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Chronic hepatitis C treatment in näive patients

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ABSTRACT

Hepatitis C (HCV) is a major public health problem worldwide and it is considered that there are about 180 millions of infected people. The natural history of hepatitis C shows that, of those individuals affected by a primo-infection, 55 to 95% evolve into chronicity. The objective of treatment for chronic hepatitis C is to prevent in the long term the complications and death that this disease may cause. In a short term the most important aim is the sustained virological response (SVR), considered a virological response, normalization of the serum ALT level, histological improvement, improvement in patients' quality of life and the risk of transmission reduction.

The association Peginterferon alpha – Ribavirin (PEG IFNα-RBV), at the moment, is the standard of care of patients with chronic hepatitis C and compensated cirrhosis. Two PEG IFNα are licensed, PEG IFNα 2a and PEG IFNα 2b. Pegylation is a procedure that allows the union of polyethylene glycol moieties (PEG) to pharmacologic active proteins; in this case, IFNα. Pegylation of the IFNα 2a and 2b provoke important modifications in these proteins: slower absorption, different distribution, slower elimination, and longer half life with major exposure to the drug and lesser antigenicity. The two pegylated interferons available are dissimilar between them. The SVR in chronic hepatitis C patients who were treated with PEG IFNα-RBV in registration trials was 54 to 61%. Patients with genotypes 1 and 4 must be treated 48 weeks and those with genotypes 2 and 3, 24 weeks. In some situations patients could be treated lesser or longer time. Results obtained from the association of PEG IFNα - RBV - Amantadine in chronic hepatitis C patients are controversial.

Meta-analysis comparing both PEG IFNs alpha shows a better SVR with PEG IFNα 2a. Therapies in patients with mild chronic hepatitis C have a similar SVR that those with more advanced liver disease and could be treated in this phase of the disease.

Key words. Hepatitis C. HCV. Chronic hepatitis C treatment. Pegylated interferon-alpha. Ribavirin.

INTRODUCTION

Hepatitis C (HCV) is a major public health problem worldwide and it is considered that there are about 180 millions of infected people.[1]

Studies that analyze the natural history of hepatitis C show that, of those individuals affected by a primo-infection, 55 to 95% evolve into chronicity.[2-4] Among the carriers of a chronic hepatic disease, the HCV is one of the principal reasons of death (liver failure and hepatocellular carcinoma) and liver transplant and, in agreement with some projections; the incidence of this last one will increase furthermore in the next two decades.[5,6]

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For more than 20 years, the empirical treatment with interferon-alpha (IFNα) in carriers of chronic hepatitis Non A Non B, showed that the disease could be curable.[7-8] Later, in 1997, based on results obtained from randomized trials, the first "Consensus on Management of Hepatitis C" of the National Institute of Health of The United States recommended IFNα's use in the treatment for chronic hepatitis C. The percentage of sustained virological response (SVR) —HCV RNA non-detectable in serum by a high sensibility technique 24 weeks after treatment — reached by this therapy was from 12 to 16%. Later trials which associated, empirically as well, Ribavirin (RBV) with IFNα showed encouraging results for the accomplishment of randomized trials and, on the base of the above mentioned, the Consensus on Management of Hepatitis C of the European Association for the Study of the Liver (EASL) also recommended this association for the therapy. The reached SVR was around 40%.[10-13]

Later, the attachment of polyethylene glycol (PEG) to IFNα molecule (pegylation) modified its pharmacokinetic and pharmacodinamic properties, allowed a weekly application and an increase on its efficacy. The therapeutic randomized trials proved a higher SVR with the association PEG IFNα-RBV when compared with PEG IFNα alone or IFNα-RBV.[14-16] Since 2002 different medical societies of the world recommend the use of the association PEG IFNα-RBV for the treatment of chronic hepatitis C. Therefore, this association is considered to be the standard of care at present and PEG IFNα monotheraphy to be indicated only when RBV is contraindicated.

