PEG-Interferon Alfa-2b for Acute Hepatitis C: A Review

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Abstract: Acute infection due to hepatitis C virus results in a chronic progression in 50-84% of cases. In the light of the risk of developing chronic disease and the response rate to treatment once the disease is established, it is very important to consider early treatment of acute hepatitis C before it progresses to the chronic form. The aim of this review is to evaluate the real efficacy and tolerance of Peg-interferon alfa-2b in monotherapy and in association with ribavirin in the treatment of patients affected by acute C hepatitis, to delineate the viral factors correlated with the sustained virological response and to consider when treatment should be started in relation to onset and what is the optimal duration of therapy. Also the pharmacodynamic and pharmacokinetic characteristics of PEG-IFN alfa-2b and ribavirin are reassessed. The analysis of literature demonstrates that Peg-interferon alfa-2b treatment is efficacious in terms of attaining sustained virological response (71-94% of cases). Treatment must be started within three months of onset and must be prolonged for three months. Only two studies have provided evidence the needed of a prolonged treatment for six months for genotype 1 infections. In all studies therapy has been generally well tolerated. Sustained virological response is independent of baseline viral load and of HCV genotypes in patients treated for six months, while in subjects treated for three months it seems to be dependent on HCV-genotype, with genotype 1 characterized by a less favourable outcome. Combination therapy with ribavirin does not seem to increase the response rate but could be proposed as a second choice to patients not responding to IFN monotherapy.

Key Words: Peg-interferon, HCV, acute hepatitis C, treatment, monotherapy.

INTRODUCTION

Acute hepatitis C is characterized by two fundamental aspects: 1) an high rate of progression to chronic form; 2) the majority of patients are absolutely asymptomatic.

Acute infection due to hepatitis C virus (HCV) results in a chronic progression in 50-84% of cases [1]. The risk is much lower in younger than in elderly individuals in relation to greater chance of spontaneous clearance of the virus in them [2]. Spontaneous viral clearance occurs in the first three months of infection in 20% of asymptomatic patients and in 40% of symptomatic patients with acute C hepatitis [3]. Chronic HCV infection (CHC) is one of the leading causes of chronic liver disease, affecting about 170 million people worldwide. In addition, it is the major cause of cirrhosis, hepatocellular carcinoma and liver failure, representing the leading indication for liver transplantation. In fact, CHC results in cirrhosis in 20-30% of patients, over a period of 20 years, and 1-6% of cirrhosis will develop epatocellular carcinoma every year. After 25 years of HCV infection the mortality related to liver disease is higher (~5%) [4-7].

The patients affected by CHC with genotypes 2 and 3, treated with Peg-interferon (PEG-IFN) alfa-2b and ribavirin for three months, presented a sustained viral response (SVR) rate of 80-90%, while in genotypes 1 and 4 the treatment for one year determines a SVR of 40-50% [8,9].

The major part of patients affected by acute hepatitis C are asymptomatic, but mild jaundice (asthenia, hyperbilirubinemia) are evidenced in 60-85% of cases [10,11]. For this reason the major part of diagnosis are causal and the best method for detecting acute HCV infection is to screen high-risk patients (intravenous drug abusers, patients on long-term hemodialysis or with needle-stick exposure, etc.) for seroconversion from a past negative to a positive anti-HCV test. In fact, he diagnosis is usually based on seroconversion to anti-HCV antibodies and on the presence of HCV RNA in the first serum sample.

In the light of the risk of developing chronic disease and the response rate to treatment once the disease is established, it is very important to consider early treatment of acute hepatitis C before it progresses to the chronic form. Several studies evaluated the efficacy of either alpha or beta interferon monotherapy in patients with acute hepatitis C, but nearly all trials are small and present great variability regarding timing, schedule, response definition and patient characteristics. To overcome these limits, IFN efficacy has been assessed by meta-analyses demonstrating that antiviral therapy during the acute phase of HCV infection significantly reduces evolution to chronic hepatitis. Accordingly, treatment of persons with acute hepatitis C is warranted. However, several issues remain to be addressed, such as the optimal regimen and timing [12-17].

