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Is β-interferon a promising therapeutic option for the management of hepatitis C?

Seyed Mohammadmehdi Hosseini-Moghaddam[1]*, Afkham Mousavi[1] and Seyed Moayed Alavian[2]

[1]Urology and Nephrology Research Center (UNRC), Shahid Beheshti University, M.C. (SBMU), Tehran, I.R. Iran; [2]Baqiyatallah Research Center for Gastroenterology and Liver Disease, Baqiyatallah University of Medical Sciences, Tehran, I.R. Iran

Using interferon-alpha (IFN-α) as the conventional therapeutic antiviral drug, physicians generally achieve a treatment success of <50% in cases with chronic hepatitis C. Owing to the structural similarities between IFN-α and interferon-beta (IFN-β), the latter is a candidate for obtaining sustained viral response. In this review, we have compiled the published information on the use of IFN-β for the management of acute and chronic hepatitis C up to 2007. We have looked at the rates of success and side effects. IFN-β might be helpful if IFN-α fails to achieve a favourable outcome. This antiviral drug may be helpful for the management of chronic hepatitis C in both age extremes, in case of a relapse after receiving IFN-α and for preventing the development of the carrier state after acute hepatitis C. Further studies are required on the efficacy of IFN-β for the management of acute and chronic hepatitis C.

Keywords: HCV, cytokines, haemodialysis

Introduction

Hepatitis C virus (HCV) infection is a major problem in high-risk groups, for example, patients undergoing haemodialysis or people receiving organ allografts. Approximately 55% to 85% of people who experience acute hepatitis C will remain HCV-infected. Chronic hepatitis C is associated with severe outcomes such as cirrhosis (a risk of 5% to 20% within a time span of ∼20–25 years) and hepatocellular carcinoma (a risk of ∼1% to 2% per year in cirrhotic patients). Haemodialysis patients experience less favourable outcomes following treatment. Since a significant percentage of patients with chronic hepatitis C receiving interferon-alpha (IFN-α) and ribavirin do not achieve a successful response, researchers have been trying to introduce other therapeutic options. Compared with interferons, no specific therapeutic antiviral has an advantage in the treatment of chronic hepatitis C.

Three major classes of interferons (natural proteins produced by the cells) with different structures and antigenicities have been described according to the type of receptors through which the host cells respond. Similar to IFN-α, the serum level of interferon-beta (IFN-β) is increased after being induced by viral infection and the other foreign nucleic acids in most types of body cells (fibroblasts, epithelial cells and macrophages).[1]

IFN-β is a well-known therapeutic agent in the treatment and control of multiple sclerosis. Owing to the structural similarities between IFN-α and IFN-β, one may assume that IFN-β might be effective in chronic hepatitis C.[1] Despite relatively extensive use of the interferons, the mechanisms of their antiviral activities and immunomodulation are not fully understood.[2] In this review, we discuss the advantages and disadvantages of IFN-β for treatment in patients with acute and chronic HCV infection, as well as the success rate in haemodialysis patients and renal allograft recipients.

Methods

We reviewed reliable reports using a search up to December 2007 in MEDLINE (since 1966) and EMBASE (since 1980). To be included, a report should have been published in full and in the English language in any format. Using several predefined combinations of the following keywords and medical subject heading terms, or their equivalents, we searched the literature for: 'interferon beta', 'beta-interferon', 'beta interferon', 'IFN-β', 'hepatitis C' and 'HCV infection'. A total of 296 published papers were identified. Of those, 240 manuscripts were in the English language. Two of us (A. M. and S. M. H.-M.) independently reviewed the final list of the titles and the abstracts identified by the search strategy to judge their inclusion eligibility. Full-text manuscripts were obtained when reports were determined to be potentially relevant. Bibliographies of the included reports were reviewed to identify and extract other relevant studies. We ultimately came to a final decision on inclusion by a consensus. Furthermore, selected keywords were used to search

*Corresponding author. UNRC, No. 44, Boostan 9th Street, Pasdaran Avenue, Tehran, I.R. Iran. Tel: +98-21-22567222; Fax: +98-21-22567282; E-mail: h_sasan@hotmail.com

Google and Alta Vista for unpublished reports on the administration of IFN-β in HCV-infected individuals.

