

Treatment of recurrent hepatitis C post-liver transplantation

Claudio Augusto Marroni*

* Associate Professor of Gastroenterology, Federal University of Health Sciences of Porto Alegre.

ABSTRACT

Recurrent hepatitis C after liver transplantation is universal. Graft reinfection occurs rapidly, with chronic hepatitis and rapid evolution from end-stage liver disease. Within 5 years until 30% of patients with recurrent disease ultimately progress to cirrhosis, and survival of transplanted patients with recurrent hepatitis C virus has been shown to be lower than of patients transplanted for other indications. Antiviral therapy in this patient population is generally recommended, but indication, optimal timing, dose and duration of therapy are not clearly defined. There are two major indications of therapy in that patients: pre-transplant antiviral therapy aiming to prevent reinfection, and post-transplant therapy with the goal of eradicating the recurrent infection. The first is limited by poor tolerance and drug side effects, and the second achieves only sustained virologic response in 25-45% of patients. Combination therapy with PEG INF and ribavirin shown the better results. Dose reduction and interruption of therapy occurs in 30 to 60% by side effects. There are no prospective randomized trials with confidence of results. More efficacious and better tolerable antiviral therapies are needed.

Key words. Recurrent hepatitis C. Liver transplantation. HCV treatment.

INTRODUCTION

Hepatitis C virus (HCV)-related liver disease is the main cause of cirrhosis and hepatocellular carcinoma and is the main indication for liver transplantation worldwide.¹⁻⁵

Liver transplantation offers an effective treatment significantly reducing morbidity and mortality in this population but re-infection with HCV of the liver graft is universal in patients who undergo liver transplantation for HCV-related end stage liver disease.¹⁻⁵ HCV re-infection is almost inevitable in patients with measurable viral RNA undergoing liver transplantation.

The recurrence of HCV infection after liver transplantation leads to the development of chronic hepatitis in at least 50% of grafts after 1 year and up to 100% after 5 years.¹⁻⁵ The natural history of hepatitis C is more aggressive after liver transplantation than in immunocompetent patients.¹⁻⁵ Graft cirrhosis has been reported in around 30% of patients 5

years after liver transplantation and the survival rate is significantly lower compared to that of HCV-negative recipients.¹⁻⁵

In a recent study by Forman⁶ of 11.036 patients, transplantation in HCV + recipient was associated with an increased death rate of 1.23 (95% CI) as compared with transplantation in recipients without HCV.

Studies that have longer follow-up than 5 years seem to indicate that patients undergoing liver transplantation for HCV have proven increased severity of recurrence HCV after liver transplantation, with rapid progression to cirrhosis, graft failure, and need for re-transplant when compared with other patients.⁷

The recurrence rate with hepatitis C virus could be dependent on several factors like: hepatitis C subtype, donor age, recipient age, recipient model for end-stage liver disease (MELD) score, warm ischaemic time, immunosuppressive regimen, use bolus of steroids, induction of immunosuppression, use of OKT3, period of time of transplantation.¹⁻⁵

Analysis of studies examining the efficacy of treatment for recurrent HCV infection are hampered by the enrollment of small numbers of patients at single centers, the use of different immunosuppressive regimens, different criteria for initiating and sto-

Correspondence and reprint request: Dr. Augusto Marroni
Federal University of Health Sciences of Porto Alegre Rio Grande Do Sul Brazil.
E-mail: nmarroni@terra.com.br

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pping therapy, and finally, different treatment regimens across the various centers.⁸

The impact of HCV recurrence on graft and patient survival determines many possibilities to treat patients with post-transplant HCV-related hepatitis: pre-transplantation antiviral therapy, post-transplant treatment of acute viral hepatitis, use of immunoglobulin anti-HCV, pre-emptive therapy initiated soon after transplantation, and therapy for established post-transplant chronic hepatitis.¹⁻⁵

PRE-TRANSPLANTATION ANTIVIRAL THERAPY

Antiviral therapy in HCV-infected cirrhotics awaiting liver transplantation

The aim of antiviral therapy prior to liver transplantation is either to achieve a sustained virological response (SVR) at transplantation or an on-treatment serum HCV RNA clearance at transplantation, prevent post-transplant recurrence and halt disease progression.⁹⁻¹⁴ HCV will recur in all liver transplant recipients who are viremic before transplantation. Biopsy proven recurrence of hepatitis C develops in the majority of patients within 1 year of transplantation and often progresses to chronic hepatitis, and a significant proportion of them will progress to cirrhosis.⁷ The proportion of patients being HCV positive developing advanced liver disease within 3 to 5 years after liver transplantation has increased from past decades.¹⁵⁻¹⁷ HCV infection adversely affects both patient and graft survival after liver transplantation.¹⁵⁻¹⁷