Some recent studies have shown that PEG-IFN alfa-2b in monotherapy or in combination with ribavirin could be considered the best option in terms of efficacy and tolerance for the treatment of patients affected by acute C hepatitis. The aim of this review is to evaluate the evidence of the real efficacy and tolerance of PEG-IFN alfa-2b alone and in combination with ribavirin in the therapy of patients affected by acute C hepatitis, to evaluate the viral factors correlated with

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the sustained virological response (SVR) and to consider when treatment should be started in relation to onset and what is the optimal duration of therapy. Also the pharmacodynamic and pharmacokinetic characteristics of PEG-IFN alfa-2b and ribavirin are reassessed.

For this review relevant literature was identified through searches of MEDLINE (2002-July 2006). Search terms included, but were not limited to, pegylated-interferon alfa-2b, acute hepatitis C, HCV, pharmacology, pharmacokinetics, adverse events, therapeutic use, sustained virological response.

RIBAVIRIN

Ribavirin is an anti-viral drug which is active against a number of DNA and RNA viruses. It is a nucleoside antimetabolite drug that interferes with duplication of viral genetic material. Though not effective against all viruses, ribavirin is remarkable as a small molecule for its wide range of activity, including important activities against influenzas, flaviviruses and agents of many viral hemorrhagic fevers, but actually the oral form is used in treatment of chronic active hepatitis HCV-related, in combination with Pegylated-interferon. Ribavirin is a pro-drug, activated by cellular kinases which change it into the 5' triphosphate nucleotide. In this form it interferes with aspects of RNA metabolism related to viral reproduction. Physically ribavirin is similar to the sugar D-ribose from which it is derived. It is freely soluble in water, and is re-crystallized as fine silvery needles from boiling methanol. It is only sparingly soluble in anhydrous ethanol. Classically ribavirin is prepared from natural D-ribose by blocking the 2', 3' and 5' OH groups with benzyl groups, then derivatizing the 1' OH with an acetyl group which acts as a suitable leaving group upon nucleophilic attack. The ribose 1' carbon attack is accomplished with 1,2,4 triazole-3-carboxymethyl ester, which directly attaches the 1' nitrogen of the triazole to the 1' carbon of the ribose, in the proper 1-β-D isomeric position. The bulky benzyl groups hinder attack at the other sugar carbons. Following purification of this intermediate, treatment with ammonia in methanolic conditions then simultaneously deblocks the ribose hydroxyls, and converts the triazole carboxymethyl ester to the carboxamide. Following this step, ribavirin may be recovered in good quantity by cooling and crystalization. Fig. (**1**) shows the chemical structure of ribavirin. Ribavirin is absorbed from the GI tract probably by nucleoside transporters. Absorption is about 45%, and this is modestly increased (to about 75%) by a fatty meal. Once in the plasma, ribavirin is transported through the cell membrane also by nucleoside transporters. Ribavirin is widely distributed in all tissues, including the CSF and brain. The pharmacokinetics of ribavirin is dominated by trapping of the phosphated form inside cells, particularly red blood cells (RBCs) which lack the enzyme to remove the phosphate once it has been added by kinases, and therefore attain high concentrations of the drug. Most of the kinase activity which converts the drug to active nucleotide form, is provided by adenine kinase. This enzyme is more active in virally infected cells. The volume of distribution of ribavirin is large (2000 L/kg) and the length of time the drug is trapped varies greatly from tissue to tissue. The mean half-life for multiple doses in the body is about 12 days, but very long-term kinetics are dominated by the kinetics of RBCs (half-life 40 days). RBCs store ribavirin for the lifetime of the cells, releasing it into the body's systems when old cells are degraded in the spleen. About a third of absorbed ribavirin is excreted into the urine unchanged, and the rest is excreted into urine as the de-ribosylated base 1,2,4-triazole 3-carboxamide, and the oxidation product of this, 1,2,4- triazole 3-carboxylic acid. The mechanisms of antiviral action of ribavirin are largely unknown. At present there are five proposed mechanisms of action of ribavirin. They can be divided into two groups. The first group consists of two possible indirect mechanisms: 1) enhancement of host T-cell-mediated immunity against viral infection through switching the T-cell phenotype from type 2 to type 1; 2) inhibition of the host enzyme inosine monophosphate dehydrogenase (IMPDH), thus depleting intracellular GTP pools. The second group consists of 2 other hypotheses: 1) direct inhibition of HCV, including NS5B-encoded RNA-dependent RNA polymerase (RdRp); 2) ribavirin as RNA mutagen that drives a rapidly mutating RNA virus; 3) ribavirin is an inhibitor of some viral RNA guanylyl transferase and (guanine-7N-)-methyl transferase enzymes, and this may contribute to a defective 5'-cap structure of viral mRNA transcripts and therefore inefficient viral translation for certain DNA viruses, such as vaccinia virus (a complex DNA virus). It has been suggested that incorporation of ribavirin into the 5' end of mRNA transcripts would mimic the 7-methyl guanosine endcap of cellular mRNAs, causing poor cellular translation of these. The primary serious adverse effect of ribavirin is hemolytic anemia, which may worsen preexisting cardiac disease. The mechanism for this effect is unknown. It is dose-dependent and may sometimes be compensated by decreasing dose. Ribavirin is not substantially incorporated into DNA, but does have a dose-dependent inhibiting effect on DNA synthesis, as well as having other effects on gene-expression. Possibly for these reasons, significant teratogenic effects have been noted in all non-primate animal species in which ribavirin has been tested. An oral dose of 800-1200 mg ribavirin is given daily according to body weight (< 65 kg: 800 mg; 65-85 kg: 1000 mg; >85 kg: 1200 mg) [18].