Treatment of non-responders to IFN-α therapy

The efficacy of IFN-β therapy in the management of the non-responders to a minimum of two courses of IFN-α therapy has been studied. In a small group of patients, intravenous IFN-β achieved a biochemical response in 25% of patients but no sustained virological response (SVR).[3]

IFN-β monotherapy and IFN-α in combination with ribavirin were administered for 12 weeks to evaluate effects at the end of week 12, and also the sustained response (at week 48 after the beginning of the treatment) in non-responders to IFN-α therapy. In this study, IFN-β therapy was more efficient than IFN-α combination therapy in the short-term response.[4]

Advantages and disadvantages of IFN-β for the management of chronic hepatitis C

In patients with chronic hepatitis C, IFN-α monotherapy provided an SVR in <20% of patients.[5] Table S1 [available as Supplementary data at *JAC* Online (http://jac/oxfordjournals.org/)] summarizes the studies conducted on the efficacy of IFN-β for the management of acute and chronic hepatitis C.

In patients with coincidental multiple sclerosis and chronic hepatitis C, IFN-β with dosages and protocols used in managing multiple sclerosis was effective to control chronic viral hepatitis C as well.[6] IFN-β has been administrated to patients who had a relapse of HCV after 24 weeks of IFN-α monotherapy with good results. The sooner the treatment was started, the better the clinical results.[7]

Short-term IFN-β therapy might be recommended as a first treatment for elderly patients with chronic hepatitis C.[8] Compared with IFN-α, IFN-β has less significant side effects.[9] Although side effects are a major concern in the elderly, no significant complications of IFN-β have been reported in this age group yet.[10] Although the treatment of chronic hepatitis C in children remains controversial, two courses of IFN-β monotherapy showed promise.[11]

In the long term, hepatocellular carcinoma is another major concern in chronic hepatitis C. The recurrence rate of hepatocellular carcinoma is noticeably high even after potentially curative therapies such as surgical resection or tumour ablation. IFN-β administration has been suggested for prevention of the recurrence of hepatocellular carcinoma after curative therapies. The mechanism of action might be either the antiviral effect of IFN-β or a direct anti-tumour effect.[12,13]

IFN-β proved to be a more effective antiviral agent than ribavirin when administered at a dosage of 3 million international units (MIU) three times a week.[14] Combination therapy with IFN-β and ribavirin has been tried for chronic hepatitis C.[15] Combination therapy including IFN-β and ribavirin provided superior outcomes compared with IFN-β monotherapy regarding biochemical response (53.3% versus 27.3%), SVR (73.3% versus 45.5%) and treatment of cases with genotype 1 (66.7% versus 20%).[16] Recombinant IFN-β, alone or in combination with ribavirin, was as effective as the current treatment of choice, pegylated IFN-α (PEG IFN-α), in the treatment of hepatitis C.[15] The cost of PEG IFN-α makes IFN-β an alternative.

IFN-β therapy was not associated with any significant biochemical or virological response in cirrhotic patients.[17] An induction period using IFN-β followed by the combination of IFN-α and ribavirin as a treatment for chronic hepatitis C did not improve the response rate of the high viral load genotype 1b hepatitis C patients.[5]

