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BRIEF ARTICLE

An extended treatment protocol with pegylated interferon and ribavirin for hepatitis C recurrence after liver transplantation

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Abstract

AIM: To evaluate the efficacy and tolerability of an extended treatment protocol and to determine the predictors of sustained virological response (SVR) after liver transplantation (LT).

METHODS: Between August 2005 and November 2008, patients with recurrent hepatitis C virus (HCV) after LT were selected for treatment if liver biopsy showed at least grade 2 inflammation and/or stage 2 fibrosis. All patients were to receive pegylated interferon (PEG)/regimens combining ribavirin (RBV) for an additional 48 wk after HCV undetectability.

RESULTS: Extended protocol treatment was initiated in thirty patients. Overall, 73% had end of treatment response and 60% had SVR. Nineteen patients completed treatment per protocol, of them, sixteen (84%) had end of treatment response, and fourteen (74%) achieved SVR. Both early virological response and 24-week virological response were individually associated with SVR but this association was not significant on multivariate analysis. Eleven patients (37%) discontinued therapy due to adverse effects. Cytopenias were the most common and most severe adverse effect, and required frquent growth factor use, dose adjustments and treatment cessations. The risk of rejection was not increased.

CONCLUSION: Recurrent HCV after LT can be safely treated with extended virological response-guided therpy using PEG/RBV, but requires close monitoring for treatment-related adverse effects, particularly cytopenias.

Key words: Hepatitis C virus; Liver transplantation; Extended treatment protocol

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INTRODUCTION

Hepatitis C virus (HCV)-related end-stage liver disease is the leading indication of liver transplantation (LT) in the United States and Europe[1]. HCV recurrence after LT is almost universal and occurs early, with histological recurrence observed in up to 70% of patients during the first year after LT[2]. Cirrhosis develops in up to 30% of transplant recipients after 5 years with persistant HCV viremia[2], and may be associated with graft failure[3] and the need for re-transplantation. This leads to lower patient survival rates compared to non-HCV transplant recipients[4]. Eradicating HCV using antiviral therapy improves patient and graft survival[5-7].

Regimens combining ribavirin (RBV) with pegylated interferon (PEG) report rates of sustained virological response (SVR), ranging from 28% to 45% with up to 48 wk of treatment[8-13]. Currently, there are no established guidelines to determine the timing and type of HCV treatment after LT. In general, the approach to the treatment of HCV after liver transplantation is similar to the pre-transplant protocol of 48 wk of treatment with viral kinetic evaluation at 12 and 24 wk[8,10-12].

Patients with recurrent HCV after LT are likely to be slow virological responders due to immunosuppression and, therefore, SVR after 48 wk of antiviral therapy is ex-pected to be lower than in immune-competent HCV patients. A few centers have reported improved SVR rates after extending treatment to 72 wk or longer in partial early virological responders (Partial EVR)[14-16]. Partial EVR is currently defined as achieving a 2-log drop in the HCV RNA pre-treatment levels at 12 wk, but not achieving HCV RNA undetectability until after 24 wk of treat-ment. Based on these observations, in August 2005 we designed a viral kinetics-driven treatment protocol that extended PEG/RBV combination therapy in order to maintain viral undetectability for an additional 48 wk of therapy. Our aim was to evaluate the safety and efficacy of this approach in patients who had significant HCV recurrence after LT, as determined by protocol liver biopsies.

MATERIALS AND METHODS

This is an IRB approved study.