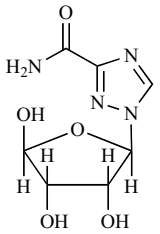

Fig. (1). Chemical structure of ribavirin.

PEG-IFN ALFA-2B

PEG-IFN alfa-2b is a covalent conjugate of recombinant alfa-2b interferon with monomethoxy polyethylene glycol (PEG). The average molecular weight of the PEG portion of the molecule is 12,000 daltons. The average molecular weight of the PEG-IFN molecule is approximately 31,000 daltons. Interferon alfa-2b, is a water-soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a

strain of Escherichia coli bearing a genetically engineered plasmid containing an interferon gene from human leukocytes. The biological activity of PEG-IFN alfa-2b is derived from its interferon alfa-2b moiety. Following a single subcutaneous dose of PEG-IFN alfa-2b, the mean absorption half-life was 4.6 hours and maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours. The maximal serum concentrations measurements of PEG-IFN alfa-2b increase in a dose-related manner. After multiple dosing, there is an increase in bioavailability of PEG-IFN alfa-2b. The mean PEG-IFN alfa-2b elimination half-life is approximately 40 hours (range 22 to 60 hours). Renal elimination accounts for 30% of the clearance. Pegylation of interferon alfa-2b produces a product whose clearance is lower than that of non-pegylated interferon alfa-2b. Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface and initiate a complex sequence of intracellular events. The effects of interferons include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells [19, 20]. PEG-IFN alfa-2b raises concentrations of effector proteins such as serum neopterin and 2'-5'-oligoadenylate synthetase, raises body temperature, and causes reversible decreases in leukocyte and platelet counts.

PEG-IFN ALFA2B IN MONOTHERAPY FOR ACUTE HEPATITIS C

In an Italian study (Santantonio *et al*.) sixteen patients affected by acute hepatitis C still viremic after 12 weeks from the onset were treated with PEG-IFN alpha-2b (1.5 mcg/kg, subcutaneous once weekly) for 6 months and followed for at least 12 months. Treatment was started after three months after infection because some previous studies had suggested that in patients with spontaneous viral clearance serum HCV RNA became negative three months after initial infection. Response to PEG-IFN alpha-2b therapy was defined as normal alanine aminotransferase (ALT) values and undetectable HCV RNA (<50 IU/ml) at the end of therapy, after 6 (sustained response) and 12 months follow-up (long-term response). At the end of treatment, HCV RNA was undetectable in 15/16 patients while ALT normalized in 14/16 patients. After 6 and 12 months follow-up, 15/16 patients (94%) showed virological and biochemical response. This study demonstrated that a 6-month course of PEG-IFN alpha-2b is effective in inducing resolution of acute hepatitis C in 94% of patients. No correlation was found between treatment response and pretreatment viral load and viral genotype [21].

