REVIEW

The Profilaxis and Treatment of C Virus Liver Disease in the Liver Transplantation Setting. Narrative Review

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Abstract

Objective: To review the use of antiviral therapy as prophylaxis or treatment of virus C liver disease in the liver transplantation setting.
Method: A search was made of the literature in PubMed with the strategy *"liver transplantation"* AND *"hepatitis C,"* AND (*"interferon"* OR *"peginterferon,"* OR *"ribavirin"*) from 1966 to June 2007 and a manual search of the journals *Gastroenterología y Hepatología, Journal of Hepatology* and *Hepatology* between 2001 and June 2007, to identify publications and communications to congresses relating to the subject. The studies identified were selected and evaluated.
Results: A total of 48 articles were chosen for review. Hepatitis C virus is one of the main indications for liver transplantation. Post-transplant re-infection is immediate and almost universal, and results, in many cases, in a recurrent liver disease that reduces the patient's survival. Four basic therapeutic strategies have been studied: pre-transplant anti-viral treatment, prophylaxis, early or preventative treatment, and treatment of acute or chronic recurrent hepatitis C.
Conclusions: Currently, the hepatitis C treatment in the liver transplantation setting is based on the use of peginterferon associated with ribavirin as pre-transplant treatment in selected patients or as treatment of recurrent post-transplant hepatitis C, achieving sustained virological responses of around 20% and 35% respectively. The main limitation of these treatments is the high frequency of the adverse effects and interruptions to treatment, meaning it is important to carry out strict follow-up of the treatment safety.

Key words: Antiviral agents. Drug therapy. Combination. Chronic hepatitis C. Liver transplantation. Ribavirin. Interferons. Polyethylene glycols.

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Received July 10, 2007.
Accepted for publication December 7, 2007

The prophylaxis and treatment of C virus liver disease in the liver transplantation setting. Narrative review

Objetivo: Revisar la utilización de terapia antiviral como profilaxis o tratamiento de la hepatopatía por virus C en el entorno del trasplante hepático.
Método: Se realizó una búsqueda bibliográfica en PubMed con la estrategia *"liver transplantation"* AND *"hepatitis C"* AND (*"interferon"* OR *"peginterferon"* OR *"ribavirin"*) desde 1966 hasta junio 2007 y una búsqueda manual en las revistas *Gastroenterología y Hepatología, Journal of Hepatology* y *Hepatology* desde 2001 hasta junio 2007, para identificar publicaciones y comunicaciones a congresos relacionadas con el tema. Se seleccionaron y evaluaron los estudios identificados.
Resultados: Se seleccionaron 84 trabajos para realizar la revisión. La hepatopatía por virus C es una de las principales indicaciones de trasplante hepático. La re-infección post-trasplante es inmediata y casi universal, y deriva, en muchos casos, en una hepatopatía recurrente que disminuye la supervivencia del paciente. Se han estudiado cuatro estrategias terapéuticas básicas: tratamiento antiviral pretrasplante, profiláctico, anticipado o preventivo y tratamiento de la hepatitis C aguda y crónica recurrente.
Conclusiones: Actualmente el tratamiento de la hepatitis C en el entorno del trasplante hepático se basa en la utilización de peginterferón asociado a ribavirina como tratamiento pre-trasplante en pacientes seleccionados o como tratamiento de la hepatitis C recurrente post-trasplante, alcanzándose respuestas virológicas sostenidas en torno al 20% y 35%, respectivamente. La principal limitación de estos tratamientos es la alta frecuencia de efectos adversos y suspensiones de tratamiento, por lo que es muy importante realizar un seguimiento estricto de la seguridad del tratamiento.

Palabras clave: Agentes antivirales. Terapia con medicamentos. Combinación. Hepatitis C crónica. Trasplante hepático. Ribavirina. Interferón. Polietilenglicoles.

INTRODUCTION

Terminal liver disease caused by chronic Hepatitis C viral infection (HCV) is the most common indication for liver transplantation in Western Europe and the United States.[1,2] In Spain, and according to data from the Eighth Report on the Results of the Spanish Liver Transplant Register 1984-2005,[3] cirrhosis due to HCV is the cause of 25.4% of liver transplants in our country, being the second main diagnosis and the main secondary diagnosis of recipients, after only alcoholic cirrhosis (29.8% of patients); in fact, during the past 20 years approximately 3000 patients have undergone liver transplants for cirrhosis secondary to chronic hepatitis C (CHC), meaning it has become a large-scale problem in the healthcare area and a priority for public health in the European Union.[4]

However, in the great majority of patients, immediately after the liver transplant (first few hours post-transplant) there is "*recurrent HCV infection" or "re-infection by HCV,"* which is detected by the presence of HCV in the patient's blood and/or the transplanted liver.[5-7] This re-infection takes place both in patients with positive plasma viral load at the time of the transplant and also in patients with negative plasma viral loads, supporting the hypothesis of re-infection from extra-hepatic cells. Therefore, liver transplantation, far from being a definitive solution for the disease, in many cases only postpones this serious health problem, and it can be confirmed that liver transplantation would be used in this setting as a palliative strategy rather than a cure, but for patients for whom the time of evolution of the post-transplant liver disease exceeded life expectancy, it would be an effective strategy.

