Very-Low-Dose Pegylated Interferon α2a Plus Ribavirin Therapy for Advanced Liver Cirrhosis Type C: A Possible Therapeutic Alternative without Splenic Intervention

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Abstract
Despite the recent progress in interferon (IFN) therapies for chronic hepatitis C, liver cirrhosis remains refractory. One of the major obstacles to successful IFN therapy is low platelet count. Currently, splenic interventions, such as partial splenic embolization (PSE) or surgical splenectomy, have been applied effectively and make standard IFN therapy possible. However, there may be a group of patients with low platelet counts who can be treated without splenic intervention. We here report two patients with advanced type C liver cirrhosis who were successfully treated using very-low-dose pegylated interferon α2a plus ribavirin. One patient had a very low platelet count (2.5×10^4/µl) due to splenomegaly before treatment. However, pretreatment serum HCV titers were low in both patients and early viral responses were obtained in both. Because PSE or splenectomy may still have some safety concerns, this attenuated IFN treatment protocol can be an alternative therapeutic option for patients with advanced type C liver disease, but good virological factors for sustained virological response.

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Introduction

Recent progress in the treatment of chronic hepatitis C has been outstanding [1–4]. Pegylated interferon α (PEG-IFN) was developed in order to ensure sustained exposure with once-weekly dosing and offers improved convenience with a better adverse effects profile. Ribavirin accelerates clearance of virus by IFN and improves treatment outcomes. PEG-IFN plus ribavirin treatment can currently achieve sustained virological response (SVR) even in about 50% of refractory patients with genotype 1b and high viral titers [2–4]. However, the SVR rate for PEG-IFN plus ribavirin treatment remains low in patients with liver cirrhosis [5–8]. In addition, a high rate of severe adverse effects is seen, and discontinuation of treatment reportedly occurs in about 10–25% of patients [5–7]. There is thus a conflict between the high risk of hepatocarcinogenesis and liver failure, which are urgent indications for therapy, and low therapeutic outcome.

One of the major obstacles to therapy in patients with type C hepatic cirrhosis are the low platelet counts which IFN treatment inevitably lowers further. Partial splenic embolization (PSE) has recently become more commonly applied to increase platelet counts and make standard IFN treatment feasible [9–15], and there has been much progress in the procedure, ensuring that it can be performed safely [9–13]. However, because of the level of skill required, it cannot be performed with equal safety in every facility. In addition, certain risks of severe complications remain [9, 14, 15]. Thus there is an urgent need for a new IFN protocol for the specific subgroup of patients that can possibly avoid the use of medical or surgical splenic intervention.

We performed such an attenuated protocol in two advanced liver cirrhosis patients, one with thrombocytopenia and one with neutropenia. We achieved SVR due to low HCV titers before treatment, and the rapid decrease in HCV titers after start of the therapy supported the continuation and completion of treatment.

Patient 1

A 61-year-old man had been followed in the outpatient clinic of Niigata University from 2003 with a diagnosis of type C liver cirrhosis. Ascites was identified in 2005, but was resolved with diuretics. Clinical data as of November 2007 are shown in **table 1**. He had low serum albumin levels. Thrombo- and leucocytopenia due to splenomegaly were also observed. Gastrointestinal fiberscopy showed a mild esophageal varix. HCV markers showed group 1 and a low titer (36 kIU/ml) according to qualitative Amplicore HCV Test, v.2.0. (Roche Molecular Systems, Branchburg, N.J., USA). A very low platelet count (2.5×10^4/μl) prevented regular-dose-based IFN therapy. Considering the possibility of severe side effects of PSE or surgical splenectomy, very low doses of PEG-IFNα2a (Pegasys; 30 μg = 1/3 of 90 μg vial, Roche Laboratories, Nutley, N.J., USA) were started after obtaining informed consent, particularly regarding the risks of hemorrhagic side effects. This dose of IFN was administered with an interval of 10–14 days (total 23 times, total dose 690 μg), and platelet count did not reach <2.5×10^4/μl. HCV RNA became negative (quantitative Amplicor Test, Roche Molecular systems) at 4 weeks after starting IFN, and then ribavirin (600 mg/day; Copegus, Roche Laboratories) was initiated. Laboratory data after the start of therapy are shown in **figure 1**. Therapy (9 months in total) was continued until computed tomography revealed a solitary HCC (S7, 13 mm). HCV RNA remained negative both during therapy and 24 weeks after the end of treatment, thus confirming SVR. HCC was successfully ablated by radiofrequency ablation and no recurrence has been identified to date (March 2010).

