Aggressive Use of Ribavirin and Prolonged Course of Peginterferon to Improve the Rate of Viral Response in Liver Transplant Patients with Recurrent Hepatitis C Viral Infection

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Abstract

Objectives: **There are different approaches for treating recurrent hepatitis C viral infection after a liver transplant. However, sustained virologic response is achieved in < 40% of infected allografts. We examined sustained virologic response improvement using a prolonged course of peginterferon and aggressive use of ribavirin.**

Patients and Methods: **From October 1998 to May 2008, 24 patients (13 male, 11 female; mean age at transplant, 49.4 ± 7.7 years) received a prolonged course of peginterferon and ribavirin (range, 48-180 weeks). The mean interval from liver transplant to hepatitis C antiviral therapy was 26.6 ± 27.8 months. Patients began weight-based standard dosages of peginterferon and ribavirin. In case of hemolysis, patients were treated with Epogen, with and without blood transfusions.**

Results: **Fourteen patients (58.3%) had an end of treatment response, and 8 patients (33.3%) maintained sustained virologic response after the first course of therapy. Of 10 patients who did not respond to the first course, 6 received an extended course of antiviral therapy after a mean of 15 ± 4.6 weeks from completion of first course. Five of these 6 patients achieved end of treatment response and maintained a sustained virologic response, resulting in an overall end of treatment response in 17 patients and a sustained virologic response in 13 patients. Twenty-two patients experienced hemolysis and were treated with Epogen. Fifteen patients received blood transfusions. Ribavirin dosage was reduced in 12 patients, and peginterferon dosage was reduced in 2 patients.**

Conclusions: **Aggressive use of ribavirin and prolonged course of peginterferon provided sustained virologic response in 54.1% of liver transplant recipients with recurrent hepatitis C virus-infection. More prospective studies are warranted to evaluate the benefit of this approach fully.**

Key words: *Liver, Transplant, Hepatitis-C, Interferon, Ribavirin*

Introduction

Among the adult population of the United States, chronic hepatitis C infection is the most common cause of liver transplant (1). However, reinfection of the grafts is universal, with graft loss in up to 25% to 30% of the patients by 10 years after transplant (1-3). These patients have accelerated fibrosis in the liver, with 6% to 23% developing cirrhosis after a median of 3.4 years (1, 4-6). The survival rates are significantly lower in patients with recurrent hepatitis C compared with the patients who receive liver transplants for other causes (1, 7).

Currently there is no uniform agreement on the indications for anti-hepatitis C virus treatment, including optimal treatment timing, dosage, and

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duration (1). The only available treatment option to achieve a sustained virologic response is combination therapy with pegylated interferon and ribavirin. However, such a response rate is currently achieved in only 30% to 43% of allografts reinfected with hepatitis C virus (8, 9). One of the most important reasons for such low sustained virologic response values has been withdrawal from therapy (range, 30%-35%) (10-13).

Dosages of ribavirin and/or peginterferon frequently have been reduced because of adverse drug effects such as hemolysis, fatigue, weight loss, depression, thrombocytopenia, and leucopenia. There are no large multicenter data that report the effect of a combination of prolonged course of peginterferon and aggressive use of ribavirin on virologic response in patients with recurrent hepatitis C virus infection after liver transplant.

We sought to examine the outcome of patients with recurrent hepatitis C virus infection after liver transplant who received antiviral therapy at our institution in the last 10 years and to see if the end of treatment response and sustained virologic response were improved by giving them a prolonged course of peginterferon (> 48 weeks) and aggressive use of ribavirin, and comparing it with available data.

Patients and Methods

From October 1998 to May 2008, 24 patients who developed recurrent hepatitis C virus after liver transplant were treated with antiviral therapy at our institution. After approval by the Temple University institutional review board, a retrospective chart review of these patients was performed. There were 13 male (54.1%) and 11 female patients (45.8%), with a mean age of 49.4 ± 7.7 years at transplant. In our study, there were 6 African American (25%), 8 Hispanic (33.3%), and 10 white patients (41.6%).

