

Safety of interferon β treatment for chronic HCV hepatitis

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Abstract

Hepatitis C is a major cause of liver-related morbidity and mortality worldwide. In fact, chronic hepatitis C is considered as one of the primary causes of chronic liver disease, cirrhosis and hepatocellular carcinoma, and is the most common reason for liver transplantation. The primary objectives for the treatment of HCV-related chronic hepatitis is to eradicate infection and prevent progression of the disease. The treatment has evolved from the use of α -interferon (IFN α) alone to the combination of IFN α plus ribavirin, with a significant improvement in the overall efficacy, and to the newer PEG-IFNs which have further increased the virological response, used either alone or in combination with ribavirin. Despite these positive results, in terms of efficacy, concerns are related to the safety and adverse events. Many patients must reduce the dose of PEG-IFN or ribavirin, others must stop the treatment and a variable percentage of subjects are not suitable owing to intolerance toward drugs. IFN β represents a potential therapeutic alternative for the treatment of chronic viral hepatitis and in some countries it plays an important role in therapeutic protocols. Aim of the present paper was to review available data on the safety of IFN β treatment in HCV-related chronic hepatitis.

The rates of treatment discontinuation and/or dose modification due to the appearance of severe side effects during IFN β are generally low and in several clinical studies no requirements for treatment discontinuation and/or dose modifications have been reported. The most frequent side effects experienced during IFN β treatment are flu-like syndromes, fever, fatigue and injection-site reactions. No differences in terms of side-effect frequency and severity between responders and non-responders have been reported. A more recent study, performed to compare IFN β alone or in combination with ribavirin, confirmed the good safety profile of both treatments. Similar trends of adverse event frequency have been observed in subpopulations such as patients with genotype-1b HCV hepatitis unresponsive to IFN α treatment or with HCV-related cirrhosis and patients with acute viral hepatitis. If further studies will confirm the efficacy of combined IFN β and ribavirin treatment, this regimen could represent a safe and alternative therapeutic option in selected patients.

INTRODUCTION

Hepatitis C is a major cause of liver-related morbidity and mortality worldwide and represents a significant public health problem^[1]. In fact, chronic hepatitis C is considered as one of the primary causes of chronic liver disease, cirrhosis and hepatocellular carcinoma, and is the most common reason for liver transplantation^[2]. Based on the increased knowledge surrounding the natural history of the disease, the primary objectives for the treatment of hepatitis C virus (HCV)-related chronic hepatitis are to eradicate infection and prevent progression to cirrhosis and thereby preventing complications associated with end-stage liver disease^[3,4]. The treatment of HCV has evolved from the use of a single agent - mainly interferon alpha (IFN α) to the combination of IFN α and ribavirin treatment. Combination therapy can significantly improve the overall treatment efficacy compared to monotherapy (i.e., from 10%-15% of sustained viral clearance to 30%-40%) and now represents the standard treatment for chronic hepatitis.

Recently, new IFN preparations, such as pegylated IFNs (PEG-IFNs), have been introduced in clinical practice. Results obtained from large, multicenter studies of combined PEG-IFN and ribavirin treatment have shown a further increase in treatment efficacy. In fact, HCV infection was eradicated in 47%-54% of patients treated with PEG-IFN α -2b^[5]. Similar results have been found with PEG-IFN α -2a treatment^[6]. However, despite these positive results, several clinical problems remain. Of primary significance is the large number of patients treated with PEG-IFN (both α -2a and α -2b) and ribavirin who discontinue treatment due to the occurrence of adverse events associated with therapy. In fact, it has been reported that 34%-42% of patients treated with PEG-IFN α -2b (high and low doses, respectively) required dose reductions due to the appearance of adverse events and 13% stopped treatment for safety reasons^[5]. In another trial concerning the efficacy of PEG-IFN α -2a, dose modifications due to adverse events were required in 8% of patients and treatment discontinuation was required in 19%^[6]. In a pivotal trial of IFN α -2b and ribavirin performed by McHutchison *et al.*^[7], dose reductions due to adverse events were needed in 13% and 17% of patients treated for 24 and 48 weeks, respectively. Treatment discontinuation rates were 8% and 21% in patients treated for 24 and 48 weeks, respectively. Furthermore, it has been recently documented that, due primarily to safety issues, the number of HCV patients eligible for current treatments and the rate of treatment completion were much lower in clinical practice than in clinical trials^[8]. These concerns are particularly relevant considering that the primary goals of HCV treatment are viral eradication and the slowing of disease progression^[9,10].