Few published studies have investigated the role of standard INF or PEG INF, with or without ribavirin (RBV) in patients with decompensated HCV cirrhosis. All these studies were with a few number of patients, were not controlled, were not randomized, and varied considerably in their objectives and modalities. A group of 168 patients enrolled in 4 studies was submitted to different regimens of INF, with or without RBV, different duration times of treatment, and several complications. Because of the high rate of complications and 10% mortality, one of this studies was terminated. The SVR varied from 0% to 22%. A total of 79 patients in this "combined experience" who received antiviral therapy underwent hepatic transplantation, and 18 (23%) were free of hepatitis C post-transplantation.¹⁸⁻²²

Recently, it has been shown that antiviral treatment taken for HCV before liver transplantation is associated with progression of fibrosis after liver

transplantation,¹² and a retrospective analysis by Smallwood,⁷ comparing INF use prior to liver transplantation for HCV patients, indicates a poor outcome of these as compared to HCV patients who never received INF, mainly those who do not have virological response. Carrión et al.¹³ in a retrospective case-control study using PEG INF with adjusted doses of RBV for creatinine clearance in HCV-infected cirrhotic patients awaiting liver transplantation, use growth factors, achieve 47% of HCV RNA negative in EOT, but only 29% were HCV RNA negative at the time of transplantation, and 20% achieved SVR after transplantation, mainly in non-1 genotype. However, the incidence of bacterial infections episodes was higher in treated patients (25%) than in controls (6%) with septic shock in 10%. Iacobellis et al.²³ in a non randomized controlled study, showed that the odds ratio in treated patients was 2.95 for severe infections and 1.97 for death from infections. Tekin et al.²⁴ in a cohort study obtained a 30% SVR in 48 weeks of therapy. No patient died during the follow-up period. In 15% with HCV-HCC a living liver donor transplantation was performed.

Allocation of grafts for HCV-HCC is legally preferred in many countries, and the majority of them are Child-Pugh A or have a MELD score lower than 12 and were submitted to liver transplantation within less than 6-12 months. These could be an ideal group to begin prospective randomized, controlled trials.

Conclusion

Few studies were conducted on this subject, all of them being retrospective and uncontrolled with low numbers of patients and, thus, with a high risk of bias. The indication of this therapy is restricted due to the high risk of complications and poor results.

Class II b – Level C.

PREEMPTIVE ANTIVIRAL THERAPY IN HEPATITIS C INFECTED PATIENTS UNDERGOING LIVER TRANSPLANTATION

A preemptive strategy would seem attractive because treatment is begun while viral levels are low and before the graft is damaged and theoretically may lead to higher SVR rates.^{2-5,8} In practice, however, only 40-60% of patients are candidates because of the high doses of immunosuppression used, underlying cytopenias, mild renal dysfunction and the presence of other medical problems during this early

period post-liver transplantation.^{2-5,8,15-22,25,26} The use of standard interferon or pegylated interferon monotherapy is not advised because of poor SVR rates (0% and 8%, respectively) as reported in randomized controlled trials.²⁷ The addition of ribavirin was associated with improved response rates (18% to 19%), but it is not well tolerated in the early peri-transplant period and dose reduction is common.^{15-22,25,26}

Conclusion

Preemptive therapy was associated with high rates of side effects, including rejection and unrelated death, and a large proportion of patients required dose reductions. Thus, given these adverse effects, the low SVR rates and the lack of improvement in graft loss or mortality, preemptive therapy cannot be universally recommended.

Class III – Level B.

TREATMENT OF ESTABLISHED RECURRENT HEPATITIS C POST-LIVER TRANSPLANTATION

Most transplant centers prefer to delay therapy until recurrent disease is confirmed by demonstra-

tion of significant fibrosis on liver biopsy (Metavir ≥ 2 or Ishak ≥ 3). The decision to initiate therapy must consider the benefits of achieving a SVR, including the potential for histologic improvement *vs.* the risk of precipitating acute cellular rejection and side effects of therapy.^{1-5,8,15-18} The early experience with therapy following liver transplantation begins in the 90's with observational studies using either interferon or ribavirin monotherapy, or its combination, which resulted in disappointing outcomes, several complications, acute cellular rejection, needs to dose reductions or stopped therapy.^{1-5,15-18} Management of chronic hepatitis C in liver transplant recipients with recurrent hepatitis C has improved significantly during the past decade,¹⁵⁻¹⁷ and the best results published to date were obtained with pegylated INF alfa in combination with ribavirin.¹⁵⁻¹⁷ The vast majority of these studies are either open-label, retrospective, no randomized, or small pilot studies and individually do not provide a reliable template on which to base effective strategies for improving treatment of patients with hepatitis C after liver transplantation.¹ There is no consensus in the set of hepatitis C recurrence after liver transplantation in managing therapy with respect of the most effective dosing regimen, the best time to initiate treatment, monotherapy or combination therapies, use of

Table 1. Studies characteristics - Cochrane.