Patients were selected for antiviral therapy based on change in inflammatory score of 4 or more points, or an increase in fibrosis score more than 1, as per the Ishak scoring system (14). These changes were found on either yearly protocol biopsies after the transplant, or on interim biopsies done for other clinical reasons. The mean time from liver transplant to antiviral therapy for recurrent hepatitis C was 26.6 ± 27.8 months. The mean viral load before starting antiviral therapy was 5 100 774 ± 7 854 397 IU/mL. Pegintron was used in dosages from 1.5 to 1.8. μg/kg/wk, and dosages of pegasys were 180 μg/kg/wk. The ribavirin dosage was aimed at 11 to 15 mg/kg/d. The dosage of Pegintron/pegasys was reduced in the event of persistent thrombocytopenia (platelets count < 25 000/mL) or depression. The ribavirin dosage was reduced when anemia was not controlled with erythropoietin factor or/and blood transfusion.

All patients were treated with a prolonged course (48-180 weeks) of peginterferon and ribavirin (Table 1). The mean follow-up was 45.5 ± 25.3 months after antiviral therapy (Table 1). A designated person in the hepatology unit consistently performed close supervision during this time. We believe that this effort to coordinate the physician's instructions and patient's understanding played a significant role in completing the therapy and in the patient's overall well being.

Table 1. Patient Characteristics.

Demographics	Number
Total No. of patients	24
Male	13 (54.2%)
Female	11 (45.8%)
Mean age at transplant	49.4 ± 7.7 years
Mean interval from liver transplant to antiviral therapy	26.6 ± 27.8 months
Mean duration of follow-up	45.5 ± 25.3 months
Mean viral load before starting treatment (IU/mL)	5 100 774 ± 7 854 396
Duration of antiviral therapy	48-180 weeks (range, 55 ± 43.7 wk)

Baseline immunosuppression consisted of tacrolimus in 16 patients (66.6%), cyclosporine in 7 patients (29.1%), and rapamycin in 1 patient (4.1%). Immunosuppression was sometimes modified because of worsening renal impairment. Overall, 6 patients (25%) received rapamycin, 7 patients (29.2%) received mycophenolate mofetil, and 19 patients (79.2%) were on prednisone at the time of antiviral therapy. However, the dosage of prednisone was gradually tapered and either maintained at 1 to 3 mg/d, or eventually stopped.

In the event of hemolysis (defined as a fall in hematocrit of ≥ 15%), patients were treated with Epogen (epoetin alfa), with or without blood transfusions, to maintain the maximum tolerable dose of ribavirin. This effort to combat the adverse effects of antiviral therapy was made with the aim of completing the course of therapy, as these patients might not be able to receive a second liver transplant.

Statistical Analyses

Values are stated as mean, median, and standard deviation using Microsoft Office Excel 2003.

Results

All 24 patients were started initially on peginterferon and ribavirin. Fourteen patients (58.3%) had an end of treatment response, and 8 (33.3%) achieved sustained virologic response with the first course of therapy. Of the 16 patients who did not achieve a sustained virologic response with this first course, 6 received an extended course of antiviral therapy after a mean interval of 15 ± 4.6 weeks from the first course of therapy. The remaining 10 patients were not considered for extension of therapy because of severe renal impairment (n=2), biochemical increase in liver function (n=2), severe thrombocytopenia (n=1), chemical pneumonitis (n=1), refusal by patient (n=1), financial problems (n=1), and loss to follow-up (n=2).

End of treatment response and extended course of antiviral therapy

End of treatment response is defined as hepatitis C virus RNA-negative at the end of 48 weeks of therapy. Initially, all patients were treated with antiviral therapy for 48 weeks. Of 24 patients, an end of treatment response was achieved in 14 patients (58.3%) at the end of the initial therapy (Table 2). Of the remaining 10 patients, 6 (60%) went on to receive an extended course of therapy. The total duration of antiviral therapy in these 6 patients was 69 months (n=1), 84 months (n=1), 96 months (n=1), 111 months (n=1), 148 months (n=1), and 180 months (n=1). The overall mean duration of therapy for these patients was 114 ± 42 months.

Table 2. Response rate to peginterferon and ribavirin.

Patient characteristics	No. of patients	Percentage	ETR (%)	SVR (%)
First treatment	24		14 (58.3)	8 (33.3)
Extended course of treatment	6		5 (83.3)	5 (83.3)
Overall treatment response	24		17 (70.8)	13 (54.1)
Dosage reduction for ribavirin	12	50.00	6 (50)	4 (33.3)
Dosage reduction for peginterferon	2	8.30	1 (50)	1 (50)
Dosage reduction for both ribavirin and peginterferon	1	4.10	1 (100)	1 (100)
Use of Neupogen	11	45.80	7 (63.6)	5 (45.4)
Use of Epogen	22	91.60	13 (59.1)	8 (36.6)
Use of both Epogen and Neupogen	11	45.80	7 (63.6)	6 (54.5)
Use of blood transfusions	15	62.50	9 (60)	6 (40)

Abbreviations: ETR, end of treatment response; SVR, sustained virologic response.