Since IFNs are a family of glycoproteins with a broad range of antiviral effects, IFN beta (IFN β) represents a potential therapeutic alternative for the treatment of chronic viral hepatitis. In fact, in some countries, mainly in Japan, IFN β already plays a central role in therapeutic protocols. Differences have been reported between the physicochemical, biological and pharmacological properties of IFN α and IFN β ^[11,12]. Three forms of human IFN β are available:^[13] 1) Natural human IFN β (nIFN β) which is produced using human fibroblasts and is currently used in Japan for the treatment of chronic hepatitis C. 2) Recombinant human IFN β -1a (rhIFN β -1a), which is

procured from mammalian cells and is identical to IFN β that occurs naturally in humans. 3) *Escherichia coli*-produced recombinant human IFN β (IFN β -1b) which contains an altered amino acid sequence with a serine substitution for the cysteine at position 17. rhIFN β -1a appears to have advantages over the other two formulations and, in particular, is less immunogenic and more potent^[14]. The aim of the present paper was to review available data on the safety of IFN β for the treatment of chronic hepatitis C. Since IFN β has been widely used for the treatment of multiple sclerosis (MS), studies referring to the safety of IFN β in MS are reviewed briefly before discussing the results of this treatment in HCV-related chronic hepatitis.

IFN β in multiple sclerosis

Recombinant IFN β is currently the gold standard for the treatment of relapsing-remitting MS (RRMS). In MS, IFN β treatment lasts several years and regimens require high doses and frequent administration. Therefore, safety data on IFN β therapy recorded in MS studies and clinical practice could be useful for providing an overview of the drug's safety characteristics.

In the PRISMS (prevention of relapses and disability by interferon beta-1a subcutaneously in multiple sclerosis) study^[15], 560 patients with RRMS received 2.2 μ g or 4.4 μ g IFN β or placebo subcutaneously (s.c.) thrice weekly (t.i.w.) for 2 years (PRISMS-2) and then, the subjects completing treatment ($n=503$) or study ($n=533$) were re-randomized to receive either 2.2 μ g or 4.4 μ g IFN β s.c., t.i.w., for an additional 2 years (PRISMS-4)^[16]. The adverse events reported during the PRISMS-4 study were similar to those observed in the PRISMS-2 trial and, in general, most adverse events were mild. During the 4-year period of observation, the most frequent events reported were injection-site inflammation, flu-like symptoms, headache and fatigue, with similar rates in both active treatment groups. In the 2.2- and 4.4 μ g groups, respectively, less frequent adverse events included laboratory abnormalities such as lymphopenia (27% and 35%), elevated ALT levels (24% and 30%), elevated AST levels (11% and 20%) and thrombocytopenia (3% and 8%). All cases of thrombocytopenia were mild and only one patient over the 4 years (in the 4.4 μ g group) stopped treatment due to lymphopenia. In two other patients, treatment was discontinued as a result of elevated liver enzymes. In the SPECTRIMS (secondary progressive efficacy trial of rebif [interferon beta-1a] in multiple sclerosis) study^[17] conducted in secondary progressive MS (SPMS) patients using a treatment schedule similar to that used in the PRISMS-2 study, the type, frequency and severity of adverse events with IFN β -1a were similar to those reported in the PRISMS study. Overall, IFN β -1a was well tolerated. Of the 618 patients enrolled, 3 receiving placebo, 8 receiving 2.2 μ g IFN β -1a and 7 receiving 4.4 μ g IFN β -1a discontinued treatment permanently. In general, liver function test abnormalities were mild or moderate and either resolved with treatment interruption or no treatment modification whatsoever. The recent EVIDENCE (The evidence for interferon dose-response: European North American comparative efficacy) study^[18] compared the safety and efficacy of IFN β -1a, 4.4 μ g, s.c., t.i.w., to IFN β -1b, 3.0 μ g, once weekly by intramuscular (i.m.) injection, in 677 patients with RRMS over 24 weeks. The most common adverse events recorded were injection-site disorders, flu-like symptoms, headaches, rhinitis and fatigue. The higher frequency of injection-site disorders in the IFN β -1a group was related to the more frequent administration of this agent. However, injection-site disorders were mild and no skin necrosis was observed in over 20 000 s.c. injections. Hepatic and hematologic laboratory abnormalities were also more common on IFN β -1a but again, these abnormalities were generally mild and responsive to dose

reductions (if required). In both treatment groups, severe laboratory abnormalities were rare (<1%).