Factors predicting response

Several pre-treatment factors are predictive of SVR in patients treated with IFN-α: young age, short duration of illness, mild activity on liver biopsy, the absence of cirrhosis and low pre-treatment serum level of HCV RNA.[18] For IFN-β, the following factors may help to predict response: (i) low pre-treatment HCV-RNA load[16] (HCV level $<10^2$ CID_{50}/mL)[19] or HCV-RNA viral load (viral load $<0.5\times10^6$ Eq/mL by b-DNA or $\leq10^6$ copies/mL);[18] (ii) younger age (<40 years);[19] (iii) HCV genotype (a genotype other than HCV-1b);[20] (iv) the existence of four or more mutations in the amino acid sequences 2209–2248 of the non-structural protein 5A gene of HCV-1b (NS5A2209-2248),[21] though this effect still remains unclear;[22] (v) Asian races, and Chinese patients in particular;[16,21] (vi) a decrease in HCV-RNA load in peripheral blood mononuclear cell with IFN-β;[23] and (vii) the interval between the start of the IFN-β therapy and the HCV-RNA serum clearance.[24,25]

IFN-β therapy in renal transplant and dialysis patients

The incidence of HCV infection in dialysis patients is higher than in the general population. In many cases, it is untreated because of the controversies surrounding management.[26] IFN-α has been used as the treatment of choice for chronic hepatitis C in dialysis patients, but because of the accumulation of the medicine in the serum, the dose should be reduced or the intervals between doses prolonged.[27,28] Ribavirin is contraindicated in patients with end-stage renal disease.

The pharmacodynamics of IFN-β in patients with end-stage renal failure have been evaluated. The plasma half-life was 6.91 ± 2.80 min, and a dose reduction was found to be unnecessary in patients with renal failure.[29]

In a case study, the administration of IFN-β 3 MIU over 1 h, three times a week after dialysis was monitored in a 24-year-old male subject and the treatment continued for 24 weeks. No significant medicine accumulation was reported and the half-life was 65 min. The patient remained HCV RNA-negative for 6 months after the completion of therapy.[29]

Allograft rejection occurs in 15% to 100% of the kidney recipients treated with IFN-α.[8,30,31] Therefore, clinical trials with a plan to determine the efficacy of IFNs in allograft recipients face ethical difficulties. To our knowledge, there is no reliable evidence indicating the efficacy of the IFN-α therapy in achieving an SVR in transplant patients. Similar to IFN-α, IFN-β seems to increase the probability of transplant rejection. Owing to differences in their molecular configuration and biological effects, the impact of IFN-β might be different to that of IFN-α in renal transplant patients. In a 44-year-old female with simultaneous renal transplantation and chronic hepatitis C, IFN-β

Table 1. Comparisons of IFN-β and IFN-α for the treatment of chronic hepatitis C

Reference	First author and year of publication	Group A	Group B	Group C	Main results
44	Furusyo 1999	60 patients with chronic hepatitis C received 6 MIU/day IFN-α for 4 weeks then 6 MIU three times a week for 5 months	40 patients with chronic hepatitis C received IFN-β 6 MIU for 4 weeks	20 patients with chronic hepatitis C received 3 MIU twice a day for 4 weeks	virological response at the second week of treatment: Group A 25/60 (41.6%); Group B 11/40 (27.5%); Group C 16/20 (80%). Sustained virological response: Group A 19/60 (31.6%); Group B 12/40 (30.0%); Group C 3/20 (15%)
15	Pellicano 2005	51 patients with chronic hepatitis C received recombinant IFN-β 6 MIU/day subcutaneously for 24 weeks	51 patients with chronic hepatitis C received 6 MIU/day recombinant IFN-β subcutaneously plus ribavirin 1000–1200 mg/day (according to body weight)	NA	end of treatment virological response: Group A 29.4%; Group B 41.2%. Sustained virological response: Group A 21.6%; Group B 27.4%
16	Han 2007	11 patients with chronic hepatitis C received IFN-β 12 MIU/day three times per week for 24 weeks	15 patients with chronic hepatitis C received placebo three times per week for 12 weeks followed by IFN-β 12 MIU/day three times per week plus ribavirin 1000–1200 mg/day for 24 weeks after a 4 week washout	NA	virological response at the end of week 12: Group A 10/11 (90.9%); Group B 14/15 (93.3%) at the end of week 12 after initiation of IFN-β plus ribavirin therapy. Sustained virological response: Group A 5/11 (45.5%); Group B 11/15 (73.3%). Sustained biochemical response: Group A 5/11 (45.5%); Group B 8/15 (53.3%) ($P=1.00$)
4	Barbaro 1999	100 patients with chronic hepatitis C non-responders to IFN-α received recombinant IFN-β for 12 weeks	100 patients with chronic hepatitis C non-responders to IFN-α received recombinant IFN-β plus ribavirin for 12 weeks	NA	end of treatment virological and biochemical response: Group A 42%; Group B 22%. Sustained virological response: Group A 21%; Group B 13%
45	Perez 1995	21 patients with chronic active hepatitis C received IFN-α 6 MIU three times a week intramuscularly for 2 months followed by IFN-α 3 MIU three times a week for 4 months	19 patients with chronic active hepatitis C received IFN-β 6 MIU three times a week intramuscularly for 2 months followed by IFN-β 3 MIU three times a week for 4 months	NA	end of treatment biochemical response: Group A 12/21 (57%); Group B 1/19 (5.2%)