Although re-infection is a basic aspect of the problem, so are the modification and acceleration of the natural history of the disease secondary to re-infection by HCV with regard to the immunocompetent, non-transplanted infected patients.

With regard to the modification of the natural history of the disease, it has been observed that the recurrence of the disease due to HCV after liver transplants takes place at different times and presents a wide spectrum of morphologic alternations, which may occur via different mechanisms of hepatocyte damage.[8,9] This heterogeneity, based on recurrence times and the anatomopathological pattern, may be very important in terms of the prognosis and selection of patients suitable for treatment. With regard to immunocompetent patients, those undergoing liver transplants present the following differences in the natural history of the disease:

– The spontaneous elimination of the HCV is practically non-existent
– A high percentage of patients may suffer from the so-called recurrent acute hepatitis (generally within the first 6 months after the transplant), which is typically associated with raised levels of transaminases that require diagnosis via a liver biopsy
– Subsequently, the so-called recurrent chronic hepatitis C disease tends to develop, which requires for the diagnosis a liver biopsy with a different morphological pattern to that of acute hepatitis. This kind of chronic hepatitis C can develop into clinical forms of varying degrees of seriousness: standard chronic hepatitis C or chronic cholestatic hepatitis C, which evolves very quickly, meaning that a differential diagnosis must be performed by way of a liver biopsy

However, in addition to modifying the natural history of the disease, it accelerates, a fact absolutely documented in all its stages,[10-15] which translates into:

1) Increased progression of the fibrosis, which in the liver transplant patient is between 3-5 times faster than in an immunocompetent patient. This translates into an average evolution time for fibrosis in an immunocompetent patient between stages I and II is around 8 to 9 years, being reduced to approximately 2 years in the liver transplant patient.
2) Reduced time to cirrhosis; while in an immunocompetent patient the time for the liver disease to reach a cirrhotic condition is between 20 and 30 years, in the liver transplant patient this is reduced to between 10-12 years.
3) Rapid evolution towards liver decompensation; after becoming cirrhotic, the likelihood of decompensation is greatly increased (by up to 50%) to 1 year and survival rate falls by up to 40% in the first year following the transplant.
4) Lower rates of survival of the graft and the patient, deriving from the accelerated progression towards fibrosis, cirrhosis, and decompensation. The National Transplant Organisation, in its reports from the years 1984-92 and 1993-2005, in the chapter dealing with the Spanish Liver Transplant Registry, states that there is a drop of around 10% in the survival of the transplanted organ and the patient due to the presence of HCV in patients at 10 years with liver transplants.[3]

Finally, indicate that donor, recipient and HCV factors have been identified as associated with the increased seriousness of the recurrence of HCV disease and with a lower level of survival of the transplanted organ[2,8,15]: gender (female), advanced age (donor and recipient), race (not white), seriousness of the underlying disease, time to recurrence, treatment of rejection (corticosteroids and OKT3), pre-transplant viral load, early post-transplant viral load, CMV, and/or HIV co-infection.

In this context (prevalence of cirrhosis from HCV, modification, and acceleration of the natural history of the disease in comparison to immunocompetent patients) it seems to be clear that a treatment is necessary before, during, and after the liver transplant to permanently eliminate the HCV, which is associated with an improvement in the inflammation or liver fibrosis (as happens in non-transplant patients) and finally avoid the loss of the transplanted organ because of the recurrence of the primary disease. Studies have been conducted in this sense[16-21] that have evaluated the virological, biochemical, and histological evolution in the long term for liver transplant patients undergoing antiviral treatment who have achieved a sustained virological response (SVR:

negativisation of the HCV 6 months after finishing the treatment), concluding that this response is maintained for at least 3-5 years (follow-up time of the studies), is associated with an improvement in the degree of liver inflammation with the fibrosis regression and a decrease in mortality. These potential benefits secondary to the introduction of an antiviral treatment in the liver transplantation setting have been analysed in different therapeutic strategies:

a) Before the liver transplant: pre-transplant antiviral treatment.
b) During the liver transplant: prophylactic treatment.
c) After the liver transplant:
  c.1) Before developing recurrent chronic hepatitis C: advance or preventative treatment.
  c.2) After developing recurrent hepatitis C: treatment of acute or chronic recurrent hepatitis C.

The purpose of this study is to review the use of antiviral therapy strategies as prophylaxis or treatment of virus C liver disease in the liver transplantation setting.

METHOD

A search was made of the literature in PubMed with the strategy "*liver transplantation"* AND *"hepatits C,"* AND ("*interferon"* OR *"peginterferon,"* OR *"ribavirin"*) from 1966 to June 2007 and a manual search of the journals *Gastroenterología* y *Hepatología, Journal of Hepatology* and *Hepatology* between 2001 and June 2007, to identify publications and communications to congresses by Spanish, European and American Associations for the Study of Liver Diseases (AAEEH, EASLD, AASLD). The studies identified were selected and evaluated.