IFN β pharmacokinetics

IFN β can be administered intravenously (i.v.), intramuscularly (i.m.) and subcutaneously (s.c.). Pharmacokinetic and pharmacodynamic studies^[19-21] have shown that the extent and duration of the clinical and biologic effects of IFN β are independent of the route of administration. Furthermore, studies evaluating the most efficacious IFN β dosing regimen^[22-25] have shown that, in general, the highest doses have the greatest efficacy. However, these higher doses are also associated with a greater incidence of side effects (see below).

Evaluation of IFN β safety

Similar to the adverse events associated with IFN α therapy^[26,27], the side effects of IFN β can be separated into different categories, namely: a) common side effects (these range from mild-to-severe in nature and do not require dose modification), b) mild-to-moderate side effects which occur less frequently (i.e., less than 10% of treated patients) and may or may not require dose modification, and c) severe or life-threatening side effects. Thus far, no severe or life-threatening side effects have been reported with IFN β use. Clinical IFN β data are based on the results of clinical studies involving 1096 patients^[23-25,28-52]. Studies have been performed on treatment-naïve patients as well as patients who did not respond to previous treatment (generally with IFN α), two other studies were performed in special populations (i.e., cirrhotic patients and patients with renal failure)^[46,54].

Discontinuation and dose modification during IFN β treatment

The rates of treatment discontinuation and/or dose modification due to the appearance of severe side effects during IFN β are generally low (Table 1). Furthermore, several clinical studies reported no requirements for treatment discontinuation and/or dose modifications. Kiyosawa *et al.*^[28] found that in naïve patients treated with i.v. IFN β , dose modifications due to leukocyte counts below $1 \times 10^9/L$ were required in only 4.2% of patients (1 of 12 patients). In a study by Villa *et al.*^[29] 5.3% of patients (1 of 19) did not complete the trial. Reasons for discontinuation were not specified. A comparison study of i.v. recombinant IFN β and IFN α -2b plus ribavirin in patients who did not respond to previous IFN α treatment found that 12% of patients in the IFN α -2b plus ribavirin group (12 of 100) withdrew from treatment due to side effects such as flu-like symptoms. In the IFN β group, the corresponding frequency was 9% (9 of 100 patients)^[30].

Table 1 Frequency of treatment discontinuation and dose modifications during therapy with IFN β

| | Number of cases | References |
|--------------------------|-----------------|-------------|
| Discontinuation | | |
| Adverse events | 14 | 25,28,29,30 |
| Laboratory abnormalities | 2 | 31 |
| Dose modifications | | |
| Adverse events | - | |
| Laboratory abnormalities | 1 | 43 |

In a comparative study of two different doses (9 MU and 12 MU) of rhIFN β produced using Chinese hamster ovaries, Habersetzer *et al.*^[25] observed a treatment discontinuation rate of 18.2% (2 of 11 patients in the lower dose group) in naïve patients due to the occurrence of side effects such as mild depression and cutaneous ulcers at the injection site. A treatment discontinuation rate of 18.2% (2 of 11 patients) was also found in a study^[31] comparing the effects of different IFN β

administration regimens (i v 6 MU once daily versus 3 MU twice daily), two patients who discontinued treatment were using IFN β twice daily. Liver enzyme alterations (serum ALT/AST levels >700 IU/L) and severe proteinuria (urinary protein excretion >40 g/L and serum albumin level <30 g/L) were the causes of discontinuation. In conclusion, the frequency of treatment discontinuation and dose modifications that occur during IFN β therapy is low.

Frequency of side effects during IFN β treatment

The frequency of side effects experienced during IFN β treatment is reported in Table 2.

Table 2 Frequency of side effects with IFN β therapy

| Side effects | Frequency (range) (%) | References |
|---|-----------------------|--------------------------------|
| Flu-like syndrome | 10-100 | 25,30,32,33,35, 36, 37, 39, 46 |
| Fever | 67-100 | 28,43,40 |
| Fatigue | 16-74 | 24, 33, 39,46 |
| Local reactions (at the injection site) | 43-76 | 25,34, 37 |
| Headaches | 8-47 | 33, 39, 46 |
| Malaise | 50 | 39 |
| Arthro-myalgias | 21-42 | 39,40,46 |
| Weight loss | 6-42 | 39,40 |
| Gastrointestinal symptoms | 20-26 | 25,37, 38 |
| Anxiety, insomnia, irritability | 10-25 | 32, 39, 38 |
| Depression | 10-21 | 25, 38,46 |
| Alopecia | 8-16 | 33, 39 |
| Proteinuria | 46-73 | 22, 51 |
| Reduced platelet count | 13-44 | 22, 32,51 |
| Reduced white-cell count | 13-20 | 32,38 |