Patient selection

Consecutive patients with HCV post-LT who were treated between August 2005 and November 2008 were screened for their eligibility for this study. Six patients were unable to start treatment due to relocation (3), non-compliance (2), or death from early recurrent cirrhosis and sepsis (1). Treatment was initiated in 30 patients. Eligibility criteria were LT for HCV-related end-stage liver disease, the presence of HCV RNA in serum by polymerase chain reaction (PCR), and histologically-proven chronic hepatitis in the graft with at least grade 2 inflammation and/or stage 2 fibrosis on METAVIR scoring of protocol liver biopsies. Additionally, antiviral therapy was initiated if features of aggressive disease (portal fibrosis or moderate-severe necroinflammation) were present on clinically indicated liver biopsies that occurred outside protocol times within the first year. Patients were ineligible for this study if they had unresolved acute or chronic rejection, severe cardiovascular disease, a history of autoimmune disease, coexistent hepatitis B, unresolved biliary complications, active alcohol use, decompensated cirrhosis, renal transplantation, untreated major depression, uncontrolled diabetes, clinically significant retinopathy or thyroid dysfunction, hemoglobin < 10 g/dL, absolute neutrophil count < 1000/mm^3, platelet < 60 000/mm^3, creatinine clearance < 50 mL/min, or patient refusal. Erythropoietin was used preemptively to increase hemoglobin to more than 10 g/dL prior to treatment in otherwise suitable treatment candidates. Data collected and analyzed included the following: patient demographics, viral genotype, interval between LT and initiation of treatment, body mass index, histological features (grade and stage), immunosuppressive therapy used, HCV viral load at baseline and kinetics during therapy, adverse events, dose adjustments and discontinuation, and the need for hematopoietic growth factors. The previous treatment records for these patients were unavailable.

Histology

A liver biopsy was performed, as per protocol, in all patients at 6 mo after LT, and then annually, to evaluate for hepatitis recurrence and to exclude histologic evidence of graft rejection and other viral infections. Samples were evaluated for inflammation (grade) and fibrosis (stage) us-ing the METAVIR scoring system. Histological assessment was carried out by our pathologists utilizing standard pro-cessing techniques and criteria. Patients who had histolo-gical evidence of cirrhosis underwent abdominal ultrasound and upper endoscopy to screen for hepatocellular carcinoma and varices, respectively.

Immunosuppression

Initial immunosuppression in all patients included a calcineurin inhibitor (tacrolimus or cyclosporine) and corticosteroids. Mycophenolate mofetil was used either as part of the initial triple immunosuppressive regimen or added later as maintenance immunosuppression. If possible, pre-dnisone was withdrawn over the first nine months after LT. No adjustments in immunosuppression took place after antiviral treatment had been initiated. Our practice of minimizing overall immunosuppression during the first year after LT was followed in all patients. Antiviral treatment was discontinued once rejection had been determined on histology, which was treated by increasing the calcineurin-inhibitor dose, with or without steroid use.

Virologic assays

Serum HCV RNA was measured by a quantitative assay (COBAS AmpliPrep or TaqMan, Roche Diagnostics, sensitivity limit 600 IU/mL) at baseline. A qualitative assay (Roche, sensitivity limit 50 IU/mL) was used at week 4, 12, at end of treatment, and every 12 wk after the end

of treatment. Rapid virological response (RVR) was defined as viral undetectability at week 4 of treatment. EVR was defined as 2-log drop in viral count at week 12 of treatment. End of treatment (EOT) response was defined as viral undetectability at end of treatment. SVR was defined as a negative qualitative HCV-RNA assay 24 wk after the end of therapy. High viral load was defined as HCV RNA of more than 800 000.

Treatment regimen

All patients were treated with Pegylated Interferon alpha 2a (Pegasys, Hoffman-La Roche, Inc. Nutley, NJ) and RBV. The initial dose of 180 mcg/week was used in patients who had transplants more than two years earlier and had an absolute neutrophil count (ANC) of > 1500/mm^3. Otherwise, an escalating dose regimen starting at 90 mcg/week, increasing as tolerated to a full dose of 180 mcg/week over 8 wk, was used. RBV was started at a dose of 10 mg/kg per day in patients who had transplants more than 2 years earlier and was increased as tolerated to 13-15 mg/kg per day over 4 to 6 wk. If fewer than 2 years had elapsed after transplantation, the starting RBV dose was 8 mg/kg per day, which was slowly increased to 10 mg/kg per day over 4 to 6 wk, then to 13 to 15 mg/kg per day as tolerated and continued at the highest tolerable dose for the duration of therapy.