Author	Year	Country	Type of Study		Patients included
Angelico	2007	Italy	Randomized clinical trial	42	Gr 1: ribavirina e peg interferon (n = 21) Gr 2: peg interferon (n = 21)
Carrión	2007	Spain	Randomized clinical trial	54	Gr 1: peg interferon e ribavirin (n = 27) Gr 2: control (n = 27)
Chalasani	2005	USA	Randomized clinical trial	67	Gr 1: peg interferon (n = 33) Gr2: control (n = 32)
Cotler	2001	USA	Randomized clinical trial	12	Gr1: interferon (n = 8) Gr2: control (n = 4)
Crippin	1996	USA	Randomized clinical trial	35	Gr1: interferon 1 million units (n = 6) Gr2: interferon 3 million units (n = 9) Gr3: interferon 6 million units (n = 6) Gr4: control (n = 6)
Gane	1998	United Kingdom	Randomized clinical trial	30	Gr1: ribavirin (n = 16) Gr2: interferon (n = 14)
Ghalib	2000	USA	Randomized clinical trial	5	Gr1: Interferon e ribavirin (n = 3) Gr2: Interferon e ribavirin (n = 2)
Ghalib	2006	USA	Randomized clinical trial	59	Gr 1: peg interferon (high dose) and ribavirin (n = 32) Gr 2: peg interferon (low dose) and ribavirin (n = 27)
Lodato	2008	Italy	Randomized clinical trial	18	Gr 1: peg interferon e ribavirin (n = 9) Gr 2: control (n = 9)
Nair	2008	USA	Randomized clinical trial	50	Gr 1: amantadine, peg interferon e ribav. (n = 13) Gr 2: peg interferon and ribav.(n = 17)
Samuel	2003	France	Randomized clinical trial	52	Gr 1: interferon and ribavir. (n = 28) Gr 2: control (n = 24)

growth factor and erythropoietin and how to mitigate the risk for allograft rejection.^{1,15-17}

There are many disparities in the several studies of the current literature. Recently, a paper from Cochrane was published with the following title: Antiviral therapy for recurrent liver graft infection with hepatitis C virus (Review) Gurusamy KS, Tsochatzis E, Xirouchakis E, Burroughs AK, Davidson BR. The Cochrane Collaboration - The Cochrane Library, Issue 1, 2010. John Wiley & Sons, Ltd.¹¹

The bibliography utilized in this study is summarized in table 1.

Objective: To compare the therapeutic benefits and harms of different antiviral regimens in patients with hepatitis C re-infected grafts after liver transplantation only randomized clinical trials comparing various antiviral therapies (alone or in combination) in the treatment of hepatitis C virus recurrence in liver transplantation were considered for the review. Two authors collected the data independently. The data were collected from twelve trials (27 publications). They were randomized in twelve trials to various interventions and controls. All the trials were of high risk of bias.

A total of 425 liver transplant recipients with proven hepatitis C recurrence were randomized. The mean proportion of genotype I was 79.9%. One to two trials were included under each comparison including single drug or multidrug regimens of interferon, ribavirin, and amantadine. There were no significant differences in the mortality, graft rejection, or in re-transplantation between intervention and control in any of the comparisons that reported these outcomes. None of the trials reported liver decompensation or quality of life. Life-threatening adverse effects were not reported in either group in any of the comparisons. Up to 87.5% of patients required reduction in the dose and up to

42.9% of patients required cessation of treatment in the various comparisons because of adverse effects or because of patient's choice to stop treatment.

