) or hemophilia in Singapore. **Methods:** Treatment-naive hepatitis patients with ESRD or hemophilia were given IFN- $\alpha_{2a}$  3 million units three times per week for 12 months in an open-label study. Hepatitis C virus RNA was determined before treatment, at the end of treatment and 6 months thereafter. Regular clinical examinations including blood counts and biochemistry were carried out during and after the treatment. **Results:** Nine consecutive patients with ESRD (8 men and 1 woman) and 6 consecutive male patients with hemophilia, with a mean age of 43 and 40 years, received treatment. Patients in both groups were predominantly infected with hepatitis C virus genotype 1 and had significant cytopenia affecting all three cell lines during the treatment; only 1 patient developed serious neutropenia, temporarily demanding a reduction of his IFN dose. Biochemical and virological responses at the end of treatment were accomplished by 8 of the 9 (89%) patients with ESRD and 4 of the 6 (67%) patients with hemophilia; however, 1

patient with ESRD and 2 with hemophilia relapsed after the treatment. Four of the 7 patients with ESRD who had sustained virological response underwent successful kidney transplantation later on. **Conclusion:** Monotherapy with IFN- $\alpha$  for 12 months is safe for treatment of the patients with chronic hepatitis C who had ESRD or those with hemophilia. A higher sustained virological response rate was observed in patients with ESRD than in those with hemophilia (78 vs. 33%).

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## Introduction

The prevalence of infection with chronic hepatitis C virus (HCV) is low in the general population of Singapore, with merely 0.37% of blood donors seropositive for anti-HCV [1]. In remarkable contrast, the prevalence of HCV infection is high in populations at risk, such as patients with end-stage renal disease (ESRD) and hematologic disorders. The prevalence of anti-HCV among Singaporean patients with ESRD undergoing peritoneal dialysis and hemodialysis was 5 and 28% [2], and that in patients with hemophilia was 46% [3]. The majority of these patients were infected with genotype 1 [3, 4]. Therefore, taking clinical and virological profiles of our patients into consideration, treatment of chronic hepatitis C, albeit in small numbers of patients, is a potential challenge for us.

Toward this goal, we examined the outcome of treatment of chronic hepatitis C in some patients with ESRD or hemophilia.

### Patients and Methods

Treatment-naive patients with chronic hepatitis C who had ESRD or hemophilia were offered to receive monotherapy with interferon (IFN)- $\alpha$  for treatment of their liver disease. Independently, 9 consecutive ESRD patients were enrolled by their attending hepatologists and 6 consecutive hemophilia patients were enrolled by their managing hematologist from June 1997 to March 2002 and from June 1998 to May 1999, respectively. An open-label study for treatment with IFN- $\alpha_{2a}$  3 million units subcutaneously three times per week was planned for these patients.

All patients were confirmed to be positive for anti-HCV by recombinant immunoblot assay (RIBA, Chiron, Emeryville, Calif., USA) with detectable HCV RNA in serum at baseline. Treatment was offered to all hemophilia patients whose serum levels of alanine aminotransferase (ALT) were greater than  $1.5 \times$  upper limit of the normal. However, there was no exclusion limit of serum ALT for treatment of ESRD patients, because they needed to clear HCV RNA from serum to be logged in the waiting list for kidney transplantation.

At the beginning of treatment, the baseline physical examination was carried out along with tests for various laboratory parameters, including blood counts, liver and thyroid functions. Genotypes of HCV RNA were determined by the line-probe assay (InnoLiPA, Innogenetics, Ghent, Belgium). Pretreatment liver biopsies were performed on all patients with ESRD. During treatment, regular clinical check-ups were carried out at week 1, 2 and 4 of treatment and monthly thereafter till the end of treatment. After the treatment, patients were examined every 3 months for the first 6 months and every 6 months thereafter. Their blood counts, liver as well as thyroid function, and blood glucose levels were monitored during these visits up to 6 months after the treatment. HCV RNA was determined by the reverse transcription polymerase chain reaction (Amplicor, Roche, N.J., USA) before treatment, at 6 months of treatment, at the end of treatment and 6 months after the treatment.