A total of 144 studies were recovered, of which revision it is important to highlight several aspects that limit the final usefulness for the care practice standardisation:

– There are very few studies with high levels of evidence (randomised clinical trials): The great majority is observational prospective or retrospective studies, cohort studies, carried out at a single research centre and with few patients
– All of them exclude from treatment the patients with thrombopaenia, anaemia, neutropaenia, and severe kidney failure, which are very common clinical situations in the liver transplantation setting, meaning that between 25%-60% of the patients recruited were excluded for those reasons
– Very few studies specify whether the patients did not receive prior antiviral treatment (independent prognostic factor in the antiretroviral treatment result)
– As in some cases these were studies conducted before 2003, the effectiveness of the current reference treatment for patients with CHC (peginterferon—PegIFN—) was not assessed in many cases
– The dosing schedules studied and the treatment durations were very variable
– No common variable was established for the results

Of the 144 studies recovered, 84 were finally assessed, as the review of studies excluded those whose principal aim was not to evaluate the safety or efficacy of antiviral treatment, did not specify when the therapy was started in relation to the liver transplant, did not specify the type of interferon or peginterferon used or the dosing schedule used was not specified.

It is important to justify that we have excluded the studies assessing amantadine in the post-transplant treatment of hepatitis C, either because they included groups of patients who are not subject to this review (re-treatment of post-transplant recurrent chronic hepatitis C following a first failed cycle of combined antiviral therapy,[22-23] because they do not contribute data regarding the sustained virological response in the single monotherapy study[24] or because the combined treatment as first post-transplant antiviral therapy has only been published in 1 study (which does not include pegIFN) having obtained very poor results in terms of safety and sustained virological response.[25] All these studies have been analysed in 2 reviews,[26-27] which conclude that triple therapy including amantadine may be effective in the re-treatment of a selected group of patients, with no benefit shown in patients who were not previously treated or in recurrent patients.

RESULTS

Pre-transplant Antiviral Treatment

One possible strategy for approaching the problem of HCV in the context of liver transplantation is to eliminate the virus before the transplant, thus avoiding re-infection of the graft or transplanted organ. As has already been stated, it is necessary to remember at all times that even patients with negative plasma viral loads before the liver transplant are at risk of re-infection and that, currently, it has not been finally established whether a reduction in the HCV viral load (without eradication) leads to a reduction in the seriousness of the recurrent disease after the liver transplant. To date, a total of 6 studies have been published which assess this strategy, but only 5 of them specify the pharmacological treatment used[28-32] (Table 1).

Crippin et al published the first pilot study[28] to determine the tolerability and efficacy of antiviral therapy in patients on the liver transplant waiting list, with a high probability of transplant within the 12 weeks following the inclusion of the patient in the study. Patients excluded from the study were those with platelet counts below 45 000 units/µL, Hb <11 g/dL, neutrophils <1250/mL, and serum creatinine >2 mg/dL. Seventy three per cent of the patients were infected with genotype 1 of HCV. Patients on the waiting list received antiviral treatment until they underwent the transplant (average time, 1.95 months; range, 0.25-5.0 months) and were randomised into 3 treatment groups. The viral load was

Table 1. Main Studies Evaluated for Pre Liver Transplant Hepatitis C Antiviral Treatment[a]

Author	Treatment, No.	Duration, Months	FVR, %	Recurrence of HCV, %	SVR, %
Crippin[28,b,c]	IFNα-2b 1 MIU/day (3)	2	33	100	0
	IFNα-2b 3 MIU-3 t/w (6)				
	IFNα-2b 3 MIU-3 t/w + RBV 400 mg/day (6)				
Thomas[29]	IFNα-2b 5 MIU/day (20)	14	60	67	20
Everson[30]	IFNα-2b+RBV ID (102)	6-12	39	48	20
Forns[31]	IFNα-2b 3 MIU/day + RBV 800 mg/day (30)	3	30	33	20
Mtnez-Bauer[32]	PegIFNα2a+RBV (50)	<6	38	33	25

[a]FVR indicates virological response at the end of the treatment; HCV, hepatitis C virus; ID, increasing dose; IFN, interferon; MIU, millions of international units; No., number of patients on treatment; PegIFN, peginterferon; RBV, ribavirin; SVR, sustained virological response; t/w, number administrations/week.
[b]Controlled study. [c]Randomised study.

negativised at the time of the transplant (defined by loss of HCV RNA via PCR) in 33% of patients (5/15), with no difference between the treatment groups, but they all relapsed after the treatment. A total of 20 serious side effects were seen in 15 patients, especially cytopaenias, hepatic encephalopathy and infectious complications. The authors considered that the poor tolerance and low safety of the IFN alone or associated to RBV, as well as the small proportion of patients complying with the treatment criteria (below 50%) limit the potential usefulness of pre-transplant antiviral treatment.