In an other Italian study (Scotto *et al*.) six patients with acute hepatitis C, based on a well-documented hepatitis C virus (HCV) seroconversion with high alanine aminotransferase (ALT) levels (> 10 x ULN) and persistent HCV RNA titers after 3 months from ALT increase, were consecutively treated with PEG-IFN alfa-2b at 1.5 microg/kg subcutaneous weekly for 24 weeks. Response was defined as undetectable HCV RNA and normal ALT levels at the end of therapy and after a 6-month follow-up. All patients completed therapy; at the end of therapy, 5/6 patients (83%) responded and no relapses were observed during follow-up. No correlation was found between treatment response and pre-treatment viral load, viral genotype, and interval between acute infection diagnosis and start of therapy [22].

In another study (Wiegand J *et al*.) 89 individuals with acute HCV infection were recruited. Patients received 1.5 microg/kg PEG-IFN alpha-2b for 24 weeks; treatment was initiated after a median of 76 days after infection (range 14-150). End-of-treatment response and sustained virological response were defined as undetectable HCV RNA at the end of therapy and after 24 weeks of follow-up, respectively. In the total study population, virological response was 82% at the end of treatment and 71% at the end of follow-up. Of 89 individuals, 65 (73%) were adherent to therapy, receiving 80% of the interferon dosage within 80% of the scheduled treatment duration. End-of-treatment and sustained virological response rates in this subpopulation were 94% and 89%, respectively [23]. In this study the high number of dropouts, due only in part with the side effects of drug, underlines the importance of thorough patient selection and close monitoring during therapy. In all of these studies PEG-IFN alfa-2b monotherapy has been prolonged for 6 months with a rate of SVR of 71-94%. In another recent study (Kamal *et al*) one hundred seventy-five patients acutely infected with HCV were screened. Patients whose infection did not spontaneously resolve by week 8 were randomized to once weekly PEG-IFN alfa-2b monotherapy (1.5 microg/kg per week) started at weeks 8 (43 patients), 12 (43 patients), or 20 (53 patients) for a duration of 12 weeks. The primary endpoint was undetectable HCV RNA, using a Real Time PCR method with a sensitivity of < 100 copies/ml, 24 weeks after the end of treatment. All patients were followed for 48 weeks after cessation of therapy. The SVR rates were 95%, 92%, and 76% with treatment onset at 8, 12, and 20 weeks, respectively. Overall, SVR rates were better for patients infected with genotypes 2, 3, and 4 than those infected with genotype 1. Earlier initiation of therapy improved SVR rates for patients infected with genotype 1 with high viral load. PEG-IFN alfa-2b was well tolerated. Subjects with SVR maintained undetectable HCV RNA 48 weeks after therapy [24]. This study, characterized by a relatively large number of patients, demonstrated that a treatment duration of three months is efficacious, but PEG-IFN alfa-2b should be started within three months of onset of infection, because in patients treated after 20 weeks there was a reduced efficacy. In addition, this study seems to support earlier initiation of therapy leading to improved SVR rates for patients infected with genotype 1 with high viral load.

De Rosa *et al*. have studied the efficacy of PEG-IFN alfa-2b in relation to dosage. Nineteen patients with acute hepatitis C were treated with PEG-IFN alpha-2b for 12 weeks in an open, non-randomized, prospective cohort study. Treatment was administered within a median of 31 days (range 0-116) of the ALT level peak at a dosage varying from 1.06 to 1.66 microg/kg/week. The natural history of HCV infection describes that the period between the onset of infection and the ALT peak ranges from 15 to 150 days (mean 60 days). Eleven of the nineteen patients treated (57.9%) had HCV genotype 1. Fourteen patients were asymptomatic. An SVR was achieved in 74% of patients and the SVR rate was 100

and 83.3%, respectively, in genotype 1 and non-1 infected patients treated with a dosage greater than or equal to 1.33 microg/kg, compared with 40 and 50%, respectively, in those who received a lower dosage. An SVR was significantly associated by multivariate analysis only with PEG-IFN dosage greater than or equal to 1.33 microg/kg/week. No significant association was found with any viral genotype. This study showed that the rate of SVR was independent of the HCV genotype and was significantly associated by multivariate analysis only with the higher PEG-IFN dosage [25].

