Pegylated interferon-alfa plus ribavirin therapies for chronic hepatitis C

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ABSTRACT

Until HCV NS3/4A protease inhibitors become available at the end of 2011, the combination pegylated-interferon (PEG-IFN)-alfa and ribavirin (RBV) will remain the standard treatment for chronic hepatitis C patients. In some hepatitis C virus-infected patients, PEG-IFN plus RBV treatment against HCV should continue to be used because of side effects of new drugs such as anemia. Our Japanese experiences should provide new information for the treatment of chronic hepatitis C.

Keywords: *Direct-acting antiviral agents (DAA), HCV, pegylated interferon, ribavirin, standard of care (SOC)*

INTRODUCTION

Hepatitis C virus (HCV) is a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) in Japan[1] as well as in the U.S.[2, 3] and in European countries.[4, 5] Chronic hepatitis C is also a major reason for liver transplantation. Until HCV NS3/4A protease inhibitors become available in the near future,[6] the combination pegylated-interferon (PEG-IFN)-alfa and ribavirin (RBV) is the standard of care (SOC) for chronic hepatitis C patients, except in situations where there are contraindications to RBV. Before treatment, genotype identifications are clinically important because genotypes 1 and 4 are more resistant than genotypes 2 and 3.[7] This treatment for 48 weeks attains only ~ 50 % sustained virological response (SVR) in patients with HCV genotype 1 and high viral loads, who in our study were mostly null-responders or relapsers. Among HCV genotypes other than genotype 1, especially genotype 4 patients showed only 40 – 70 % SVR by this 48-week treatment.[6] When patients with genotypes 2- and 3-patients are adequately treated with a 24-week course, SVR rates approach 80 %.[8] Throughout the four main islands of Japan, the prevalence of genotypes 1 and 2 is similar: HCV genotypes 1 and 2 are ~ 70 % and ~ 30 %, respectively.[9] In Asian countries, genotypes 1 - 6 are seen.[10] There are also important issues to clarify regarding the benefit of a 72-week extended duration therapy in genotype 1-slow responders and an adequate shortened duration therapy in genotype 1- and genotype 2/3-rapid responders.[11] Although no vaccines for HCV are available yet, HCV NS3/4A protease inhibitors are expected to be available in the near future. In this review, we have documented the response patterns in PEG-IFN-alfa plus RBV therapies from our experiences. We believe that these findings will be useful while making decisions about whether protease inhibitors should be added or not.

Pegylated-interferon (PEG-IFN)

IFN has a very short half-life, must usually be administered multiple times per week, and is associated

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with significant side effects. "PEGylation" is a process whereby the inert polymer, polyethylene glycol (PEG), attached to a protein, resulting in the properties of PEGylated proteins in a manner that significantly extends the half-life, reduces immunogenicity and enhances anti-viral activity. PEG-IFNs have a significantly prolonged half-life and improved SVR when compared with standard IFN.[12] There are two kinds of PEG-IFNs. Covalent attachment of a 40-kd branched-chain PEG moiety to IFN alfa-2a results in a compound (PEG-IFN alfa-2a) that has sustained absorption, a slower rate of clearance, and a longer half-life than unmodified IFN alfa-2a.[13] PEG-IFN alfa-2b consists of a conjugate of straight-chain PEG (molecular weight, 12-kd) and IFN alfa-2b in a 1:1 ratio. The main effects of pegylated proteins are to delay clearance and prolong half-life, allowing for less-frequent dosing and possibly increased efficacy.[14,15] These two compounds differ markedly in size, structure, site of attachment of the PEG moiety, and type of bond involved in pegylation, which ultimately confer different pharmacokinetics and biological activity.[16] In patients infected with HCV genotype 1, the rates of sustained virological response and tolerability did not differ significantly between the two available PEG-IFN plus RBV regimens,[17,18] although there are several disputes.[19, 20]

IFN lambda 1 [interleukin-29 (IL-29)] is a type III IFN that produces intracellular responses similar to those of IFN alfa but in fewer cells because of differences in the receptor distribution pattern, and this could potentially result in improved safety profiles. Now, the pegylated form of IFN lambda 1 is under development (Table 1). Albumin is a natural carrier molecule with a long half-life. Albinterferon alfa-2b (albIFN) is a single polypeptide comprising human IFN alfa-2b genetically fused to human albumin and is also under clinical trials (Table 1).