Thomas et al[29] studied the effect of the high daily doses of IFNα-2b (5 MIU/day) in 20 patients on the liver transplant waiting list, which had received no prior antiviral treatment (67% genotype 1). The average duration of the treatment was 14 (2.5) months (0.5-33.5). Sisty per cent of the patients (12/20) negativised the HCV RNA before the transplant, although 67% of patients relapsed after this (8/12). With regard to the treatment safety, the development of cytopaenias, the worsening of depressive symptoms and peripheral neuropathy were particularly noteworthy. The authors point out in their conclusions the importance of viral elimination in 12 of the 20 patients treated prior to transplant and in 4 of the 12 after this.

Everson[30] studied the use of IFNα-2b and RBV at increasing doses, with the objective of increasing patient compliance and limiting possible side effects. Of the 102 patients included in the study (77% infected with genotype 1), around 40% (40/102) managed to eliminate the plasma virus before the liver transplant, although only half of them (21/40) managed to get a sustained virological response after this. Even though an increasing dose schedule was used, up to 20% of the patients suspended the treatment because of side effects, the most serious of these being cytopaenias, hepatic encephalopathy, and infectious complications. One of the most interesting conclusions of this study is the importance of modulating the moment of the liver transplant, delaying this as far as possible until the negativisation of HCV.

Forns coordinated a study[31] conducted in 4 Spanish hospitals, in patients on the waiting list expecting to receive a liver within 4 months, who were treated during an average of 12 weeks with IFN associated with RBV. Of the 30 patients on treatment (83% genotype 1), 9 negativised their pre-transplant viral loads (30% response), and 3 of them relapsed after this (SVR of 20%). Among the adverse effects, there were 2 cases of sepsis and the development of leucopoenia and thrombocytopenia. The authors conclude that this is a valid strategy in selected patients, and a strict safety follow-up of the treatments must be carried out.

Martínez-Bauer published the only study[32] that used combination therapy with peginterferon (PegIFNα-2a and RBV; unspecified dosing schedule) during at least 6 months prior to the transplant. Response rates of around 38% were obtained, producing a 33% recurrent infection rate 6 months after the liver transplant. There were serious haematological side effects (anaemia, neutropaenia, and thrombocytopenia) in 66% of the patients, 32% decompensations, and 32% infections. A total of 60% of the patients needed adjustments to the doses of antiviral agents, 30% interrupted the treatment, while there were 2 deaths caused by bacterial peritonitis. The authors consider that this treatment is of limited use in patients on the waiting list with poor liver function.

In short, with this therapeutic strategy, a sustained virological response is achieved after the liver transplant in around 20% of very carefully selected patients, although the tolerability and safety is poor in patients on the waiting list, which limits its usefulness to a great extent:

1) The hypersplenic condition, which frequently develops in patients with cirrhosis, limits the possibility of using antiviral drugs.
2) They can also worsen base cytopaenias (leucopoenia, anaemia, thrombocytopenia).
3) They can present other potentially serious risks deriving from interferon, decompensation of the liver disease, risk of bleeding, and most specifically bacterial infections or depression.

In accordance with different authors and consensus,[8,10] it has been recommended that the use of this treatment is limited to patients on the waiting list with a high probability of liver transplant within 3-4 months, with Child-Pugh Score ≤7 or MELD ≤18, with favourable virological response variables (genotypes 2-3 of HCV or 1-4 and low viral load) and which do not present cytopaenias (thrombocytopenia, anaemia, and leucopoenia),

kidney failure, or depression, which contraindicate or limit the use of antiviral therapy. It is estimated that approximately 20%-25% of patients with advanced fibrosis or cirrhosis could be candidates for pre-liver transplant antiviral treatment.

Prophylactic Antiviral Treatment

The second approach to solving the HCV problem in liver transplantation could be based on the use of specific intravenous immunoglobulins (IVIg) or monoclonal antibodies (IVmAb) against HCV, from day 0 of the liver transplant. The hypothesis is that these transplants prevent, delay or decrease re-infection by HCV in transplant patients, reproducing the good results obtained with the intravenous administration of specific anti-hepatitis B immunoglobulins on the rates of hepatitis B virus re-infection after liver transplant.

To date, 2 Phase II clinical trials have been conducted into the use of anti-HCV IVIg.[33,34] In these studies, the patients on the waiting list were distributed randomly into 3 treatment groups: high or low doses of anti-HCV IVIg, and placebo. A dose was administered during the anhepatic phase of the transplant, 1 dose/day for 10 days and 1 dose every 2 weeks for a treatment period median of 3 months. Although there were positive results in terms of the biochemical variables (transient decrease of transaminases), the virological results were totally negative: none of the patients negativised plasma HCV. Furthermore, the study performed by Davis[34] showed that the side effects are usually moderate in seriousness (backache, headache, nausea, vomiting, mainly related to the medication infusion), there were 6 serious side effects, which were possibly, probably, or definitely related to the treatment.