#### Patients with ESRD

We treated 1 female and 8 male patients with ESRD, whose mean age was 43 years. They were all on regular hemodialysis, which was continued throughout their treatment of chronic hepatitis C. Genotyping was performed on 5 patients which were all infected with HCV genotype 1; 4 had infections with HCV genotype 1b, including 1 with a mixed infection with genotype 3a, and the remaining subject had an infection with HCV genotype 1a (table 1). Their mean serum levels of ALT and aspartate aminotransferase (AST) at the baseline were 88 and 54 U/l, respectively. Two of the 9 patients had a Knodell score for hepatic fibrosis  $\geq 3$  at the baseline. Clinically, all patients were in Child's class A.

#### Treatment Outcome

Treatment was discontinued in 1 patient at 6 months, because his HCV RNA stayed positive and serum ALT remained elevated at the same time point; therefore, he was considered a nonresponder

**Table 1.** Baseline characteristics and treatment response to 1-year IFN monotherapy in patients with chronic hepatitis C who had ESRD or hemophilia

Features	ESRD	Hemophilia
Number of patients (men:women)	9 (8:1)	6 (6:0)
Mean age, years	43	40
HCV genotypes		
1a	1	1
1b	3	2
3a	0	1
Mixed with 1b	1 (plus 3a)	1 (plus 4a)
Mixed with 3	0	1 (plus 4)
Mean ALT level, U/l		
Pretreatment	88	190
Posttreatment	19	101
Mean AST level, U/l		
Pretreatment	54	117
Posttreatment	22	90
Response to IFN, number of patients (%)		
Sustained response	7 (78)	2 (33)
End-of-treatment response with relapse	1 (11)	2 (33)
No response	1 (11)	2 (33)
Mean treatment duration, weeks	53 <sup>a</sup>	53
Mean follow-up period in sustained responders, months	32	41

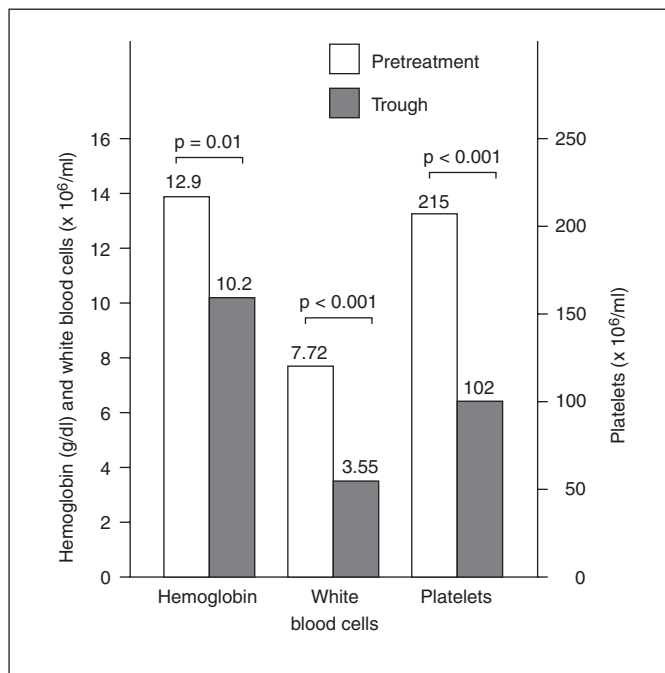
Figures in parentheses are percentages, unless otherwise indicated.

<sup>a</sup> Not including treatment of a nonresponder to IFN that was discontinued at 24 weeks after the treatment.