Patient 2

A 67-year-old woman had been followed in the outpatient clinic of Niigata University since 1998 with a diagnosis of type C liver cirrhosis. Surgical resection of HCC (S3, 20 mm) was performed in 2003 and ascites were treated using diuretics in 2006. She was very interested in the progress of treatment for

hepatitis C, particularly with regard to PEG-IFN, and she requested therapy. As she had a low titer of HCV (110 kIU/ml), we started IFN therapy from September 2007 with a dose of 90 μg PEG-IFNα2a (Pegasys). As neutrophil count fell to <750/μl the following week, the dose was reduced to 45 μg and then to 30 μg in November. Serum HCV RNA decreased to <5 kIU/ml at 4 weeks and became negative 8 weeks after starting IFN. Ribavirin (Copegus, 200 mg/day) was added from November to facilitate viral clearance. Weekly treatment with PEG-IFN (11 months in total) was continued (total dose 1,475 μg) until computed tomography revealed a solitary HCC (S7, 10 mm). The HCC was successfully ablated using radiofrequency ablation and no recurrences have yet been identified (March 2010). HCV RNA remained negative both during therapy and 24 weeks after the end of treatment, thus indicating SVR.

Discussion

We present two patients with advanced liver cirrhosis due to HCV who were successfully treated with very-low-dose administration of PEG-IFNα2a plus ribavirin. The main reason we decided to treat these patients was the low titer of HCV, which is a good viral condition for obtaining SVR [1].

Patient 1 had severe thrombocytopenia due to splenomegaly. The pretreatment platelet count (2.5×10^4/μl) was even below the standard level for discontinuation of PEG-IFN plus ribavirin (5.0×10^4/μl). Currently, PSE or surgical resection is typically performed in order to raise the platelet counts, then enabling standard IFN therapy [9–13]. The increase in platelet counts after PSE may also improve the SVR rate in chronic hepatitis C patients with thrombocytopenia [11–13]. However, this procedure is associated with serious complications, such as splenic abscess, that are potentially life-threatening [14, 15]. It should also be noted that the long-term effects of PSE and surgical splenectomy remain unknown [10]. We therefore selected a very low dose of PEG-IFN rather than splenic intervention, after obtaining careful informed consent from the patient. Fortunately, platelet count did not decrease significantly during treatment, and the treatment was well tolerated without any significant side effects.

Even with the recent progress of predicting IFN treatment outcome, it remains difficult to perfectly predict SVR [16]. The response-guided concept is thus predominant [2–4]. Virus decrease during IFN treatment can give patients motivation to adhere to therapy, while discontinuation of therapy to avoid a handful of adverse effects and therapeutic costs is possible when negative predictive value is high. Currently, early viral response (negative HCV RNA after 12 weeks of therapy) is the most commonly used marker to determine the outcome of IFN therapy [17]. Fortunately, HCV RNA in the sera became negative shortly after the start of treatment (4 weeks in the patient 1 and 8 weeks in patient 2). These good responses enabled the continuation of treatment and predicted the possible achievement of SVR. In other words, discontinuation of treatment should always be considered if viral decrease is insufficient. Initially, we did not administer ribavirin, deciding instead to monitor viral response to PEG-IFN, but we added ribavirin after a good viral response was obtained, and this might have accelerated viral clearance in the patients. We administered PEG-IFNα2a, which is normally used weekly, with a 10- to 14-day interval in patient 1. As PEG-IFNα2a has a longer half life than PEG-IFNα2b [18], significant effects were seen, despite the longer interval between doses.

Unfortunately, both patients developed complicating HCC. It remains uncertain whether the SVR obtained in the patients will benefit their prognosis. HCC too small to be visualized on imaging might have been present at the start of IFN treatment. If the primary goal of IFN treatment is the prevention of HCC occurrence, this was not achieved in either patient. However, SVR after HCC ablation is reported to improve

prognosis in patients with HCC associated with hepatitis C [19–22]. Moreover, viral eradication suppresses the hepatic inflammation, lowers ALT levels and maintains hepatic reserve function. To date (March 2010), both patients have been free from HCC recurrence and quality of life has remained satisfactory.

In conclusion, an attenuated PEG-IFN protocol for patients with good viral parameters for SVR without splenic intervention should be the subject of a clinical trial in order to determine the cost-benefit balance between the risk of splenic intervention, prediction of IFN therapy outcome, and adverse effects, finally examining whether there are actual long-term clinical benefits. Careful and strict monitoring of both the antiviral effects and the appearance of severe adverse effects is absolutely necessary.