With regard to the use of monoclonal antibodies against HCV, only 1 phase II, randomised, double-blind dosing scaled clinical trial was performed to evaluate the efficacy and safety of HCV-AB^{XLT}68 (a neutralising monoclonal antibody anti E2 totally human and with high affinity) in comparison to placebo, on 24 HCV-positive liver transplant patients.[35,36] Although the HCV viral loads of all the patients from the group treated were decreased during the study, none of these were negativised, with serious side effects that were no greater than those experienced by the placebo group, although there were side effects in 42% of the patients.

These bad safety and efficacy results mean the use of this treatment in HCV therapy as regards liver transplantation unacceptable. However, new treatment dosing regimens are being studied in order to obtain more satisfactory response rates.

Early or Preventative Antiviral Treatment

A third strategy is based on starting the antiviral treatment between 2 and 4 weeks after the liver transplant, when re-infection by HCV has already occurred but the recurrent hepatitis caused by this virus has not yet developed (it does not usually become established until 2-8 weeks after the transplant). At this time (immediately post-transplant) there are positive predictive factors for the virological response of a combined antiviral treatment, such as, for example, a lower rate of viraemia than that produced after the first month post-transplant or the inexistence of advanced fibrosis, or cirrhosis in the transplanted organ. A series of potential drawback are also mentioned, such as the high doses of immunosuppressive agents used to prevent acute rejection that could reduce the likelihood of a sustained virological response, the presence of cytopaenia, kidney failure, and other complications could limit tolerance to interferon and/or ribavirin, or the patients' clinical instability. Furthermore, more than 1 in 3 patients had a benign course of recurrent hepatitis by HCV and it will be not necessary to treat then later.

Several studies have been published assessing interferon, peginterferon, ribavirin in monotherapy, or as combined therapy in this therapeutic strategy, with quite discouraging results in terms of efficacy, but especially with regard to tolerability. Table 2 summarises the most outstanding.

The first studies by Singh[37] and Sheiner[38] were performed with interferon α in monotherapy, started 2 weeks after liver transplant and maintained for 24-48 weeks; in both studies none of the patients achieved a sustained virological response or was survival modified after 1 or 2 years. Neither was there any positive results obtained from monotherapy in the study by Chalasani[39] with peginterferon α-2a, with a sustained virological response of 8%, in addition to producing a high rate of interruption to the treatment due to adverse effects (31%).

Much more favourable are the results with combined therapy.[40-45] In these cases, treatments with IFNα-2b+RBV or PegIFNα-2b+RBV, started between week 3-6 after liver transplant and maintained for 48 weeks. The SVR rates are quite similar to those obtained in immunocompetent patients. However, the Shergill study shows a 18% of SVR, probably due to the high rate of interruption to treatments. One of the aspects to be highlighted from among the results of these studies on combined therapies is the high number of patients requiring adjustments to the doses of IFN, PegIFN, or RBV due to the appearance of side effects (30%-90%).

One aspect that should be evaluated when using IFN- and RBV-based therapy after a transplant is the influence of antiviral treatment on the frequency of the transplanted organ rejection and the interaction of this treatment with post-transplant immunosuppressive therapy. IFN increases the expression of class 1 HLA antigens, involved in the cell immune response in rejection, although its role in the development of rejection in transplant patients is very controversial. All the studies assess the frequency of rejection as a safety parameter, but a very different frequency is observed according to the study. This is so, regardless of the patients and the different treatments in each case, due to the different definitions of "rejection" used in each study: in some cases all the probable clinical cases of rejection were taken into account, while in others only those shown by liver biopsy were included, as were those requiring corticoids or those considered acute in the remaining cases. In any case, what could be observed, as it is argued by the

Table 2. Main Studies Evaluated of Early or Preventative Antiviral Treatment in Comparison to Post-liver Transplant Hepatitis C Treatment[a]

Author	Treatment, No.	Start, Wpost-tx	Interruption, No.	↓Dose, % No.	Rejection, % No.	SVR, % No.
Singh[37,b,c]	IFNα 3 MIU-3 t/w(12)	2	–	–	8	
	No treatment (12)				8	
Sheiner[38,b,c]	IFNα-2b 3 MIU-3 t/w(30)	2	27	–	57	0
	No treatment (41)				56	
Chalasani[39,b,c]	PegIFNα-2a 180 µg/w (26)	3	31	–	12	8
	No treatment (28)				21	8
Mazzaferro[40]	IFNα-2b 3 MIU-3 t/w + RBV 10 mg/kg (36)	3	0	50	0	33
Sugawara[41]	IFNα-2b 3-6 MIU-3 t/w + RBV 400-600 mg/day (21)	4	29	33	26	39
Shergill[42,b,c]	IFNα-2b or PegIFNα-2b (22)	2-6	48	77	56	5
	Idem + RBV 400-800 mg/day (22)			91	18	

↓ dose indicates reduction of antiviral doses; IFN, interferon; No., number of patients on treatment; MIU, millions of international units; PegIFN, peginterferon; RBV, ribavirin; SVR, sustained virological response; t/w, number administrations/week; Wpost-tx, weeks post liver transplant.
[b]Controlled study.
[c]Randomised study.

authors in their articles, is that this treatment does not appear to have any influence on the rejection rate in liver transplant patients. This can be seen clearly in the comparative studies on monotherapy, were no significant differences are obtained in this variable. With regard to the combination therapy studies, Mazzaferro[40] and Sugawara[41] hardly discuss the results obtained in their studies, while Shergill[42] indicates that the proportion of the patients with acute rejection before and after the start of the antiviral treatment is practically the same (8% vs 11%) and that the patients with an episode of acute rejection requiring treatment with corticosteroids during the antiviral treatment did not have different rates at the end of the treatment after 48 weeks in comparison to those who did not present rejection.