NA, not applicable.

6 MIU/day (iv) was administered for 6 weeks. The patient had a low load of HCV genotype 2. After 3 weeks, HCV RNA was completely cleared from the serum and an SVR was achieved after 6 months. This patient did not experience allograft rejection.[32]

Specific considerations in using IFN-β

This immunomodulator is usually administered once a day intravenously, but due to its early serum clearance and the short half-life, a twice-a-day administration of IFN-β has been suggested.[33,34] As shown in Table 1, although the response rate to IFN-β regimen is low in patients with chronic hepatitis C genotype 1 and a high viral load (more than 1 million copies/mL), twice-a-day administration has been demonstrated to provide a better response[33] even in patients with an HCV-RNA viraemia of less than one million copies/mL.[35]

It has been shown that there is a rapid decrease in the viral load within 48 h of initiating treatment with IFN-β (the first phase) due to an inhibition of HCV replication. Afterwards, a slow decrease (the second phase) in the viral load occurs that might be related to the degeneration of the infected cells.[36] An induction therapy using IFN-β 3 MIU twice a day for 2 weeks, plus 6 MIU once a day for the next 2 weeks and then three times weekly for 12 weeks has been reported to result in a better response compared with the once-a-day regimen.[37]

Neither an interval of 5–19 h nor an interval of 10–14 h between the doses caused a significant difference in the clinical response and both of these intervals had the same effect on the viral decline slopes.[36]

No benefit was shown for induction therapy with IFN-β twice daily followed by 6 months of consensus IFN compared with 6 months of consensus IFN monotherapy.[38] A variety of side effects have been reported in a twice-a-day administration, such as an increase in the serum alanine aminotransferase and aspartate aminotransferase levels (hepatic damage), hypoalbuminaemia, thrombocytopenia and renal toxicity as well as severe proteinuria.[39]

The tolerability and the efficacy of the subcutaneous IFN-β have been evaluated. While subcutaneous IFN-β 6 MIU three times a week for 6 months had little impact on the virological response in hepatitis C, a low occurrence of adverse events suggested that a higher dose might have been tolerated.[40] The efficacy of higher doses of IFN-β (9 and 12 MIU three times a week) administered subcutaneously has been studied. It has been suggested that these doses of IFN-β might be effective in treating chronic hepatitis C.[41]

An intramuscular IFN-β dose of 3 MIU three times a week was ineffective in the treatment of either acute or chronic hepatitis C.[42,43] When IFN-β is administered either subcutaneously or intramuscularly, the agent is absorbed via the lymphatic route, enters the plasma pool slowly and is hardly detectable in serum. Table 2 demonstrates different dosages and routes of administration of IFN-β for the treatment of chronic hepatitis C.