Flu-like syndromes, fever, fatigue and injection-site reactions are the most frequently observed side effects of IFN β therapy. No differences in terms of the frequency and severity of side effects between therapeutic responders and non-responders have been reported. In order to better evaluate the clinical significance of these side effects, results have been analysed with reference to the type of study.

Clinical studies evaluating the safety of IFN β

In a study of 8 naïve patients, Chemello *et al*^[32] found that treatment with i v natural human fibroblast IFN β was well tolerated, the predominant side effect was a mild form of a flu-like syndrome, which lasted between 3 and 23 days after the initiation of therapy. No hematologic toxicity was observed and reductions in white-blood-cell and platelet counts occurred in only one patient. A low side-effect rate was also observed in a study of 90 naïve patients treated with i m IFN β for 6 months^[33]. In fact, mild flu-like syndromes appeared in less than 10% of treated patients and asthenia in 16% of patients. The frequency of other side effects was less than 10%. The same investigators^[34] obtained similar results in another study of naïve patients treated with s c IFN β . A good safety profile with mild, transient flu-like syndromes as the predominant side effect was documented in two Italian studies^[35,36] performed in patients previously unresponsive to IFN α and subsequently treated with i v IFN β . Pellicano *et al*^[37] treated 30 patients who did not respond to a standard course of IFN α therapy with rhIFN β -1a (12 MU s.c., t.i.w.) for 3 months. The observed rate of flu-like symptoms, inflammation at the injection site, abdominal symptoms and psychiatric disturbances were 63%, 43%, 26% and 13%, respectively.

Clinical studies comparing different doses of IFN β

In a study of 92 naïve patients, Fesce *et al*^[24] compared two

different doses of i m natural human fibroblast IFN β : 3 MU and 6 MU t.i.w. for 12 months. Compared to the low-dose group, an increased frequency of flu-like syndromes (17% vs 9%), weakness (73% vs 57%), headache (48% vs 30%) and irritability (23% vs 11%) was documented in the high-dose group. However, these differences were not statistically significant. Habersetzer *et al*^[25] compared two different doses of recombinant IFN β -1a administered s c for 24 weeks in 21 naïve patients: 9 MU t.i.w. and 12 MU t.i.w. No differences were found between the two groups with regards to individual side effects. In a study aimed at comparing i v IFN β 3 MU twice daily vs 6 MU once daily in genotype-1b HCV-infected patients with high virus titres^[23], side effects were found to be more prevalent in the 3-MU group, particularly proteinuria (56% vs 30%) and thrombocytopenia (44% vs 20%).

Clinical studies comparing the safety of IFN β to IFN α

Several studies comparing the safety of IFN β and IFN α have been performed^[29,30,38-42].

Frosi *et al*^[38] compared IFN α and IFN β in 20 naïve patients treated for 6 months and did not observe any significant differences between the two treatment groups in terms of the frequency of adverse events. In another study^[39], flu-like syndromes and hair loss were less frequent in the IFN β group (16% and 16%, respectively) compared to the IFN α group (86% and 57%, respectively), the frequency of other adverse events were similar between the two groups. Cecere *et al*^[40] evaluated the efficacy and tolerability of the following types of IFN in 150 patients: lymphoblastoid IFN α , leukocytic IFN α and natural IFN β . The frequency of side effects was lower in the IFN β group than in the other treatment groups. In the IFN β , the frequency of lymphoblastoid IFN α and leukocytic IFN α , respectively, fever was present in 66.8%, 83.9% and 73.4%, the frequency of bone and muscle pains in 33%, 72.5% and 46.3%, fatigue in 21%, 52% and 31%, and the frequency of weight loss in 6%, 21% and 15%. Barbaro *et al*^[30] found no significant differences in the rates of side effects and treatment discontinuation between IFN β -treated and recombinant IFN α -2b plus ribavirin-treated patients ($n=200$) who were non-responders to previous IFN α -2b therapy.