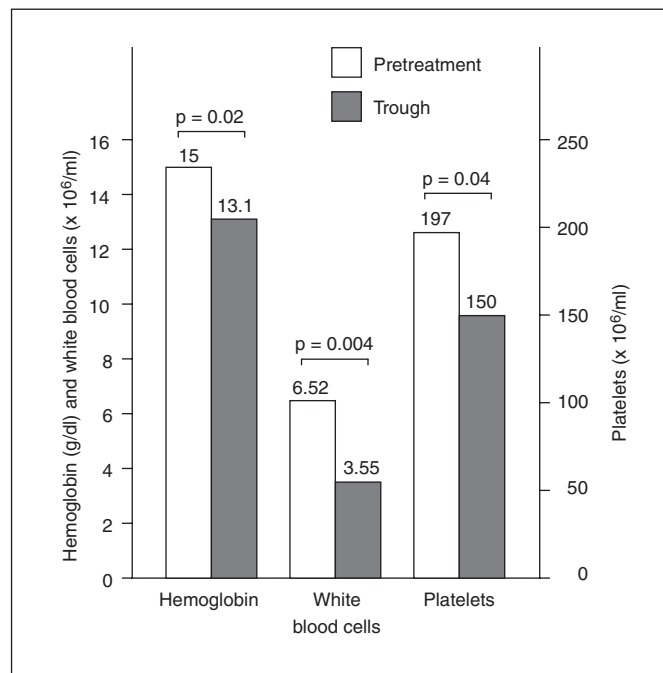
to IFN. All the other 8 patients completed the course of treatment during a mean period of 53 weeks and achieved virological and biochemical responses at the end of treatment; they were negative for HCV RNA in serum, and their mean serum levels of ALT and AST at the end of treatment were 19 and 22 U/l, respectively. Unfortunately, 1 of the 8 patients developed a virological relapse and HCV RNA turned positive at 6 months after treatment. This patient was the only one who required transient attenuation in the dose of IFN due to significant neutropenia. However, he resumed the standard dose of IFN 1 week later. Thus, sustained virological and biochemical responses were accomplished in 7 of the 9 (78%) patients with ESRD. Up to the present, these 7 sustained responders to IFN remain well and aviremic through a mean follow-up period of 32 months after the treatment, and 4 of them have successfully undergone kidney transplantation. The incidence of allograft rejection did not increase in these patients.

#### Adverse Reactions

Overall, the ESRD patients tolerated well the IFN monotherapy at the conventional standard dose for treatment of hepatitis C. Seven of the 9 patients experienced some flu-like symptoms, with fever, myalgia and easy fatigability being the most persistent symptoms that lasted for 3–4 months. While the baseline blood counts of all



**Fig. 1.** Influence of IFN treatment on peripheral blood counts in patients with chronic hepatitis C who had ESRD.



**Fig. 2.** Influence of IFN treatment on peripheral blood counts in patients with chronic hepatitis C who had hemophilia.

three cell lines were normal (table 1), there were statistically significant decreases in cell counts affecting all lineages during the treatment (fig. 1). However, transient attenuation of the IFN dose was required in only 1 patient. None developed sepsis related to neutropenia. All patients were on routine subcutaneous erythropoietin before and throughout the course of IFN treatment. Subclinical and reversible thyroid dysfunction was found in scheduled blood tests in 3 of the 9 patients. Two patients developed elevated levels of thyroid-stimulating hormone on and off, while their free thyroxine (T<sub>4</sub>) levels remained normal throughout treatment. The other patient already had hypothyroidism before the treatment and required an increased dose of L-thyroxine replacement towards the end of the course of IFN treatment, as thyroid-stimulating hormone levels increased despite the usual maintenance treatment. However, the patient was asymptomatic of his hypothyroid state even before he had received an increased dose of L-thyroxine.

#### Patients with Hemophilia

Six patients with hemophilia, all men, with a mean age of 40 years, received IFN during a mean period of 53 weeks. Three patients were infected with HCV genotype 1b (including 1 having a mixed infection with HCV genotype 4a), 1 with HCV genotype 1a and 2 others with HCV genotype 3 (1 with genotype 3a infection and the other having a mixed infection with genotypes 3 and 4) (table 1). All of them were negative for antibody to human immunodeficiency virus type 1. Their mean serum levels of ALT and AST at the baseline were 190 and 117 U/l, respectively. No liver biopsy was performed on any of the 6 patients treated. None had clinical evidence of liver cirrhosis or hepatic decompensation.