Side effects of IFN-β therapy in chronic hepatitis

Severe or life-threatening side effects have been seldom described. Side effects that have been reported for IFN-β in

Table 2. Different dosages and routes of administration of IFN-β for the treatment of chronic hepatitis C

Reference	First author and year of publication	Patients and methods	Main results
33	Kakizaki 1999	38 patients with chronic hepatitis C treated with IFN-β 3 MIU/twice a day for 4 weeks followed by 10 MIU/day IFN-α for 2 weeks and then 10 MIU three times a week for 18 weeks	sustained biochemical response: 21/38 (5.3%). Virological response according to the genotype of the HCV: genotype 1, 9/21 (42.9%); genotype 2, 9/12 (75.0%). Virological response according to HCV-RNA titre: HCV-RNA titre >1 MEq/mL, 9/24 (37.5%); <1 MEq/mL, 12/14 (85.7%). Virological response in patients with HCV-RNA titre >1 MEq/mL and genotype 1, 4/15 (26.7%)
40	Castro 1997	15 patients with chronic hepatitis C received 6 MIU/day IFN-β three times a week subcutaneously for 6 months	biochemical response: 4/15 (27%); sustained biochemical response, 1/15 (6.5%). Virological response, 0%
46	Miyajima 1996	25 patients with chronic hepatitis C received 6 MIU/day IFN-β three times a week for two weeks followed by 6 MIU/day IFN-α three times a week for 10–22 weeks	sustained biochemical response: 40%. Sustained virological response: 16%

Table 3. Side effects of IFN-β therapy

Mild	Mild to moderate	Moderate to severe
Mild depression (8.3% to 21%)[15,17,41]	cutaneous ulcers at the injection site and atrophic scar[41]	severe proteinuria[16,51]
Anxiety	asthenia (16%)[40,48]	rapid evolution of a chronic viral hepatitis into a hepatocellular carcinoma[52]
Irritability (21% to 23%)[43,47]	thrombocytopenia (9.1% to 13.3%)[15,41,48]	monoclonal gammopathy[56]
Flu-like syndrome (9% to 16%)[17,40,43,47–50]	leucopenia (5.7% to 9.1%)[15,40,41,48,53]	poliomyelitis[57]
Liver enzyme elevations[16,51]	anaemia (0% to 17.1%)[15]	autoimmune haemolytic anaemia[58]
Hypoalbuminaemia[16,51]	increase in plasma triglycerides by 21%[52]	monoarthritis[59]
Weakness (57% to 73%)[43,48]	changes in peripheral levels of pituitary hormones and cytokines[55]	severe fatigue[54]
Headache (5.7% to 48%)[15,17,43,47,48]		
Hair loss[49,50]		
Fatigue (11.4% to 33.3%)[15,17,48]		
Arthromyalgia (13.3% to 27.3%)[48,49]		
Erythema (16.7%)[15]		
Eczema (0% to 6.7%)[48]		
Psychosomatic (0% to 6.7%)[48]		
Insomnia (0% to 2%)[15]		
Weight loss (0% to 5.7%)[15]		
Drug-metabolizing enzymes activity in the liver[49]		
Decrease in HDL concentration and lipoprotein lipase by 36%[52]		
Pyrexia (8.3% to 66.8%)[15,48]		
Diabetes mellitus type I (rare)[53]		
Menstrual cycle-dependent fever (a temperature of above 38°C)[54]		

HDL, high-density lipoprotein.

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chronic hepatitis C patients are summarized in Table 3. Discontinuation of the drug because of side effects was reported in 6.3% of patients treated with IFN-β once a day, and in 33.3% of patients given twice-daily injections.[38]

Conclusion

IFN-β seems promising in several situations in which IFN-α has either failed or is contraindicated: at both age extremes; relapse after receiving IFN-α; in renal transplant and dialysis patients; and in preventing the development of a carrier state after acute hepatitis C. The evidence supporting all these uses is weak and clinical practice is under debate. We strongly recommend conducting further studies on the efficacy of IFN-β for the clinical settings mentioned earlier.

Transparency declarations

None to declare.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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