Sustained virologic response

A sustained virologic response is defined as hepatitis C virus RNA-negative 24 weeks after cessation of therapy. At the end of the first course of therapy, 8 patients (33.3%) maintained a sustained virologic response. Of the 6 patients who were treated with a second course of therapy, 5 patients (83.3%) maintained a sustained virologic response, leading to an overall sustained virologic response in 13 patients (54.1%) (Table 2).

Response rate in relation to genotype

Ten patients (41.6%) had genotype 1a, 5 patients (20.8%) had genotype 1b, 1 patient (4.1%) had genotype 2b, and 8 patients (33.3%) had unknown genotypes. After the first course of therapy, an end of treatment response was achieved in 6 patients (60%) with genotype 1a, 2 patients (40%) with genotype 1b, 1 patient (100%) with genotype 2b, and 5 patients (62.5%) with unknown genotypes. Sustained virologic responses were maintained in 2 patients (33.3%) with genotype 1a, 2 patients (40%) with genotype 1b, 3 patients (37.5%) with unknown genotype, and no patients (0%) with genotype 2b. After the second course of therapy, 5 patients (genotype 1b, n=1; unknown genotype, n=4) achieved both an end of treatment response and a sustained virologic response. Only 1 patient who had genotype 1a did not achieve both an end of treatment response and a sustained virologic response.

Response rate in relation to ethnicity

After the first course of therapy among the 6 African American patients, 2 patients (33.3%) achieved an end of treatment response and a sustained virologic response. One patient (16.6%) who achieved an end of treatment response but not a sustained virologic response was genotype 2b. The remaining 3 patients (50%) did not have end of treatment response. Two of these 3 patients had genotype 1a, and 1 had an unknown genotype. One of these 3 patients received the extended course of therapy and achieved both end of treatment response and sustained virologic response.

Of 10 white patients, 4 (40%) achieved an end of treatment response and a sustained virologic response after the first course of therapy, 4 (40%) achieved an end of treatment response but no sustained virologic response, and 2 (20%) did not achieve an end of treatment response after the first course of therapy.

Of the 8 non–African-American–Hispanic patients, 2 (25%) achieved an end of treatment response and a sustained virologic response, 1 (12.5%) achieved an

end of treatment response but no sustained virologic response, and 5 (62.5%) did not achieve an end of treatment response after the first course of therapy. Two of these 5 patients got an extended course of therapy, and both achieved an end of treatment response and a sustained virologic response after that.

Hematologic abnormalities and their management

During the first course of therapy, 22 patients (91.6%) experienced hemolysis. Epogen was the first course of therapy to maintain their hematocrit. Fifteen patients (62.5%) did not respond adequately to Epogen and were given blood transfusions to maintain hematocrit. In 12 patients (50%), Epogen and blood transfusions failed to maintain a stable hematocrit (> 25%). The dosage of ribavirin was reduced in these patients.

Eleven patients (45.8%) who developed neutropenia during the course of treatment were treated with filgrastim. Eleven patients (45.8%) were treated with both Epogen and Neupogen (Table 2).

Dosage reduction of peginterferon

Peginterferon dosage reduction was made in 2 patients (8.3%). In 1 patient, it was reduced by 40% owing to severe thrombocytopenia (platelets < 25 000/μL). This patient did not achieve an end of treatment response. In the other patient, it was reduced by 50% owing to depression (Table 2), and this patient achieved both an end of treatment response and a sustained virologic response at the end of the first course of therapy.

Changes in laboratory values before and after therapy

The mean, standard deviation, and median were calculated for liver function tests, renal function tests, and hematologic parameters in all patients before starting antiviral therapy and 12 months after completing therapy. These values are shown in detail in Table 3. We also categorized these values as those for responders and for nonresponders. There was an overall improvement in biochemical parameters after therapy in all patients. However, there was a much better improvement in these values in responders (mean pre/post total bilirubin [t bili] - 59.85/13.68 μmol/L; alkaline phosphatase [ALP] - 156/161 IU/L, median 128/95 IU/L; aspartate aminotransferase [AST] - 131/66 IU/L; alanine aminotransferase [ALT] - 152/80 IU/L) as compared to nonresponders (mean pre/post t bili - 20.52/15.39 μmol/L; ALP - 174/240 IU/L, median 157/142 IU/L; AST - 117/73 IU/L; ALT - 118/79 IU/L).