Ribavirin (RBV)

The synthetic guanosine analogue RBV (1-ß-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) has shown action against a range of DNA and RNA viruses, and is available in oral form.[21] RBV monotherapy does not have strong anti-HCV activities,[22, 23] but when combined with PEG-IFN, RBV can improve the treatment response. There are several mechanisms of RBV (Table 2). It has been reported that RBV acts as a mutagen, resulting in error catastrophe,[24-26] and inhibits the HCV RNA-dependent RNA polymerase.[27] RBV is an inhibitor of the inosine monophoshate dehydrogenase (IMPDH) enzyme, resulting in depletion of intracellular guanosine pools, which are needed for efficient viral replication.[28, 29] RBV has also been shown to stimulate a T helper 1 antiviral response that favours viral clearance.[30] Thomas et al.[31] reported that RBV potentiates IFN action by augmenting IFN-stimulated gene (ISG) induction in HCV. Given the increased response rates to therapy observed with PEG-IFN compared with standard IFN, it is natural to assess the combination of PEG-IFN-alfa plus RBV.[8] It has been shown that equilibrative nucleoside transporter

Table 1 Comparison of pegylated-interferon (PEG-IFN), standard interferon and so on.

Drugs	Type of IFN	Fusion protein(s)	Half-life/ administration
Natural IFN alfa	IFN alfa	-	~6-hour/ 3-6MU thrice weekly
IFN alfa-2a	IFN alfa-2a	-	~6-hour/ 6MU thrice weekly
IFN alfa-2b	IFN alfa-2b	-	~6-hour/ 6MU thrice weekly
IFN beta	IFN beta	-	~6-hour/ 6MU (i.v.) thrice weekly
PEG-IFN alfa-2a	IFN alfa-2a	branched-chain PEG (40-kd)	72.4-hour/ 45-180μg per weekly
PEG-IFN alfa-2b	IFN alfa-2b	straight-chain PEG (12-kd)	~45-hour/ 0.5-1.5μg/kg weekly
Albumin IFN alfa-2b	IFN alfa-2b	albumin (66-kd)	~20 days /900~1,200μg q2wk
PEG-IFN lambda-1	IFN lambda-1	linear-chain PEG (20-kd)	~4-days /1.5μg/kg weekly

MU, million units; i.v., intravenously; IFN-lambda-1, interleukin-29 (IL29);q2wk, every 2 weeks.[85-88]

Table 2 Mechanism of action ribavirin (RBV).

RBV acts as a mutagen, resulting in error catastrophe
RBV inhibits the hepatitis C virus RNA-dependent RNA polymerase (HCV NS5B)
RBV is an inhibitor of the IMPDH enzyme,
resulting in depletion of intracellular guanosine pools
RBV has an effects on an immune system
RBV potentiates IFN action

NS5B, non-structural protein 5B; IMPDH, inosine monophoshate dehydrogenase.

1 (ENT1), ENT2, concentrative nucleoside transporter 2 (CNT2), and CNT3 can transport RBV but CNT1 cannot.[32] It has also been shown that their mRNAs are expressed human liver. Fukuchi et al.[33] reported that ENT1, but not ENT2 or CNTs, is a major RBV uptake transporter in human hepatocytes.

One of the side effects of RBV is anaemia, which could make heart disease worse. RBV also has a teratogenic effect. Female patients and the female partners of male patients should avoid getting pregnant. Clinicians should always pay attention to these side effects.

PEG-IFN monotherapy for chronic hepatitis C

Three large randomized controlled trials of comparison monotherapy with PEG-IFN and standard IFN were performed to determine their efficacies.[34-36] Response rates to monotherapy with PEG-IFN were 23 ~ 39 % when 52 ~ 70 % had genotype 1 in these studies. On the other hand, PEG-IFN-alfa-2a without RBV induces SVR in some transplant recipients with recurrent hepatitis C[37] or in some dialysis patients infected with HCV.[38] In patients with cirrhosis, IFN, either alone or in combination with ribavirin, has been used cautiously, largely because it may exacerbate existing neutropenia and thrombocytopenia.[35] In general, PEG-IFN-alfa-2a monotherapy was better tolerated than the combination with RBV, although PEG-IFN-alfa-2a monotherapy was associated with a ~ 20 % rate of SVR in patients infected with HCV genotype 1.[34] However, in some cases, and especially in older patients, RBV cannot be administered because of possible side effects, including severe anemia. As patients tend to be older in Japan compared to Western countries, more therapeutic options are needed.[39] According to our experiences, PEG-IFN-alfa-2a monotherapy (180 μg/week) for 24 weeks or less was possibly sufficient for treating selected patients with HCV genotype 2, especially those with a low viral load and obtaining rapid virological response (RVR, negative for HCV RNA by week 4 of treatment) (data not shown). For some genotype non-1 patients, PEG-IFN-alfa-2a monotherapy might be useful leading to SVR. Prolonged therapy of advanced chronic hepatitis C with low-dose PEG-IFN did not reduce the rate of disease progression.[40] Long-term PEG-IFN does not reduce the incidence of HCC among patients with advanced hepatitis C who have not achieved SVRs,[41] and is associated with excess overall mortality, which was primarily due to non-liver-related causes among patients with bridging fibrosis.[42]