Comments

Antiviral therapy to treat recurrent hepatitis C infection after liver transplantation is controversial due to unresolved balance between benefits and harms. This systematic review of randomized clinical trials was performed to compare the benefits and harms of different antiviral therapies in patients with hepatitis C re-infected grafts after liver transplantation. All the trials were of high risk of bias

(risk of systematic error due to inadequate methodological quality) and high risk of play of chance (risk of random error due to few patients randomized). A total of 425 liver transplant recipients with proven hepatitis C recurrence were randomized in 12 trials to various interventions and controls (including single drug regimen or multidrug regimen of interferon, ribavirin, and amantadine). Nine trials reported the proportion of patients belonging to genotype I (a subtype which is more difficult to treat than other subtypes). More than three-quarters of the patients belonged to genotype I in these nine trials. Only one or two trials were included under each comparison. Further randomized clinical trials at low risk of systematic errors or random errors are necessary to assess the long-term survival benefits for various treatment options, particularly combination pegylated interferon and ribavirin therapy with or without the use of granulocyte colony-stimulating-factor and synthetic erythropoietin, which may be helpful in treating the adverse effects of the therapies without reducing the dosage.

This study has a correct methodological design and analyses 27 studies from 12 authors from 1996 to 2008, with a small number of patients. There were no significant differences in the mortality, graft rejection, or re-transplantation in any comparison in the few trials that reported these outcomes. Adverse effects were frequent. The patients were followed up only for 24 weeks to 26 weeks after the end of treatment. Longer periods of follow-up are necessary to determine any clinical benefit.

Conclusions

Considering the lack of clinical benefit and the frequent adverse effects, there is currently no evidence to recommend antiviral treatment for recurrent liver graft infection with HCV. Further randomized clinical trials with adequate trial methodology and adequate duration of follow-up are necessary.

Class II b – Level A.

The AASLD PRACTICE GUIDELINES – Diagnosis, Management, and Treatment of Hepatitis C: An Update, published in *Hepatology*, April 2009, by Marc G Ghany et al.⁸ in Liver Transplantation chapter, after an analysis of more than 30 recent trials considering therapy for hepatitis C recurrent post-liver transplantation (1998 – 2007), recommends the treatment with PEG INF alfa, with or without ribavirin, the preferred regimen to treat pa-

tients with hepatitis C after liver transplantation. Predictors of response to treatment post-transplantation have not been well studied. There is no consensus in this wide range of information.

Adverse events were common in all trials of patients with recurrent HCV post-liver transplantation, cytopenias being the most common reported.

The risk of acute cellular rejection is an important concern that has been difficult to estimate. Uncontrolled trials report 11% to 30% SVRs but randomized trials report lower rates (0% to 5%). Profound graft dysfunction may occur after viral clearance. Efforts should be made to define criteria for diagnosis, therapy and to define the optimal timing, duration and dose to treat recurrent HCV post-liver transplant before the disease becomes severe.

Recommendations

Treatment of HCV-related disease following liver transplantation should be initiated in appropriate candidates after demonstration of recurrent histologic disease but should be undertaken with caution and under the supervision of a physician experienced in transplantation.

Class IIa – Level A.

Peginterferon alpha either with or without ribavirin should be the preferred regimen when treat-

ing patients with hepatitis C after liver transplantation.

Class II a – Level B.

Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. Review. Berenguer, M. *Journal of Hepatology* 49 (2008) 274-287.¹ The bibliography utilized in this study is summarized in table 2.²⁷⁻⁴⁶

Nineteen studies were eligible for inclusion in this analysis and all were published between 2004 to 2007. Most studies were retrospective and consisted of a review of hospital experience in treating hepatitis C recurrence post-liver transplantation with PEG INF and ribavirin. There were no randomized comparative studies. Inclusion criteria were generally homogeneous across all studies and included detectable HCV RNA and histologic findings consistent with chronic liver damage of different degrees. A total of 611 liver transplant recipients treated with PEG INF alfa and ribavirin were included in the 19 studies. The main observations of Berenguer are: the ETVR was 42.2% and the SVR was attained in 30.2% of treated patients.

Results from 2004-2005 –SVR was 19.7% and in 2006-2007– SVR was 35.2% and could be dependent of a learning curve. Treatment duration after transplantation is generally instigated for a standard 12-

Table 2. Studies characteristics - M. Berenguer.