With regard to the interaction of the antiviral treatment and the immunosuppressive treatment the results of a meta analysis have recently been published including 5 studies[46] that have compared immunosuppressive regimens based on tacrolimus versus cyclosporine on transplant patients infected with HCV, finding no significant differences between both regimens in terms of mortality, survival of the graft, histologically demonstrated acute rejection, corticoresistant acute rejection, and fibrosing cholestatic hepatitis In 1 of the studies, no significant differences were found in serious fibrosis in the first year either. The authors conclude that the survival of the graft and the patient in HCV-positive liver transplants are similar regardless of the calcineurin inhibitor selected for basic immunosuppression, that the data on the recurrence seriousness and on the viraemia are insufficient and that well-designed randomised, prospective studies are required to determine whether there are any differences in these anti-calcineurins with regard to these specific variables.

As general conclusions for these studies, it is worth to point out:

1) The low level of applicability of the antiviral treatment motivated by the basal situation of the patient immediately after the liver transplant.
2) Only the combination therapy obtains anywhere near satisfactory results.
3) Better results were obtained from transplants from living donors and in the infection by the HCV genotype different from 1.
4) Very low tolerability requiring dosing modifications in up to 50% of the patients.
5) Possibility of "over-treatment," as there is a tendency to use this strategy in patients who can tolerate it, patients who are not always those who are going to have an aggressive relapse of hepatitis.

Given the limitations of this strategy, different experts[8,10] consider that the candidate patients, the factors involved and the precautions that must be taken into account if this treatment is chosen are:

- Patients requiring a liver re-transplant secondary to a recurrent disease from progressive HCV or patients co-infected with HIV
- Consider the following factors in the candidate patients:
  - Clinical stability of the patient (not during the stay in the ICU)
  - Appropriate haematological parameters
  - No contraindication to IFN and/or RBV
- Before starting the treatment, define the variables for interrupting the treatment
- Be extremely careful if another organ is transplanted (heart, kidney), because of the likelihood of increasing the frequency of rejection

Treatment of Recurrent Hepatitis C

Finally, one last possibility is the use of antiviral therapy at the time when a recurrent liver disease due to post-transplant HCV

becomes evident, ie, when the hepatitis C has been reproduced in the transplant patient.

Few studies have evaluated the efficacy and safety of antiviral treatment during the acute stage of recurrent hepatitis. It is worth noting the work by Castells,[47] in which 24 patients re-infected with genotype 1b of HCV after a liver transplant because of cirrhosis associated to HCV were treated for at least 6 months with an initial dose of 1.5 µg/kg/week of PegIFNα-2b associated with 800 mg/day of oral ribavirin (adjusted to blood haemoglobin levels). The sustained virological response obtained was reached in 35% of the patients and anaemia and leucopoenia developed in 71% and 96% of the patients respectively.

However, given the difficulties involved in diagnosing acute hepatitis, especially after a liver transplant, most studies have been carried out when the recurrence of hepatitis C has been histologically proven. In the same way as the other strategies analysed, there are few randomised clinical trials and the majority of the data available comes from uncontrolled, single-centre studies, on a small sample of patients and with great heterogeneity with regard to the moment the treatment is initiated, the type of drugs used, dosing and duration of the treatment, and the use or non-use of growth factors for correcting cytopaenias. With regard to the treatment used, this can be classified in:

a) Monotherapy

- IFNα-2b treatment has been evaluated in studies with a small number of patients for 24 or 48 weeks obtaining very poor rates of biochemical, virological, and histological response[48-51]
- RBV has been used as monotherapy at lower doses than those authorised due to its low tolerability and the influence of tacrolimus or cyclosporine on the glomerular filtration rates, being shown to have an effect on the lowering of the figure of transaminases during treatment (rising again after the treatment is interrupted), but without affecting the viraemia or significantly improving histological activity, thus being considered ineffective[50]
- PegIFNα as monotherapy during 48 weeks has been evaluated in 3 studies,[39,52,53] where sustained virological responses were obtained in between 12%-33%, also showing biochemical and histological responses

b) Combined Therapy

- IFNα+RBV: there are multiple studies[54-69] with different treatment regimens (Table 3). In the majority of them, IFNα-2b 3 MIU was used 3 times a week associated with 400-1200 mg/day of RBV for 12 months. SVR rates were obtained varying between 10%-30%. The greatest limitation of this work is low tolerability and the development of serious side effects (cytopaenias which in some cases required treatment with erythropoietin and filgrastim) which led to the interruption of the treatment in many patients (20%-50%) or to a decrease in the dose of IFN and/or RBV which significantly lowers the response to the treatment
- PegIFNα+RBV; several studies have been developed,[70-85] whose virological results regarding the SVR rate surpass the combination of IFN and RBV (between 26%-50%), meaning this combination has been the treatment of choice for recurrent chronic hepatitis C after liver transplant for many transplant groups. Table 4 presents a summary of these studies, which are characterised by:

  – The small number of cases analysed
  – The dose of PegIFN used is 1-1.5 µg/week for α-2b and 135-180 µg/week for the α-2a. The dose of ribavirin is 600-1200 mg/day. The most recent studies tend to use the highest doses and obtain better results, with rates only slightly lower than those obtained in immunocompetent patients
  – The duration of the treatment is 24 weeks for the 2 and 3 genotypes and 48 weeks for the 1 and 4 genotypes. It has not been assess if prolonging the treatment for more than 48 weeks may offer a persistent virological response
  – The tolerability of the treatment continues to be an important limitation, even in stable patients that initiate the antiviral treatment several years after the transplant. This involves reducing the dose and even interrupting the treatment due to the frequent side effects, especially in the case of RBV, whose pharmacokinetics are heavily influenced by renal function, which may be affected by the use of calcineurin inhibitors as immunosuppressive agents in transplant patients; in fact, in many cases the dose of RBV that can be used is 200-600 mg/day (lower than those used in immunocompetent patients)
  – A high rate of use of growth factors, given the frequent complications of anaemia and leucopoenia. However, there are still no controlled studies available evaluating the benefits of the use of adjuvant growth factor on improved tolerability, fewer dose reductions or improvements in SVR

With regard to patients who are candidates for post-transplant antiviral treatment of the recurrent CHC, the national and international consensus specifies that they must present histological evidence from biopsy of the hepatitis recurrence after the liver transplant and the progression of the fibrosis, positive predictive factors for response to antiviral treatment and not presenting contraindications to combined antiviral treatment (cytopaenia, renal function, depression…).

With regard to the choice of PegIFNα-2a or PegIFNα-2b, the results of 2 studies having made a comparative evaluation of both drugs used for the treatment of recurrent post-transplant CHC[85,86] associated with RBV show no differences in SVR. Therefore, there is no preference for one over the other.

Table 3. Main Studies Evaluated for Antiviral Treatment of Recurrent Chronic Hepatitis C After Liver Transplant With Interferon and Ribavirin[a]

Author	Treatment, No.	Interruption, % No.	FVR, % No.	SVR, % No.
de Vera[54]	IFNα-2b 1.5-3 MIU-3 t/w + RBV 400-1000 mg/day (32)	46	77	9
Shakil[55]	IFNα-2b 3 MIU-3 t/w + RBV 800-1000 mg/day (38)	42	13	9
Lavezzo[56]	IFNα-2b 3 MIU-3 t/w + RBV 800 mg/day (57)	3	23	19
Samuel[58,b,c]	IFNα-2b 3 MIU-3 t/w + RBV 800-1200 mg/day (28)	43	32	25
	No treatment (24)			
Burra[59]	IFNα-2b 6 MIU-3 t/w + RBV 1000 mg/day (30)	20	37	20
Alberti[61]	IFNα-2b 3 MIU-3 t/w + RBV 600 mg/day (18)	22	44	28
Ahmad[62,b]	IFNa-2b 3-5 MIU-3 t/w (40)	25	15	2.5
	IFNα-2b 3-5 MIU-3 t/w + RBV 600 mg/day (20)	25	40	20
Gopal[63]	IFNα-2b 1-3 MIU-3 t/w + RBV 600-1200 mg/day (12)	17	50	8
Narayanan[64]	IFNα-2b 3 MIU-3 t/w + RBV 800-1000 mg/day (26)	50	35	23
Giostra[65]	IFNα-2b 3 MIU-3 t/w + RBV 10 mg/kg/day (31)	29	45	26
Berenguer[66]	IFNα-2b 1.5-3 MIU-3 t/w + RBV 600-1200 mg/day (24)	29	25	12
Mukherjee[68]	IFNα-2b 3 MIU-3 t/w + RBV 1000-1200 mg/day (38)	37	33	26

[a]FVR indicates virological response at the end of the treatment; IFN, interferon; MIU, millions of international units; No., number of patients on treatment; RBV, ribavirin; SVR, sustained virological response; t/w, number administrations/week.
[b]Controlled study.
[c]Randomised study.