Regardless of genotype, all patients were treated for a minimum of 48 wk, even if they had undetectable viremia at week 4. Treatment was discontinued if virus was detectable at week 48.

Erythropoietin (40 000 units subcutaneously once a week) was used if hemoglobin dropped below 10 g/dL. Where there was no improvement, the RBV dose was decreased. RBV was discontinued if hemoglobin fell below 8 g/dL. Patients who had hemoglobin < 8 g/dL or became symptomatic received blood transfusions. During the period of dose adjustment, hemoglobin was monitored weekly. Once the hemoglobin had been stabilized or increased by at least 1 g/dL with erythropoietin, RBV dosage was increased gradually as tolerated weekly, aiming for baseline hemoglobin of 10 g/dL and RBV dose of 13-15 mg/kg per day. Patients with ANC < 750/mm^3 were treated with weekly granulocyte colony stimulating factor (G-CSF, Filgrastim 480 mcg subcutaneously) initially, and if there was no improvement, PEG dose was reduced or held. Dose escalation was attempted once ANC increased to 750/mm^3. PEG dose was also reduced if platelet count was < 30 000/L and discontinued if platelet count was < 25 000/L. Antiviral therapy was also reduced or suspended for antidepressantrefractory depression or disabling fatigue.

Statistical analysis

Continuous variables were presented as median (range) or number (percentages) and analyzed with the Wilcoxon rank test. Categorical variables were expressed as percentages and compared with the Fisher's exact test. *P* values less than 0.05 were considered statistically significant.

Table 1 Baseline characteristics (*n* = 30)

Characteristics	Value
Gender (M:F), *n*	23:07
Age (years), median (range)	56 (38-70)
Genotype 1, *n* (%)	23 (77)
Overweight, *n* (%)	22 (73)
Diabetes Mellitus, *n* (%)	18 (60)
Months from Liver Transplant, median (range)	40.5 (2-132)
High HCV RNA, *n* (%)	17 (57)
Cirrhosis, *n* (%)	3 (10)

M: Male; F: Female. Overweight: Body mass index > 25 kg/m^2; High HCV RNA > 800 000 IU/mL.

RESULTS

Patient characteristics

Baseline characteristics of the 30 patients are summarized in Table 1. The median age at inclusion was 56 years (38-70), 23 patients were male. Twenty-two patients (73%) were overweight (body mass index > 25 kg/m^2) and seven (23%) were obese (body mass index > 30 kg/m^2). The median time to treatment from LT was 40.5 mo (2-132). The HCV genotype was 1 in 23 patients (77%), 2 in 4 (13%), and 3 in 3 patients (10%). Three patients had histologic evidence of cirrhosis. There were no patients with evidence of fibrosing cholestatic hepatitis.

Efficacy

Overall twenty-two patients (73%) had EOT response and 18 patients (60%) had SVR. Nineteen patients completed treatment per protocol. Of these, 15 (79%) were aviremic at the end of therapy and 14 (74%) achieved SVR. Eleven patients were unable to complete treatment per protocol and discontinued prematurely at an average of 23 wk due to adverse effects (8 patients) or viral breakthrough (2 patients), and one patient stopped treatment on his own. Of these eleven patients, six (54%) achieved EOT response, and 4 (36%) achieved SVR. The difference between SVR rates among the patients who completed the treatment protocol and those who did not was not statistically significant ($P = 0.052$).

Virologic response

Viral kinetics and virologic response has been summarized in table 3. Six patients (21%) had undetectable virus at week 4 (RVR), and all of them achieved SVR. Among the 21 patients with EVR, 16 (76%) achieved SVR ($P = 0.03$), whereas only two of nine patients (22%) without EVR achieved SVR. Fifteen of eighteen patients (83%) with aviremia at week 24 achieved SVR ($P = 0.008$), whereas the other 3 patients relapsed. Five patients had detectable viremia at week 24, only one (20%) of them achieved SVR. Both early virological response (EVR) and 24-week virological response were individually associated with SVR but this association was not significant on multivariate analysis.