Combination PEG-IFN with RBV

The main goal of treatment in chronic hepatitis C is the prevention of cirrhosis and HCC. Eradication of HCV by IFN treatment reduced the risk for HCC.[43-45] RVR, defined as undetectable HCV RNA at week 4 of treatment, predicts a high likelihood of achieving SVR.[46, 47]

We investigated 76 patients infected with HCV of genotype 1 patients who were treated with PEG-IFN-alfa 2a plus RBV for 48 weeks. 36.8 % had SVR, 17.1 % did not respond, and 21.0 % discontinued treatment due to side effects. In the 46 treatment-naive patients, 45.6 % had SVR, 21.7 % relapsed, 6.5 % did not respond, and 26.0 % discontinued treatment due to side effects. In the 30 previously treated patients, 23.3 % had SVR, 10.0 % relapsed, 53.3 % did not respond, and 13.3 % discontinued treatment due to side effects.[47] Extending the treatment duration from 48 to 72 weeks in genotype 1-infected patients with late virological response improved SVR.[48, 49] However, the proportion of patients with a late virological response that might benefit from a 72-week therapy appears to be small, so specifically-targeted antiviral therapies against HCV (STAT-C) or direct-acting antiviral agents (DAAs) should be considered for such patients.[6, 50]

The current SOC for patients infected with genotype 2 HCV is the combination of PEG-IFN plus RBV for 24 weeks.[6] We investigated 138 consecutive Japanese HCV-positive patients and 21, 97 and 20 patients were treated with PEG-IFN-alfa 2b plus RBV for 16, 24 and 48 weeks, respectively.[51] The overall SVR rate was 82.6 %: treatment-naive patients, 86.4 %; patients with history of previous treatment, 71.4 %. Patients treated for 16, 24 and 48 weeks obtained SVR rates of 66.6 %, 86.5 % and 80.0 %, respectively. More accuracy of patient selection may be needed to allow shortening of the combination treatment.[52, 53]

Special situations and host factors influencing treatment outcomes

Anemia is more common in those with human immunodeficiency virus (HIV) co-infection,[54] renal insufficiencies,[38, 55] tharassemia,[56] solid-organ transplants[57, 58] or cirrhosis.[59, 60] Monotherapy is considered the first-line therapy in these patients on a case-by-case basis. Attention should also be paid to children,[61] pregnant women[62] and the elderly.[39] The combination of antiretroviral (ARV) therapies introduced at the end of the 1990s profoundly changed the natural history of HIV infection. Liver diseases are one of the three primary causes of 'non-AIDS-related' death in people infected with HIV.[54] HCV infection is also a major health problem in patients with end-stage renal disease (ESRD). Approximately one-third of the patients can achieve a SVR after standard IFN or PEG-IFN monotherapy. ESRD patients infected with HCV should be encouraged to receive antiviral therapy.[55] Patients with β-thalassemia major receive chronic blood transfusions and have an increased prevalence of chronic HCV infection. The prevalence of chronic hepatitis C infection ranges from

25 to 75 % in thalassemic patients.[56] HCV infection recurs after liver transplantation and progression is accelerated in the graft. It is well-known that severe hepatitis C recurrence (cholestatic hepatitis) and forms with rapid fibrosis progression have a poor survival retransplantation. To avoid retransplantation, we prevent severe hepatitis C recurrence by antiviral therapies.[58] We should treat patients with compensated cirrhosis except when included on the transplant list.[59] It is generally accepted that SVR should be obtained when cirrhotic patients are treated.[60] RBV introduces mutations into HCV genomes.[26] Clinicians should not use RBV for pregnant women and should pay attention to its use in children. We also reported that the occurrence of HCC was not a rare event during and immediately after antiviral treatment in HCV-positive patients and a regular check for the possible development of HCC is needed especially in elderly patients.[39]

IL28B genotypes and treatment outcomes

Recent genome-wide association studies (GWASs) of patients infected with HCV showed a strong association between the single nucleotide polymorphisms (SNPs) close to the gene encoding IFN lambda-3 (IL28B) and SVR in HCV genotype 1-infected patients treated with PEG-IFN-alfa plus RBV.[63] The distribution of these SNPs might account for the differences in treatment response among East Asians, Europeans and Africans.[64-67] We also determined IL28B rs8099917 SNP and revealed that the proportion of null virological responders in the combined TG/GG group was significantly higher than that in the TT group, suggesting that minor allele is one of the important factors playing crucial roles in IFN resistance in HCV genotype 1 patients.[63] It was reported that Taiwanese patients with CHC receiving PEG-IFN plus RBV therapy have a lower daily viral production rate than Western patients, and the rs8099917 TT genotype may contribute to the increased viral clearance rate and better virological responses in these patients.[68] The reduction of HCV RNA after 7 days of therapy was more pronounced in patients with CC(rs12979860) or TT(rs8099917) than in patients carrying TT(rs12979860) or GG(rs8099917), respectively.[69] Concomitant assessment of pretreatment IFN-gamma inducible protein-10 (IP-10) and IL28B-related SNPs augments the prediction of the first phase decline in HCV RNA, RVR, and the final therapeutic outcome.[70] A combined assessment of these SNPs in conjunction with other response predictors may better predict the outcome in difficult-to-treat patients.[69] IL28B gene testing may identify patients carrying genotype 2 or 3 who could benefit from extended treatment.[71] The rs8099917 TT genotype is significantly independent predictive of RVR, which is the single best predictor of SVR, in Asian HCV genotype 2 patients.[72]