**Table 1.** Laboratory data at the start of PEG-IFNα2a therapy

Patient 1			
WBC	1,700/µl	TP	7.0 g/dl
Neutro	71.1%	Alb	3.2 g/dl
Eosino	2.4%	T.Bil	1.9 mg/dl (D 0.1, ID 1.8)
Baso	0.6%	AST	67 IU/l
Lympho	20.0%	ALT	70 IU/l
Mono	5.9%	ALP	261 IU/l
RBC	396×10^4/µl	γ-GTP	55 IU/l
Hb	10.8 g/dl	LDH	233 IU/l
Plt	2.5×10^4/µl	ChE	113 IU/l
		BUN	16 mg/dl
HBsAg	–	Cr	0.6 mg/dl
HCV RNA	36 kIU/ml	T.Chol	158 mg/dl
HCV serogroup	1	FBS	82 mg/dl
AFP	7.1 ng/dl		
Patient 2			
WBC	3,170/µl	TP	8.4 g/dl
Neutro	24.0%	Alb	2.6 g/dl
Eosino	2.5%	T.Bil	0.7 mg/dl (D 0.1, ID 0.6)
Baso	0.3%	AST	39 IU/l
Lympho	63.5%	ALT	67 IU/l
Mono	9.7%	ALP	338 IU/l
RBC	391×10^4/µl	γ-GTP	17 IU/l
Hb	10.1 g/dl	LDH	304 IU/l
Plt	15.8×10^4/µl	ChE	84 IU/l
		BUN	15 mg/dl
HBsAg	–	Cr	0.6 mg/dl
HCV RNA	110 kIU/ml	T.Chol	131 mg/dl
HCV serogroup	1	FBS	88 mg/dl
AFP	5 ng/dl		

Fig. 1. Changes in laboratory data (ALT, WBC, platelets) for patients 1 and 2 after the start of PEG-IFNα2a. The vertical axis shows the values for ALT and WBC (left) and platelets (right).

Patient 1
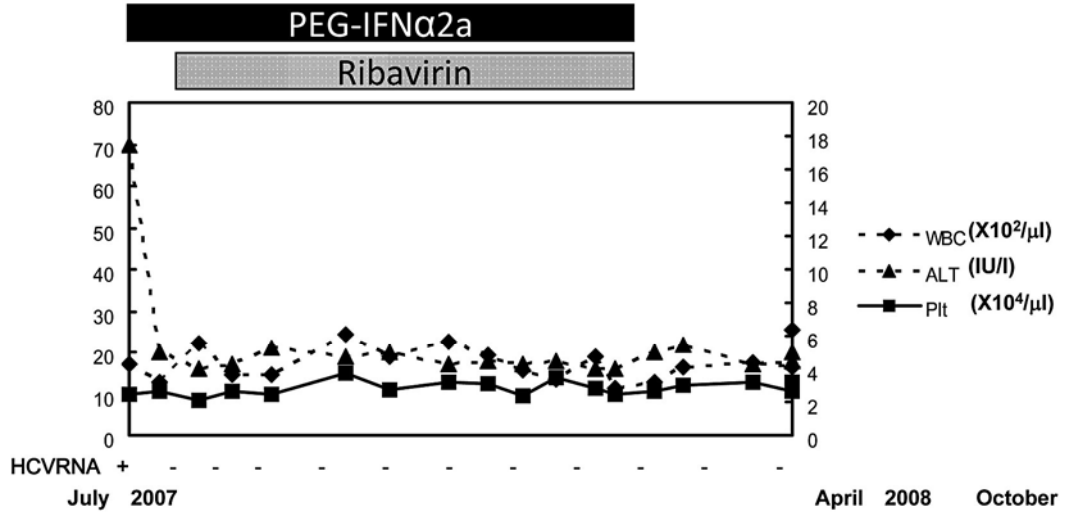
Patient 2
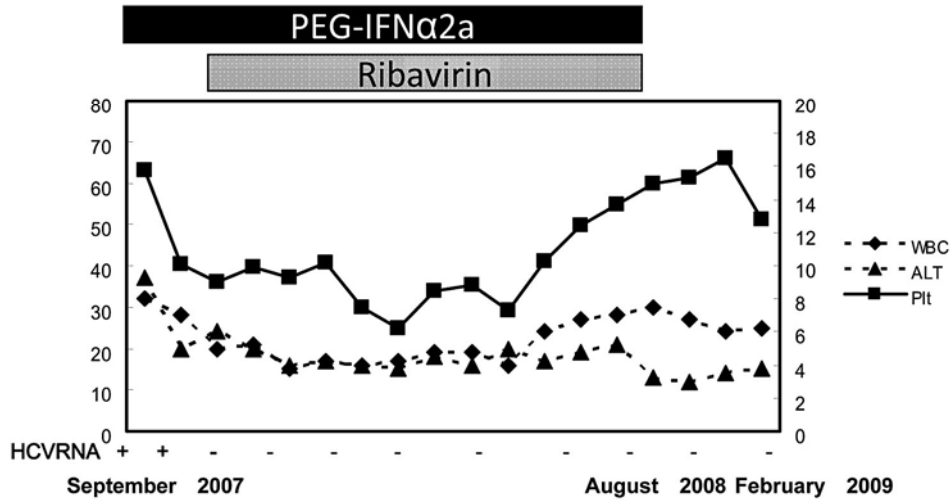
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