Table 2 Comparison between SVR and Non-SVR groups

Variable	SVR	Non-SVR	*P*-value
Number of patients	18	12	
Age, median (range)	55(38-67)	59 (48-70)	
M: F, *n*	13 : 5	9 : 3	
Overweight, *n*	14	8	0.396
Diabetes Mellitus, *n*	12	6	0.296
Months from LT, median (range)	60 (4-116)	26 (2-132)	
High HCV RNA, *n*	10	7	0.590
CMV antibody positive, *n*	13	8	0.528
Genotype 1: non 1, *n*	13 : 5	10 : 2	0.403
Pre-Treatment biopsy, *n*			
Stage 0-1	3	5	
Stage 2-3	12	7	
Stage 4	3	0	
Grade 0-1	1	2	
Grade 2-3	16	10	
Grade 4	1	0	
Total weeks of treatment, median (range)	56 (13-84)	44.5 (2-60)	
Erythropoietin use, *n* (%)	17 (94)	6 (50)	0.009
G-CSF use, *n* (%)	10 (56)	2 (17)	0.038

M: Male; F: Female; LT: Liver Transplantation; G-CSF: Granulocyte-colony stimulating factors; SVR: sunstianed virological response. Overweight: Body mass index > 25 kg/m^2; High HCV RNA: > 800 000 IU/mL.

Baseline characteristics were compared between the SVR and non-SVR groups (Table 2). The probability of achieving SVR was not related to baseline serum HCV RNA level, genotype, histologic grade or stage, interval between LT and initiation of therapy, BMI, presence of diabetes, duration of steroid use, presence of CMV antibody and total duration of antiviral therapy. SVR rate was 57% in patients with genotype 1 and 71% in genotypes 2 or 3. Sixteen of the 19 patients who completed treatment per protocol were treated for 48 weeks after achieving aviremia. Fourteen (88%) patients in that group achieved SVR. The interval between initiation of therapy and viral eradication ranged between 4-36 wk.

Tolerability and adverse events

Eleven (37%) patients failed to complete therapy, mostly due to treatment-related adverse events. Two (7%) patients developed moderate acute cellular rejection, one at week 2 and another at week 13. Treatment was discontinued and corticosteroids were used to treat both patients. Four (13%) patients discontinued therapy for anemia, one developed pancreatitis, another developed pneumonia requiring hospitalization, two had virological relapse, and one discontinued treatment on his own. Growth factors and transfusions were frequently used. Twenty-three patients (77%) required therapy with erythropoietin for anemia, twelve (40%) required G-CSF, and ten (33%) required blood transfusions. Dose reductions were also instituted frequently. PEG and RBV doses were reduced in four (13%) and twelve (40%) patients, respectively. One patient developed biopsy-proven de novo autoimmune hepatitis 12 mo after completing a 72-week course of therapy and achieving an SVR[17-20].

There was no incidence of chronic rejection.

DISCUSSION

Hepatitis C recurrence remains a major cause of graft loss after liver transplantation. Studies using the same treatment protocol as in the non-transplant population have reported a lower overall sustained virological response among patients who have undergone transplants. Treatment-related adverse effects in transplant recipients are also more severe and dose-limiting. Specifically, cytopenias are more pro-nounced, due to concurrent bone marrow toxicity from immunosuppression. Our treatment protocol was designed to overcome these obstacles by timing the start of treatment to the severity of HCV recurrence, as determined by protocol liver biopsies. To keep dosing as high as possible, we also used growth factors prophylactically with at risk pa-tients, and to maximize the likelihood of response, we ex-tended treatment to maintain 48 wk of viral undetectability.