PEGYLATED INTERFERONS

Pegylation is a procedure that allows the union of polyethylene glycol moieties (PEG) to pharmacologic active proteins; in this case, IFNα. PEG is an amphiphilic polymer formed from the union of a changeable number of monomers of ethylene glycol. Polymers can change in length, chemical structure and molecular weight. In addition, polyethylene glycol is inert, water-soluble, and nontoxic and does not adversely affect the safety profile of the interferon product.[17-18]

Pegylation of the IFNα 2a and 2b provoke important modifications in these proteins: slower absorption, different distribution, slower elimination, and longer half life with major exposure to the drug and lesser antigenicity (and thus reduced immunogenicity). The two pegylated interferons available are dissimilar between them. PEG IFNα 2a is joined to a branched PEG molecule of 40 kDa and PEG IFNα 2b to a linear chain of 12 kDa. Also, the sites and types of union of the aminoacids to PEG are different. The branched PEG molecule of 40 kDa joins in stable unions of amide to lysine (of the IFNα 2a) and the IFNα 2b PEG of 12 kDa does it with by residues of histidyne creating an urethane bridge, sensitive to hydrolysis. These unions determine that PEG IFNα molecule 2a circulate without changing until its elimination interacting with its receptor in a totality permitting its pharmacological activity, whereas PEG IFNα 2b hydrolyzes easily and its pharmacological action is originally done by IFNα 2b when letting go its pegylated molecule.

PEG IFNα 2a 180 μg per week when subcutaneously applied is absorbed slowly in a supported way and reaches its mean maximum serum concentration (C_{max}) (14.2 μg/L) after one only dose at 80-100 hours and its terminal elimination half-life after a single dose is approximately 80 hours. After 5 to 8 weeks the C_{max} is 25 μg/L in 45 hours of supported stable serum levels for approximately 168 hours and will still be undetectable 4 to 6 weeks after 48 weeks therapy. PEG IFNα 2a displays restricted biodistribution with highest concentrations occurring in the liver.[18-19]

A subcutaneous dose of 1.5 μg/kg per week of PEG IFNα 2b is absorbed more rapidly than PEG IFNα 2a and reaches its C_{max} between 20 and 32 hours after one application. Passed the fourth week, the C_{max} is similar and its terminal elimination half-life after a single dose is around 40 hours maintaining circulation levels of diminishing concentration between the doses.[18-20]

The serum concentration of HCV RNA is inversely proportional to PEG's IFNα levels. Reason why a major tendency is observed especially during the first weeks of treatment on the fluctuation of the HCV RNA in individuals that received PEG IFNα 2b. This increase in the serum level of the HCV RNA at the end of the period between PEG IFNα 2b doses can be diminished if the dose is increased or if there are two weekly doses applied .[20-22]

THERAPY FOR CHRONIC HEPATITIS NAÏVE PATIENTS

Treatment objectives

The objective of treatment for chronic hepatitis C is to prevent in the long term the complications and death that this disease may cause. In a short term the most important aim is the SVR, considered a virological response, normalization of the serum levels of ALT and histological improvement (decrease of 2 points in the necro-inflammatory score without worsening of the fibrosis).[14,15] On the other hand, SVR has shown an improvement in patients' quality of life when comparing previous and post treatment with specific tests as SF36. At a sanitary level, HCV eradication reduced transmission risks.

First treatment for chronic hepatitis C

It is widely confirmed that the treatment for chronic hepatitis C patients must be done with the association PEG IFNα-RBV due to the major efficacy when compared with the monotherapy done with PEGα IFN and with the association IFNα-RBV.[14,15] The SVR in chronic hepatitis C patients who were treated with PEG IFNα-RBV in registration trials

Table 1. Registration trials with PEG IFNα-RBV in näive patients with chronic hepatitis C.