To improve the treatment response

The quantitation of serum levels of HCV RNA in chronic hepatitis C has been regarded as providing one of the most important indicators for the outcome of IFN-based therapy because SVR can be expected in patients with a low virus load.[73] A RVR predicts a high likelihood of achieving SVR.[46] Early virological response (EVR), in which HCV RNA disappears [complete EVR (cEVR)] or shows 2-log-reduction at 12 weeks [partial EVR (pEVR)], is the most accurate predictor of not achieving SVR.[46, 74,75] However, to determine whether the patient's treatment duration could be shortened, RVR is more important than EVR for predicting SVR, and patients with RVR have a good chance of achieving SVR and thus may not need newer antiviral therapy.[6] In the near future, we will use DAAs with and later without IFN HCV RNA testing will be done at weeks 1 - 4, and HCV RNA negativity will be the preferred parameter for determining the duration of therapy.[47] The utilization of both undetectable RNA and < 1.7 Log IU/mL HCV RNA by COBAS TaqMan HCV test, one of highly sensitive methods, is useful and could predict SVR and non-SVR patients with greater accuracy.[47] To obtain better SVR rates, better RVR rates are needed in the present therapies. IFN reduced the risk for HCC, especially among patients with SVR.[76, 77] It is important to accurately judge whether the patient obtained SVR or not.

Future prospects for anti-HCV therapies

At the end of 2011, telaprevir and boceprevir, which are potent oral protease inhibitors that bind to the HCV genotype 1 non-structural 3 (NS3) active site, will be available for use for HCV treatment. [6, 78-81] Telaprevir with PEG-IFN plus RBV, as compared with PEG-IFN plus RBV alone, was associated with significantly improved SVR rates in HCV genotype 1 treatment-naive patients, with only 24 weeks of therapy administered in the majority of patients.[81] The addition of boceprevir to SOC, as compared with SOC alone, significantly increased the SVR rates in HCV genotype 1 treatment-naive patients, too.[79] The rates were similar with 24 weeks and 44 weeks of boceprevir.[79] For retreatment of HCV infection, telaprevir[80] combined with SOC or boceprevir[78] combined with SOC improved SVR rates. Almost all STATs-C and DAAs have to be used with combination of PEG-IFN plus RBV (Table 3).[6, 78-81] Many patients are either unsuitable for or decline current treatment because of the significant side-effects associated with PEG-IFN plus RBV therapies, including those with decompensated cirrhosis or severe psychiatric illness.[82] It is hoped that the combination of multiple DAAs which target different steps of HCV replication should provide a IFN-free treatment regimen.[83, 84]

Table 3 **Treatments and their duration for chronic hepatitis C**

Treatment	Duration (weeks)	Naïve	Genotype
PEG-IFN monotherapy[89]	24	Yes	2/3
PEG-IFN plus RBV	24	Yes	2/3
PEG-IFN plus RBV	48	No	2/3
PEG-IFN plus RBV	48	Yes	1
PEG-IFN plus RBV	48	No (relapser)	1
PEG-IFN plus RBV	72	Yes (LVR)	1
PEG-IFN, RBV plus Telaprevir[68,69]	24～48	Any	1
PEG-IFN, RBV plus Boceprevir[66,67]	32～48	Any	1

PEG-IFN, pegylated interferon; RBV, ribavirin; Naive, treatment-naive; LVR, late virological responder.

CONCLUSIONS

STAT-C and DAAs such as telaprevir and boceprevir should become available near the end of 2011. [6, 78-81] Rates of anaemia were higher among these drug containing regimens, and many patients required erythropoietin treatment, although these drugs added to PEG-IFN plus RBV lead to high rates of SVR in difficult-to-treat patients compared with SOC. Until we have new therapies with more effective outcomes and better-tolerated side effects, PEG-IFN plus RBV treatment should be used in certain patients infected with HCV.

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ERRATUM:

Case report: Bilateral eventration of sciatic nerve by Lalit et al.

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Figure 3 was inadverently typed as figure 2.

In fig 3, please read L1 as L5