Discussion

Treatment of recurrent hepatitis C virus infection after liver transplant remains a challenge. Highly

Table 3. Laboratory values before and after antiviral therapy.

	T Bili	ALK	AST	ALT	BUN	Creatinine	Hemoglobin	Hematocrit	White Cells	Platelets
					Anti-viral therapy before surgery					
Overall										
Mean ± standard deviation	2.5 ± 6.8	164 ± 103	125 ± 115	137 ± 129	28.6 ± 12.5	1.6 ± 1.5	12.8 ± 1.9	37.9 ± 5.6	4.3 ± 1.9	140 ± 41
Median	1	128	90	88	25	1.3	13.2	37.6	4	142
Responders (ETR)										
Mean ± standard deviation	3.5 ± 9	156 ± 85	131 ± 109	152 ± 139	26.7 ± 9.1	1.3 ± 0.5	13.1 ± 1.9	38.2 ± 5.9	4.5 ± 1.8	133 ± 34
Median	1	128	59	89	23	1.1	13.7	37.8	4.2	139
Nonresponders										
Mean ± standard deviation	1.2 ± 0.9	174 ± 125	117 ± 128	118 ± 119	31 ± 15.7	2.1 ± 2.2	12.5 ± 1.9	37.6 ± 5.5	4.1 ± 2.2	149 ± 49
Median	0.9	157	90	73	25	1.5	12.7	37.6	3.8	145
					Anti-viral therapy after surgery					
Overall										
Mean ± standard deviation	0.9 ± 0.7	188 ± 154	68 ± 79	80 ± 76	26.7 ± 12.1	1.7 ± 1.6	10.9 ± 2.4	33.7 ± 8.2	3.6 ± 1.2	122.2 ± 56.6
Median	0.7	122	40.5	52.5	24	1.4	10.9	33	3.6	119
Responders (ETR)										
Mean ± standard deviation	0.8 ± 0.4	161 ± 138	66 ± 97	80 ± 90	23.3 ± 5	1.4 ± 0.4	10.3 ± 2.5	31 ± 7.9	3.3 ± 1.3	126 ± 70
Median	0.6	95	34	46	22.5	1.4	10.5	30.9	2.9	123
Nonresponders										
Mean ± standard deviation	0.9 ± 0.4	240 ± 181	73 ± 32	79 ± 46	33.7 ± 19	2.3 ± 2.6	12.2 ± 1.9	38.6 ± 6.9	4.2 ± 1	116 ± 26
Median	0.8	142	81	79	30	1.4	12.8	39.6	4.4	109

Abbreviations: ALK, alkaline phosphatase (IU/L); ALT, alanine aminotransferase (IU/L); AST, aspartate aminotransferase (IU/L); BUN, blood urea nitrogen (mg/dL; 1mg = 0.357 mmol/L); ETR, end of treatment response; T bili, total bilirubin (mg/dL; 1mg = 17.1 μmol/L).
Values: Creatinine (mg/dL; 1mg = 88.4 μmol/L), hematocrit (%), hemoglobin (g/dL; 1gm/dL = 10 gm/L), platelets, ($\times 10^3/\mu$L), white cells ($\times 10^3/\mu$L).

effective treatment is required owing to the shortage of donor livers and the frequently aggressive course of hepatitis C in transplant recipients (15). Treatment must be highly individualized depending upon patients' response to therapy and tolerance to adverse effects.

Various approaches have been tried to treat recurrent hepatitis C in patients after liver transplant in the past. In the study conducted by Shakil and associates, 38 patients were treated with standard interferon and ribavirin 800 mg/d for 72 weeks, and an end of treatment response and a sustained virologic response of 13% and 5% were achieved respectively (15). Oton and associates studied 55 patients treated with high-dose ribavirin (> 11 mg/kg/d) and full-dose peginterferon for 48 weeks, achieving an end of treatment response and a sustained virologic response of 66.7% and 43.6% (9). In another study involving 60 hepatitis C virus-positive patients after liver transplant, 55% patients achieved an end of treatment response, and 35% maintained a sustained virologic response (8).