Association	Global SVR (%)	Genotype 1 SVR (%)	Genotypes 2 and 3 SVR (%)
PEG IFNα 2b 1.5 ug/kg/week-RBV (14)	54	42	82
PEG IFNα 2a 180 ug/week-RBV (15)	56	46	76
PEG IFNα 2a 180 ug/week-RBV (16)	61	51	84 (24 weeks therapy)

was 54 to 61% (Table 1).[14-16] An important advance was made by a study done by Hadziyannis *et al*.,[16] who compared the efficacy of different doses and time of therapy according to the genotype, establishing that RBV's dose in patients with genotypes 2 and 3 is of 800 mg per day associated with PEG IFNα 2a during a period of 24 weeks, whereas in patients with genotype 1 the RBV's most effective dose is of 1-1.2 g per day associated with PEG IFNα 2a during a period of 48 weeks.

In these trials was possible to establish the importance of undetectable HCV RNA or a reduction in the viremia level ≥ 2 $\log_{10}$ in the twelfth week of treatment. Those patients who were presenting a decrease of HCV RNA level < 2 $\log_{10}$ had a predictive negative value for reaching the SVR of order 98%. This observation was determinant to indicate the early suspension of the therapy in the week 12 in the latter group of patients, especially genotype 1. Nevertheless, it is necessary to consider that the methodological rigor of clinical trials is not always carried out in welfare practice. For example, it is necessary that the level of initial viremia is determined in absolute values and not as sometimes happen, that an informed result is bigger than a cut value determined by the manufacturer of the method or the biochemist that performs the study. It is also important to perform the study with internationally approved commercial methods, and that the later controls be done with the same method, since the results of the different available commercial techniques or those developed "in house" are not equivalent.

Predictive factors in sustained treatment viral results

In registration trials of PEG IFNα-RBV'S, both predictive factors of SVR to the treatment are the viral genotype and the viremia level of pretreatment basal. SVR is most elevated in genotype 2 and 3 patients who have a virema level of 600.000 IU/mL.[14-16] It is also included in-between these factors, the PEG IFNα 2b dose (1.5 μg/kg per week) and the Ribavirin dose (> 10.6 mg/kg), female sex, under age of 40, weight < 75 kg, non Afro-American race, absence of insulin resistance, ALT higher than 3 times the normal value and absence of bridging fibrosis or cirrhosis in the liver biopsy.

THERAPY FOR CHRONIC HEPATITIS PATIENTS WITH GENOTYPES 2 AND 3 WHO HAD RECEIVED NO PREVIOUS TREATMENT

As mentioned above, the work done by Hadziyannis *et al*.,[16] established that the time of treatment in genotype 2 and 3 patients had to be of 24 weeks, with the association PEG IFNα-RBV, and this last one in a dose of 800 mg per day. Because of the fact that about 90% of the treated present a more than 2 $\log_{10}$ decrease of the HCV RNA in the week 12, with normal or high aminotransferases, it is not suggested to investigate the RVT.

Standard or individualized treatment

Subsequently different studies tried to determine if it was feasible to shorten the therapeutic standard period from 24 weeks to 12-16 (short treatment).[23-27] All these trials have different designs, reason why it is very important to be careful when they are interpreted. In 2, the analysis of the rapid virological response (RVR), this is non-detectable HCV RNA in the fourth week, constitutes a part of the original design and was a determinant of the interpretation of the results.[23-27] In agreement with the results of these two trials, patients who achieve RVR can receive the short treatment since the SVR is equivalent to the obtained with the standard treatment of 24 weeks. Nevertheless, in the study done by Shiffman et al (the protocol with major number of included patients) which was not designed to evaluate RVR, results prove a major percentage of SVR in those that are treated for 24 weeks. The predictive factors (with a statistically significant value) of SVR in this protocol were: genotype

2, baseline HCV RNA ≤ 400.000 IU/mL, age ≤ 45 years, weight ≤ 80 kg, ALT 3 times higher than the normal value, absence of bridging fibrosis or cirrhosis and standard treatment of 24 weeks. The analysis of genotypes 2 and 3 patients proved that the predictive factors of SVR had low viremia level, minor weight and absence of bridging fibrosis or cirrhosis in both groups. The standard treatment was only predictive of SVR in those patients with genotype 2 and not in those with genotype 3 .