Our rationale for prolonged treatment was based on the immune-competent experience, where extending treatment beyond 48 wk has led to improved SVR rates in slow responders[21,22] who were likely to be over represented after liver transplant. Compared to a recent single center, observational study treating recurrent HCV after LT for 48 wk after viral undetectability that reported 26% SVR[15], we observed an overall SVR rate of 60%. The reasons for this difference could be attributed to a lower percentage of patients with advanced disease, and a longer interval between transplant and antiviral treatment in our study, as well as possible differences in immunosuppression.

A more recent study by Schmidt *et al*[12], showed that virological response at week 24 has a high predictive value for SVR in patients with recurrent HCV after LT. Similarly, we found that EVR and the 24-week virological response are associated with SVR with a positive predictive value of 76% and 83%, respectively. Only one patient with persistent viremia at week 24 was able to achieve SVR, which suggests that the 24-week stopping rule in the non-transplant population may be applicable to transplanted patients. On the other hand, lack of EVR has a negative predictive value of 98% in the immune-competent population, and has become a treatment stopping point[23-25]. This was not observed in our transplanted cohort where two (22%) of the nine patients who had not achieved EVR, actually went on to achieve SVR. This confers a negative predictive value of 78%. Although the improved SVR rate in the per-protocol group was not statistically significant, our findings suggest that a viral response-guided therapy using this protocol may be considered in a select group of

Table 3 Viral kinetics and outcomes

Serial No.	VL Baseline	VL Week 4	VL Week 12	VL Week 24	EOT	Total Duration of Rx(wk)	Treatment per Protoco	Virological Outcome
1	700 000	< 50	< 50	< 50	Y	46	N	SVR
2	700 000	292 000	45700	22700	Y	84	Y	SVR
3	700 000	< 50	< 50	< 50	Y	52	Y	SVR
4	282 000	62300	< 50	< 50	Y	56	Y	SVR
5	6 870 000	12700	< 50	< 50	Y	60	Y	SVR
6	1 500 000	2750	< 50	< 50	Y	60	Y	Relapsed
7	771 000	18400	< 50	NA	Y	21	N	Relapsed
8	700 000	< 50	< 50	< 50	Y	56	Y	SVR
9	11 000 000	1 980 000	< 50	< 50	Y	60	Y	SVR
10	100 000	15000	< 50	< 50	Y	45	N	Relapsed
11	700 000	700 000	< 50	2420	N	44	N	Breakthrough
12	700 000	33400	< 50	< 50	Y	60	Y	SVR
13	753 000	683 000	309 000	117 000	N	48	Y	NR
14	2 459 000	62100	< 50	< 50	Y	56	Y	SVR
15	6 140 000	311 000	NA	NA	N	7	N	NR
16	2 226 210	3186	< 50	< 50	Y	56	Y	SVR
17	700 000	243 000	1430	< 50	Y	72	Y	SVR
18	962 000	NA	NA	NA	N	2	N	NR
19	101 000	33800	< 50	< 50	Y	42	N	SVR
20	50 000 000	817 000	50 000 000	NA	N	13	N	NR
21	3 200 000	445 000	44500	< 50	Y	72	Y	Relapsed
22	9 340 000	< 50	< 50	NA	Y	13	N	SVR
23	3 550 000	56	< 50	NA	Y	13	N	SVR
24	1 280 000	398 000	20800	670	N	48	Y	NR
25	305 777	36463	1059	NA	N	15	N	Breakthrough
26	3 020 000	< 50	< 50	< 50	Y	52	Y	SVR
27	1 609 966	78800	175	< 50	Y	72	Y	SVR
28	1 360 000	< 50	< 50	< 50	Y	56	Y	SVR
29	11 300 000	1 040 000	1 060 000	1 790 000	N	48	Y	NR
30	15 100 000	295 330	240 000	< 120	Y	72	Y	SVR

VL: Viral load; EOT: End of treatment response; Rx: Treatment; NA: Not applicable; SVR: sunstianed virological response; NR: Non responder; Y: Yes; N: No.

slow responders.