#### Treatment Outcome

Of the 6 patients treated with IFN, 2 did not respond to it, with HCV RNA persisting in serum despite treatment. The other 4 patients gained virological and biochemical responses at the end of treatment and accomplished normalization of ALT levels and clearance of HCV RNA from serum. Unfortunately, 2 patients relapsed 4 and 6 weeks after the end of treatment. Therefore, sustained response was achieved in only 2 of the 6 (33%) patients who were followed up for 38 and 44 months after the treatment, respectively.

#### Adverse Reactions

All 6 patients treated with IFN complained of fever that lasted 6 weeks at the longest. The other two most common complaints were myalgia and easy fatigability, each affecting 4 of the 6 (67%) patients. In addition, there was a statistically significant drop in the mean hemoglobin level and a decrease in white cell and platelet counts during treatment, although they did not incur any clinical consequences (fig. 2). There was no increase in the bleeding diathesis during the treatment. No serious adverse events were documented in this cohort of patients.

#### Discussion

It is well known that chronic hepatitis C in patients with ESRD, if left untreated, increases their mortality and morbidity, with [5–7] or without kidney transplanta-

tion [8, 9]. However, as there is a substantial risk of allograft failure during IFN treatment of chronic hepatitis C in patients with kidney transplantation [10, 11], it makes sense to treat chronic hepatitis C before transplantation, with the aim of achieving sustained virological response (SVR) in patients with ESRD.

Earlier studies suggested poor SVR and high incidence of adverse events associated with IFN treatment of chronic hepatitis C in patients with ESRD [12, 13]. However, recently reported clinical data seem more encouraging [14, 15], and our findings are in agreement with these reports. Longer duration (12 instead of 6 months) and the use of the full dose, rather than attenuated doses, of IFN would contribute to an improved therapeutic outcome. Fortunately, our patients tolerated the full course of IFN treatment fairly well. None, with the exception of 1 patient, required temporary attenuation of the IFN dose. It is likely that the motivation of patients to receive kidney transplantation determines the tolerability for adverse symptoms. In Singapore, in view of a shortage of organ donors and a less favorable outcome associated with liver diseases after kidney transplantation, the absence of viremia with HCV has determined chances of patients on the waiting list for transplantation for receiving an allograft. This background may have been an important motivating factor and incentive for the treatment compliance. In addition, provision with adequate moral supports along with effective treatments, such as erythropoietin, during the course of treatment is probably just as important as the active treatment with IFN itself.

Unfortunately, we did not gain the same success in treatment of chronic hepatitis C in patients with hemophilia as we did in those with ESRD. However, the limited response accomplished was consistent with that reported in other published series in the Western populations, even with combined IFN and ribavirin [16–18].

Following the therapeutic success with the advent of pegylated (peg)-IFN, taken together with the established efficacy of combination therapy with ribavirin and IFN in the treatment of chronic hepatitis C in adult patients without high risks, we should explore possible benefits of these newer modalities of treatment on our subgroups of patients with ESRD or hemophilia. While ribavirin is generally not recommended for patients with ESRD, its use has been attempted by some investigators. These studies involving a small number of patients have proven the feasibility of ribavirin usage, but with limited therapeutic success [19, 20]. As for the usage of peg-IFN in patients with ESRD, it seems that we need to take into consideration the molecular sizes of various available

peg-IFN, in relation to diverse ranges of permeability and the pore size of dialysers [21], in planning therapies with it. Given the current contradictory data [22, 23], not only the safety of the use of peg-IFN in patients with ESRD is required to be established, we also need to ascertain if SVR is influenced by different pharmacokinetics of various peg-IFN preparations in patients who are on maintenance hemodialysis.

## Conclusion

Treatment with subcutaneous IFN- $\alpha_{2a}$  at a dose of 3 million units three times per week for 12 months gained SVR in 78% of patients with chronic hepatitis C and ESRD. The treatment was well tolerated and patients remained well after they received renal transplantation later on. However, a similar therapeutic regimen yielded poorer response, with only 33% accomplishing SVR in patients with chronic hepatitis C and hemophilia. Large-scale, randomized, controlled studies with newer agents, such as peg-IFN used singly or in combination, need to be conducted to evaluate the potential of various therapeutic regimens in these subgroups of patients for the purpose of establishing treatment guidelines.

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