Based on the analysis of the five studies mentioned before we may conclude that in patients with genotype 2 and 3 the standard treatment of 24 weeks is the recommended one. Nevertheless, a short therapy might be considered for those individuals by pretreatment HCV RNA ≤ 400.000 IU/ml, with RVR and intolerance to the treatment. On the other hand, in those patients who do not have RVR, especially with genotype 3 and bridging fibrosis or cirrhosis might be considered to be a therapy of 48 weeks.

THERAPY FOR CHRONIC HEPATITIS PATIENTS WITH GENOTYPE 1 WHO HAD RECEIVED NO PREVIOUS TREATMENT

Chronic hepatitis C patients with genotype 1 are considered to be "difficult to cure", and in this group of patients the SVR is significantly minor that in those with genotypes non 1, since it was demonstrated by the registration trials.[14,15] It was demonstrated in these studies that there a better SVR in association with PEG IFNα-RBV that with the monotherapy with PEG IFNα-RBV or that with the combination IFNα-RBV.

In the study of Manns et al was observed that those patients with genotype 1 that were receiving highest PEG IFNα 2b dose (1.5 μg/ kg per week) and RBV dose (> 10.6 mg/kg per day) for 48 weeks, were reaching a major SVR (48%). A later randomized study evaluated RBV's dose according to weight and SVR, showed that SVR was higher when administering RBV's dose of 800 mg in those with a weight <65 Kg, 1000 mg per day for those with 65 to 85 kg, 1200 mg per day for a weight between 85 and 105 kg and 1400 mg per day when weight was between 105-125 kg.

The study of Hadziyannis, *et al.,* showed one similar find since those patients with genotype 1 that they were receiving PEG IFNα 2a (180 μg per week) and RBV's dose 1000-1200 mg/kg per day for 48 weeks, were reaching a major SVR (52 %).

Strategies of improvement for SVR

Some studies related to chronic hepatitis C patients with genotype 1 suggest that a treatment with higher doses of PEG IFNα and or RBV for longer periods of 48 weeks, might obtain a greater percentage of SVR. On the other hand, they proposed to diminish the time of therapy in some cases.

Probably the most representative study for the design shows that a longer therapy (72 weeks) could be a good strategy in those patients who do not present RVR (HCV RNA non detectable in fourth week) defined like "slow responders", since in this group the SVR was significantly superior when treatment was spreading to 72 weeks (42 %) comparing it with those without RVR and that received the therapeutic association for 48 weeks (35%).[45-47] Long therapy (72 weeks) can be indicated for slow responders.

Other investigated alternative to improve SVR was the use of PEG IFNα higher doses, which did not prove to be superior to the standard dose. In counterpart, the use of RBV's higher doses, though it was associated to a greater significant of SVR, was also associated with the significant increase of the anemia that needed –in a few studied cases– the use of Eritropoyetin and even in someone of them blood transfusions. The disadvantage of this strategy is the managing of this adverse event and the inherent risks for the patients.

Another option that was investigated was a short treatment of 24 weeks. In a recently published meta-analysis of 7 randomized controlled trials comparing the standard PEG IFN – RBV treatment (48 weeks) to less than 48 weeks in around 800 patients with HCV-1 with RVR, showed a significantly less SVR in those with a short duration of therapy (p = 0.004). There was no significant difference in SVR rates between 24 and 48 weeks of treatment only in the subgroup of 212 patients with baseline low level of viremia (HCV RNA ≤ 400,000 IU/mL) and RVR (p = NS) suggesting that 24 weeks of therapy could be the appropriate treatment duration in this subgroup of HCV-1 patients.[48] Therefore, in patients with these characteristics is possible to consider a short therapy.