Cariti *et al*. enrolled ten patients affected by acute hepatitis C. As seven patients had fenotype 1 and three genotype non-1. Treatment was given within 20 days (range: 8-30) of the ALT peak. All patients completing 12 weeks of treatment (n = 7) had undetectable HCV-RNA. Five patients who completed the 24-week follow-up after the end of treatment had a SVR with ALT levels within normal range. Therapy was well tolerated in all patients. No correlation was observed between response and HCV genotype [26].

Kamal SM *et al*. randomly assigned 102 patients affected by acute hepatitis C to PEG-IFN alpha-2b (1.5 microg/kg/week) for 8 weeks (34 patients), 12 weeks (34), and 24 weeks (34). SVR was achieved in 23/34 (67.6%), 28/34 (82.4%), and 31/34 (91.2%) of patients in the three groups, respectively. All had undetectable HCV RNA 48 weeks after the end of therapy. Treatment for 8 or 12 weeks was effective in genotypes 2, 3, and 4, whereas genotype 1 required 24 weeks of therapy. The 8- and 12-week regimens were associated with fewer adverse events compared with the 24-week regimen. Also this work suggests that genotype 1 is more resistant to treatment and it is necessary to prolonged therapy for 24 weeks [27].

PEG-IFN ALFA-2B IN COMBINATION WITH RIBAVIRIN FOR ACUTE HEPATITIS C

The current standard of care in patients affected by active chronic hepatitis C is a combination therapy PEG-IFN alfa 2a or 2b plus ribavirin. Clinical data suggests that this combination therapy does not increase the SVR rate in patients affected by acute hepatitis C, but it results in a similar response rate. For this reason the combination is not actually used for acute form. Only one experience in literature seems evidence an increased in SVR, with a rate of 100%. In fact, in a recent study (Coery KE *et al*.) the authors describe the clinical course of 28 episodes of acute hepatitis C infection. Of the 28 infections, 7 episodes resolved spontaneously, while of the remaining 21 episodes, 16 were treated, and 5 did not receive treatment. Of the 16 treated cases, 4 received interferon-alfa and ribavirin, 11 received PEG-IFN alfa-2b and ribavirin, and 1 was treated initially with interferon-alfa monotherapy followed by PEG-IFN alfa-2b monotherapy. All patients were treated for six months. Among the patients treated with interferon, 3 of 4 experienced sustained virologic response. Among the subjects treated with pegylated interferon, all 12 achieved SVR. In total, 15 of 16 treated patients (94%) experienced SVR. In all, 18 of the 24 patients (75%) experienced spontaneous or treatment-induced sustained virologic clearance [28]. In this study the small number of patients treated with PEG-INF alfa-2b plus ribavirin has lead to a response rate of 100%, which is not confirmed by other similar studies. However, other studies in the literature have demonstrated a similar SVR rate among patients affected by acute hepatitis C treated with PEG-IFN alfa-2b monotherapy and subjects treated with combination therapy [29]. As an example Palumbo *et al* have treated 18 patients affected by acute hepatitis C with PEG-IFN alfa-2b in monotherapy for six months and 16 patients with combination therapy PEG-IFN alfa-2b plus ribavirin for six months with a similar SVR (91% in both groups) [30]. No studies are available in the literature that present data on the combination therapy in patients that did not respond to PEG-IFN alfa-2b monotherapy.

CONCLUSIONS

This review demonstrates that current evidence supports the conclusion that PEG-IFN alfa-2b with a dosage of 1.5 microg/kg subcutaneously once weekly is highly efficacious in treating acute HCV infection in terms of SVR (71-94% of cases). Treatment must be started within three months of onset of infection and must be of three months duration. Only two studies have shown evidence that for genotype 1 there is a need of a prolonged treatment for six months. In all studies therapy has been generally well tolerated. The rate of SVR is independent of baseline viral load and of HCV genotypes in patients treated for six months, while in subjects treated for three months it seems to be dependent on HCV-genotype, with genotype 1 characterized by a less favourable outcome. Combination therapy with ribavirin does not seem to increase the response rate but could be proposed as a second choice to patients not responding to IFN monotherapy, particularly in patients affected by genotype 1. However, additional data are required to improve the identification of the patients at great risk of progressing to chronic disease and to establish the optimal treatment in terms of risk/benefit and cost-effectiveness ratio.

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