Clinical studies evaluating combination therapy (IFN β plus ribavirin)

Kakumu *et al*^[43] compared the efficacy of ribavirin alone, IFN β alone and combined ribavirin/IFN β therapy. The combined therapy was found to significantly reduce red-blood-cell count and hemoglobin concentrations. A significant reduction in white-blood-cell count was documented in the IFN β and combined treatment groups. Despite these findings, all enrolled patients completed the study. More recently, a multicenter, randomised and controlled study has been performed^[44] to compare rhIFN β alone or in combination with ribavirin. One hundred and two naïve patients with chronic hepatitis C were randomized to receive either rhIFN β -1a alone (6 MU, s c, everyday) or in combination with ribavirin for 6 weeks. All patients in the IFN β -alone group completed the study, while 3 of 51 patients in the combined treatment group stopped therapy due to adverse events. Overall, both treatment regimens were well tolerated, hematological and hematochemical parameters remained unchanged by the end of the study period (except for a significant decrease in hemoglobin levels in the combined treatment group).

Clinical studies in sub-populations of patients

Vezzoli *et al*^[45] evaluated the efficacy and safety of IFN β in 10 patients with genotype-1b HCV hepatitis who were

unresponsive to a previous cycle of IFN α treatment, no reference to side effects was reported. Bernardinello *et al*^[46] examined the safety and tolerability of natural i m IFN β in 61 patients with HCV-related cirrhosis and found that the treatment was well tolerated, the most frequent side effects were fatigue (24%), irritability or depression (21%), arthromyalgias (21%), headache (21%) and flu-like symptoms (16%). The frequency of these adverse events are similar to those found in chronic hepatitis patients without cirrhosis using IFN β . Interestingly, in this study, the probability of developing clinically significant liver-related events during the follow-up period was not significantly different in untreated *versus* treated patients (the cumulative probability of decompensation at 60 months was 24% in treated patients and 35% in untreated ones). Although a recent Cochrane review^[47] states that there is no definitive conclusion about the safety of IFN β in acute hepatitis, IFN β has been used in patients with acute hepatitis without causing significant side effects^[48-50]. Takano *et al*^[49] studied the effects of six different IFN β treatment schedules in 97 patients with acute non-A, non-B hepatitis. The authors did not report data regarding the safety of IFN β , however, all enrolled patients completed the study. A pharmacokinetic study^[54] has been performed in patients with end-stage renal failure, i v infusion of natural human IFN β was found to be safe.

CONCLUSION

HCV infection is a major health problem and efforts have been made to identify drugs able to eradicate the disease and, thereby reducing HCV-related morbidity and mortality. According to recent consensus conference reports^[55,56], treatment of IFN α in combination with ribavirin represents the standard therapy for HCV-related chronic hepatitis. However, the use of high treatment doses for long periods, which is often required in subgroups of patients (i.e., those with genotype 1 disease) to reach acceptable levels of efficacy, increases the risk of side effects and as a result, can reduce patient compliance to treatment. In these cases, the search for further treatment strategies could be useful. IFN β has been proposed as a possible therapy for chronic hepatitis. Studies examining the use of IFN β in hepatitis originated in Japan^[57] but, in recent years, studies have also been performed in Europe^[25,29,30,32-38,40,44-46,53]. According to the available data, the treatment of chronic hepatitis C with IFN β is associated with a good safety and tolerability profile. In fact, in most clinical studies, the frequency of side effects is lower, or at least similar, to that reported with IFN α therapy. Furthermore, the rate of dropouts in controlled clinical studies as well as the need for dose reductions or treatment discontinuation are very low. IFN β has also been shown to be well tolerated and has an excellent safety profile in special patient populations, such as those with acute hepatitis^[48-50], cirrhosis^[46], and renal insufficiency^[54].

The goals of treatment strategies for HCV-related chronic hepatitis are to eradicate HCV infection and to reduce disease progression. The availability of different therapeutic choices is critical in achieving these goals, particularly in patients unresponsive to a standard course of antiviral therapy. Due to its good safety profile, IFN β may represent a possible second-line therapy if additional clinical studies can confirm this drug's efficacy, mainly in combination with ribavirin.

The eradication of HCV and the prevention or slowing of disease progression are clinical challenges that require a careful cost/benefit analysis. In order to expand the population of patients eligible for therapy and to treat subjects who cannot tolerate first-line treatments, new therapeutic options should be evaluated. If further studies will confirm the efficacy of combined IFN β and ribavirin treatment, this regimen can represent a safe, alternative therapeutic option.

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