PEG IFN - RBV - AMANTADINETREATMENT

The results obtained from the association of PEG IFNα - RBV - Amantadine in chronic hepatitis C patients are controversial. Some studies do not show an increase of the SVR when comparing triple the-

rapy with the standard treatment PEG IFNα - RBV and others; on the contrary they show a better significant improved SVR in patients with genotype 1, 2 and 3.[52,53]

THERAPY FOR PATIENTS WITH CHRONIC HEPATITIS C GENOTYPE 4 WHO HAD RECEIVED NO PREVIOUS TREATMENT

Patients with chronic hepatitis C genotype 4 are relatively slightly frequent in our way, even in registration trials where appear poorly represented. Different studies which evaluate the therapy with the association PEG IFNα - RBV as well as a meta-analysis show that the scheme of 48 weeks have a greater SVR in those with genotype 1, but smaller in those with genotype 2 and 3.[49] RVR have a similar impact on SVR that the observed in other genotypes, allowing to shorten the therapeutic period to 24 weeks in this patients' subgroup.[50]

PEG IFNα 2A *VERSUS* PEG IFNα 2B

The information offered by trials which compare PEG IFNα 2a with PEG IFNα 2b, both associated or not to RBV, in patients with chronic hepatitis C is controversial. Recently, four studies published, 3 of them were prospective[38,39,42,44] and one retrospective, conclude in a different way. The first, prospective, shows that both pegylated IFN are comparable in efficiency and adverse events.[32] Other two, also prospective, show that the safety profile of both is similar and that SVR is significantly greater (statistically significant) when patients are carriers of genotype 1 or non 1,[38-39] receive treatment with PEG IFNα 2a. The fourth study (the PRACTICE study) includes 3414 patients treated in the routine clinical daily practice of 23 centers of Germany. In this one, when matched the included ones, its observe that SVR is significantly greater in carriers of genotype 1 when they were treated by PEG IFNα 2a, whereas in those with genotypes 2 or 3 SVR was similar.[44]

A more global contribution on this controversy among the comparison of the efficacy of both pegylated interferons (partners to RBV) offers Awad, et al., a meta-analysis of the Cochrane Hepato-Biliary Group. These authors, after a systematic search of publications which compare PEG IFNα 2a *vs.* PEG IFNα 2b (with or without RBV) in different databases of the medical bibliography -until July 2009- select, because they fulfill the strict methodological criteria 12 clinical randomized trials[32-43] and 8 in which it is evaluated SVR.[32,36-39,40,42,43] The meta-analysis using intention-to-treat analysis for SVR included 4,335patients. In this sub-analysis SVR together with PEG IFNα 2a (47%) is superior to the observed with PEG IFNα 2b (41%) ($p = 0.004$) for patients with genotype 1 and 4 as well for those with genotypes 2 and 3. Reason why the authors of this meta-analysis conclude that the available evidence of today suggests that SVR with PEG IFNα 2a is superior that the observed with PEG IFNα 2b. On the other hand, the meta-analysis of adverse events leading to treatment discontinuation included 11 trials and showed not significant differences between the two PEG IFNα.

CHRONIC HEPATITIS C PATIENTS WITH MILD HISTOLOGICAL LIVER INJURY

Guidelines of treatment for chronic hepatitis C suggest to treat those patients with hepatic injury moderated to severe.[4] Patients with bridging fibrosis or cirrhosis, independently of the genotype that they present, have one significant minor percentage of SVR.[51]

A recently published meta-analysis which includes 10 clinical randomized trials, evaluates SVR to treatment with the association IFNα - RBV as well as PEG FNα - RBV in patients with chronic hepatitis C and histological hepatic mild injury. This study results showed that carriers of a histological mild lesion have a similar SVR as those with moderate or severe injury. Therefore, the therapy in this phase of the disease, if effective, would allow the accomplishment of the general objectives of the treatment for chronic hepatitis C and to improve the quality of life and to reduce simultaneously the transmission of HCV.[52]

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