This extended treatment protocol is complex, highly individualized and demanding for both patients and health care providers. The cost in terms of personnel time, laboratory testing and medication use is high, and may be prohibitive for general use. We observed similar treatment-related adverse events leading to dose reduction or treat-ment cessation in 20%-66% of transplanted patients[15,16,24]. Despite the aggressive and pre-emptive use of growth factors and blood transfusions, we observed similar results in our group, where treatment was prematurely discontinued due to severe side effects, principally cytopenias in 37% of patients. Our acute rejection rate of 7% (2 patients) was within the previously reported range of 5%-20%[9,11,14,15].

Our study has several limitations inherent to a retrospective case series. First, we didn't have a comparison group, due to lack of complete virological data on other patients having had transplants who had received HCV treatment prior to the initiation of our current treatment protocol. Second, we cannot explain why 2 patients achieved an SVR after treatment for only a relatively short period. Third, post-treatment liver biopsy data was available in only 8 patients, so we could not examine the changes in liver histology to determine the beneficial effects of prolonged antiviral therapy, i.e., histological improvement or stability, beyond achievement of SVR. Our small number of patients with cirrhosis did not allow us to examine whether achievement of SVR is associated with prevention of hepatic decompensation. Finally, although our results showed a trend towards a positive association between extended treatment protocol and SVR, statistical significance could not be achieved, possibly due to the small sample size.

In conclusion, our single-center observational pilot study suggests that extended treatment protocols may be utilized for HCV recurrence after LT. A response-guided treatment approach that aims to achieve SVR in patients who have viral undetectability by week 24 of treatment is feasible. However, this approach requires intense monitoring, frequent growth factor use and comes at a high cost, both in personnel and medical expense. Further studies comparing extended treatment protocols to standard 48 wk therapy can be helpful to determine the adequate duration of treatment for recurrent HCV after LT before extended treatment can be recommended unequivocally. It also remains to be seen whether the imminent addition of the direct acting antivirals to our armamentarium of treatment for HCV will obviate the need for extended antiviral therapy after LT, as more

patients could potentially achieve desirable viral kinetics earlier in the treatment.

COMMENTS

Background

Hepatitis C virus (HCV)-related end-stage liver disease is the leading indication of liver transplantation (LT) in the United States and Europe. HCV recurrence after LT is almost universal and occurs early. Cirrhosis develops in up to 30% of transplant recipients after 5 years with persistant HCV viremia, and may be associated with graft failure and need for re-transplantation. Patients with recurrent HCV after LT are likely to be slow virological responders due to immunosuppression and, therefore, SVR after 48 wk of antiviral therapy is expected to be lower than immune-competent HCV patients.

Research frontiers

It has been reported that a few centers have improved SVR rates after extending treatment to 72 wk or longer in partial early virological responders (Partial EVR). Partial EVR is currently defined as achieving a 2-log drop in the HCV RNA pre-treatment levels at 12 wk but not achieving HCV RNA undetectability until 24 wk of treatment.

Innovations and breakthroughs

Our single-center observational pilot study suggests that extended treatment protocols may be utilized for HCV recurrence after LT. A response-guided treatment approach that aims to achieve SVR in patients who have viral undetectability by week 24 of treatment is feasible.

Applications

This treatment protocol can be applied to patients who have HCV recurrence after LT to achieve SVR and decrease the incidence of graft loss.

Terminology

"Viral breakthrough" is when the patient goes from undetectable to detectable viral loads while undergoing treatment. "Virological relapse" is when a patient has an undetectable virus at the end of treatment, but also has a detectable viral load after the treatment stops.

Peer review

The authors describe their experience using an extended treatment protocol for recurrent hepatitis C after liver transplantation. Since hepatitis C invariably recurs after transplant and the treatment options are limited, this study is significant and adds important data to the literature.

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