Attempts at treating recurrent hepatitis C virus preemptively after liver transplant showed poor sustained virologic response rates with peginterferon monotherapy (8%) (1). Although, addition of ribavirin improved the sustained virologic response, it is not well-tolerated in the early peritransplant period, and dosage reductions are common (1, 16, 17). Preemptive therapy is not recommended owing to the adverse effects; low, sustained virologic response rates; and lack of improvement in graft loss or mortality (1). Adherence to treatment regimen has been shown to be an important predictor of a sustained virologic response (1).

The only treatment option available today is combination therapy with pegylated interferon and ribavirin. However, uniform agreement has yet to be reached on indications for treatment, optimal timing, dosage, and duration of treatment for patients with recurrent hepatitis C virus infection after liver transplant. In addition, the adverse affects of this therapy are a major obstacle to completing the entire course of antiviral therapy. Discontinuation of therapy or dosage reductions occurs in up to 30% to 35% of patients in clinical trials (10-13). Cytopenia is the most-frequently reported laboratory anomaly, which prompts dosage reduction and discontinuation (10-13). Also, decline in hemoglobin levels during combination therapy are associated independently with decreased renal function, higher baseline hemoglobin levels, and older age (10, 18). Anemia related to therapy tends to be more pronounced in patients after liver transplant (10, 19). The standard of care for anemia during antiviral therapy is to reduce the dosage of ribavirin to 600 mg/d, discontinuation, or transfusion (10, 20). Many patients use Epogen despite its off-label indication. We try to overcome anemia by use of Epogen and blood transfusions. Only 1 clinical trial has assessed the effect of epoetin α on sustained virologic response (10). In an open-label, randomized, controlled study by Shiffman and associates, 150 patients were assigned to receive standard dosages of peginterferon plus ribavirin (13.3 mg/kg/d) (group 1), peginterferon plus ribavirin (13.3 mg/kg/d) plus epoetin α (40 000 U/wk) (group 2), and peginterferon plus high-dose ribavirin (15.2 mg/kg/d) plus epoetin α (40 000 U/wk) (group 3). A sustained virologic response was significantly greater in group 3 (49%) as compared with groups 1 (29%) and 2 (19%) ($P < .05$) (21).

In the REPEAT study by Jensen and associates, "induction dosing" with 1000-1200 mg/d of ribavirin was tried along with extension of duration of treatment in genotype 1 patients who failed to respond to peginterferon and ribavirin. Though the induction dosing by itself did not significantly improve the sustained virologic response rates, a pooled analysis was done comparing 72 weeks and 48 weeks of therapy, and it was concluded that extending the duration of treatment in previous nonresponders improved the outcome (ie, sustained virologic response = 16% vs 8%) ($P = .0006$) (22).

In the proceedings of the hepatitis C virus council in April 2009, a statement was made that dosages of pegylated interferon and ribavirin beyond the standard of care can overcome poor antiviral response. It mentions that extending the duration of therapy in a selected group of previous nonresponders may improve sustained virologic response (10).

In our study of 24 patients, it appears that the combination of aggressive use of ribavirin and prolonged course of peginterferon in liver transplant patients with recurrent hepatitis C virus infection can provide an end of treatment response in 71% and a sustained virologic response in 54% of the patients. There are few studies where a similar approach has

been tried, but they have either incorporated the use of a prolonged course of anti-viral therapy or a high-dose of ribavirin, but never a combination of both. The duration of therapy was prolonged up to 180 weeks, and we tried to maintain an aggressive dosage of ribavirin throughout the therapy. We believe that achieving a sustained virologic response of more than 50% does support our approach to the treatment of these patients. There currently is no accepted ideal time before restarting the therapy for nonresponders. From other studies (23-24), we presume that a shorter interval between the first and extended courses of therapy, such as that in this study, may contribute to a better response rate among the recipients.

Liver transplant recipients represent a unique subset of the population who require a special consideration regarding the treatment of recurrent hepatitis C virus infection. Owing to the accompanying immunosuppression, the disease tends to be much more-aggressive and life-threatening compared with immunocompetent patients. We propose that a prolonged course of peginterferon and aggressive use of ribavirin may be a useful approach that will uphold the benefit of liver transplant with recurrent hepatitis C in these patients. Aggressive use of ribavirin and a prolonged course of antiviral therapy can provide a sustained virologic response in up to 54% of the liver transplant recipients; however, more prospective studies are required to evaluate the benefit of such an approach fully.

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