Author	Year	Country	Type of study	Patients included
Rodríguez-Luna, <i>et al.</i>	2004	USA	Prosp no cont	56
Neff, <i>et al.</i>	2004	USA	Retros no cont	57
Ross, <i>et al.</i>	2004	USA	Retros no cont	16
Dumortier, <i>et al.</i>	2004	France	Prosp no cont	20
Babatin, <i>et al.</i>	2005	Canada	Retros no cont	13
Toniutto, <i>et al.</i>	2005	Italy	Retros no cont	12
Castells, <i>et al.</i>	2005	Spain	Prosp cont	24
Biselli, <i>et al.</i>	2006	Italy	Retros no cont	20
Berenguer, <i>et al.</i>	2006	Spain	Retros no cont	36
Oton, <i>et al.</i>	2006	Spain	Prosp no cont	55
Mukherjee, <i>et al.</i>	2006	USA	Retros no cont	32
Mukherjee, <i>et al.</i>	2006	USA	Prosp no cont	39
Fernández, <i>et al.</i>	2006	Spain	Prosp no cont	47
Neumann, <i>et al.</i>	2006	Germany	Prosp no cont	25
Picciotto, <i>et al.</i>	2007	Italy	Prosp no cont	61
Angelico, <i>et al.</i>	2007	Italy	Prosp cont (1 arm with PEG-IFN monotherapy)	42 (21 treated with PEGIFN + RBV)
Carrión, <i>et al.</i>	2007	Spain	Prosp cont	81 (54 treated)
Sharma, <i>et al.</i>	2007	USA	Retros no cont	35
Zimmermann, <i>et al.</i>	2007	Germany	Prosp no con	26

Table 3. Studies characteristics, 2007-2009.

Author	Year	Typen of study	Patients included
Hanouneh IA, <i>et al.</i>	2008	Retrospective (no cont)	53
Roche B, <i>et al.</i>	2008	Retrospective (no cont)	113
Kuo A, <i>et al.</i>	2008	Retrospective (controlled)	86
Shackel NA, <i>et al.</i>	2009	Retrospective study (no cont)	118
Belli LS, <i>et al.</i>	2007	Retrospective (controlled)	354
Berenguer M, <i>et al.</i>	2009	Retrospective (no cont)	107
Alkhoury N, <i>et al.</i>	2009	Prospective (no cont)	47
Fernández I, <i>et al.</i>	2009	Prospective (no cont)	79
Manousou P, <i>et al.</i>	2009	Clinical randomized study (no cont)	103
Berenguer M, <i>et al.</i>	2009	Clinical experiment (no cont)	171
Walter T, <i>et al.</i>	2009	Retrospective (no cont)	70
Walter T, <i>et al.</i>	2007	Retrospective (no cont)	70
Cescon M, <i>et al.</i>	2009	Prospective (no cont)	99

month period, regardless of HCV genotype. The reduced tolerance to ribavirin induces to start it at low doses and increase doses slowly according the patient tolerability. Growth factor supplementation and erythropoietin were used in half of patients. Dose reduction of one or both therapeutic agents was done in 60% to 70% of treated patients. Histological and biochemical benefits occurs in some patients with continued treatment even in absence of SVR.

Recommendations

Treatment of HCV-related disease following liver transplantation should be initiated in appropriate candidates after demonstration of recurrent histologic disease but should be undertaken with caution and under the supervision of a physician experienced in transplantation.

Class IIa – Level A.

Peginterferon alpha with ribavirin should be the preferred regimen when treating patients with hepatitis C after liver transplantation.

Class IIa – Level B.

Thirteen studies (Table 3)⁴⁷⁻⁵⁷ were eligible for summary analysis and all were published between 2007 to 2009. Nine of them were retrospective, four prospective and no one randomized. All consisted of review of experience in treating hepatitis C recurrence post-liver transplantation with PEG INF and ribavirin. Inclusion criteria were detectable HCV RNA and histologic findings consistent with chronic liver damage of different degrees. A total of 1400 liver transplant recipients treated with PEG INF alfa and ribavirin were included.

The main results are:

- SVR 30% (9% to 49%),
- Death 16% (8% to 27%).
- Stop treatment 33% (11% to 49%).
- Dose reductions 43% (16% to 62%).
- Rejection 9% to 21%.

The results are similar to the observed in AASLD paper and in the review from Berenguer, and the recommendations could be same as that they do.

Class II a – Level B.

Recent studies suggest that the role of EVR in predicting treatment outcome among hepatitis C virus recurrent post-liver transplantation patients could be similar to the results obtained in chronic hepatitis C who have not undergone transplantation, in applying the 12-week stopping rule.^{8,56}

Further randomized clinical trials are necessary to evaluate optimal treatment of patients having recurrent hepatitis C virus infection after liver transplantation (particularly combination pegylated interferon and ribavirin therapy with or without the use of granulocyte colony-stimulating-factor and synthetic erythropoietin). Such trials must also include a control group (untreated group) to determine if treatment provides any benefit.

Studies such as PHOENIX in phase 4, and PROTECT in phase 3b, are, therefore, urgently needed to improve our understanding of the most effective manner in which the full potential of the therapeutic resources available can be harnessed.⁸

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