Table 4. Main Studies Evaluated for Antiviral Treatment of Recurrent Chronic Hepatitis C After Liver Transplant With Peginterferon and Ribavirin[a]

AutAuthor	Treatment, No.	Interruption, % No.	HGF, % No.	G-CSF, % No.	Rejection, % No.	SVR, % No.
Mukherjee[71]	PegIFNα-2b 1.5 µg/kg/w + RBV 800 mg/day (39)	44	Np	Np	NA	31
Rodriguez-Luna[72]	PegIFNα-2b 0.5-1.5 µg/kg/w + RBV 800-1000 mg/day (19)	37	74	47	5	26
Dumortier[73]	PegIFNα-2b 0.5-1.0 µg/kg/w + RBV 400#fderecha1000-1200 mg/day-IC (20)	20	Np	Np	25	45
Mukherjee[75]	PegIFNα-2a 180 µg/w + RBV 1000-1200 mg/day (32)	16	NA	NA	NA	41
Oton[76]	PegIFNα-2a (4) or a-2b (51), full doses, + RBV >11 mg/kg/day	29	NA	NA	2	44
Biselli[77]	PegIFNα-2b 1 µg/w + RBV 600 mg/day (20)	5	35	45	0	45
Berenguer[78,b,c]	IFNα-2b + RBV (31)	40	25	13	3	13
	PegIFNα-2a or a-2b + RBV (36)				14	50
Carrion[79,c,d]	PegIFNα-2b 1.5 µg/kg/w + RBV 400-1200 mg/day (27)	38	78	52	4	33
	No treatment (27)	–	0	0	0	0
Angelico[80,c,d]	PegIFNα-2a 180 µg/kg/w (21)	–	0	0	0	0
	PegIFNα-2a 180 µg/kg/w + RBV 200→MTD mg/day (21)	33			4	33
Neff[82]	PegIFNα-2b 1.5 µg/kg/w + RBV 400→800 mg/day (57)	31	43	35	NA	14
Neumann[83]	PegIFNα-2b 1 µg/kg/w + RBV 400-1000 mg/day (25)	4	12	44	0	36
Fernández[84]	PegIFNα-2b 1.5 µg/kg/w + RBV 600-800 mg/day (47)	21	36b	NA	6	23

[a]G-CSF indicates granulocyte colony-stimulation factor (filgrastim); HGF, hematopoietic growth factor (erythropoietin or darbepoetin); ID, increasing doses; NA, not available; Np, not initially protocolised; µg/kg/w, dose peginterferon/week; MTD, maximum tolerated dose; No., number of patients on treatment; PegIFN, peginterferon; RBV, ribavirin; SVR, sustained virological response.
[b]This article did not report the dose. The data for interrupting the treatment and the use of HGF and G-CSF are given for both treatment groups.

The duration of the combined therapy was chosen depending on the viral genotype (6 months for genotypes 2 and 3 and 12 months for genotypes 1 or 4), but the optimum duration is not clear. In patients with recurrent cholestatic CHC, some authors have evaluated indefinite maintenance therapy, with the objective of avoiding relapses after stopping the antiviral treatment.[87]

As a consequence of the low safety profile of antiviral treatment of recurrent hepatitis in the liver transplantation context, special follow-up must be carried out of cytopaenias, liver function, infections, rejection, and psychiatric disorders. With regard to monitoring the safety and use of supporting therapies, the following proposal has been made[88]:

– Anaemia: start the treatment with erythropoietin if there is a fall in haemoglobin (Hb) of 3 g/dL from the base value to dose of 40 000 IU/week (or twice a week) up to the time the hematocrit reaches 36% or until reaching base values of Hb. Lower the dose of RBV by 50% if there is no response and consider stopping it if the desired Hb values are not achieved
– Neutropaenia: start filgrastim if there is a total drop in neutrophils below 1000 cells/mL, a dose of 5 µg/kg/week (or twice a week) until resolution. Consider reductions in the dose of PegIFN
– Impaired liver function: stop the treatment and consider liver biopsy to rule out other causes
– Infections: interruption to treatment (can be re-established after the resolution of the infection)
– Rejection: stop the treatment definitely
– Psychiatric disorders: start antidepressant treatment, which is supervised by specialists, preferentially with SSRIs. Consider reducing the dose of PegIFN until resolution or stabilisation of the condition

CONCLUSIONS

According to the studies assessed, it can be concluded that prophylactic antiviral treatment does not achieve virological responses and the preventative or anticipated post-transplant antiviral treatment has very little application, tolerability and response, meaning that neither of them is the treatment of choice for the prophylaxis and/or treatment of hepatitis C in the liver transplantation setting. Most experts look to the other 2 possible therapeutic approaches, the pre-transplant antiviral treatment and post-transplant antiviral treatment of the recurrent CHC, as this is more effective, although the high recurrence rates of HCV and the low safety profile are still a serious limitation on the achievement of the therapeutic objectives. Although there are no studies comparing the safety and efficacy of the 2 strategies, given the low applicability of pre-transplant antiviral treatment, the majority of the patients are treated after the liver transplant when there is evidence of recurrent CHC.

Although it has not been finally established which therapeutic regime is better, when it should be started and for how long it should be administered, the evidence available suggests that the treatment of choice in both cases is combination therapy with peginterferon associated with ribavirin.

Strict monitoring of the safety must also be performed, given the high incidence and seriousness of the side effects in this type of patients.

Acknowledgements

Begoña Feal Cortizas, for her useful observations while reviewing the manuscript.

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