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ORIGINAL ARTICLE

Sustained Virologic Response to Therapy of Recurrent Hepatitis C After Liver Transplantation Is Related to Early Virologic Response and Dose Adherence

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Sustained virologic response (SVR) after antiviral therapy for recurrent hepatitis C virus (HCV) infection in liver transplant (LT) recipients is consistently lower than that achieved in non-LT patients. We evaluated efficacy and safety of pegylated interferon (IFN) and ribavirin (RBV) therapy in LT recipients with recurrent HCV and factors associated with SVR. All subjects with histologic evidence of recurrent HCV were intended to be treated for 48 weeks with full-dose pegylated IFN; target dose of RBV was 800 mg/day. Thirty-five LT recipients with recurrent HCV, median age 48.5 years, 77% genotype 1, and median pretreatment HCV RNA 6.4 $\log_{10}$ IU/mL were treated between January 2000 and February 2006. Antiviral therapy was discontinued prematurely in 15 subjects as a result of adverse events. Median overall treatment duration was 46 weeks. Early virologic response at week 12 was seen in 17 (49%) and an end-of-treatment virological response in 19 (54%) patients. SVR was achieved in 13 patients (37%), and all 9 patients followed for >1 year after treatment had durable response. Patients with SVR had significantly lower pretreatment HCV RNA (5.7 vs. 6.5 $\log_{10}$ IU/mL, $P = 0.003$), more likely to have a week 12 virological response (85% vs. 27%, $P = 0.0009$) and received higher cumulative doses of pegylated IFN (75% vs. 33%, $P = 0.029$) and RBV (90% vs. 26%, $P = 0.016$) compared with patients whose disease did not respond to therapy. In conclusion, SVR was achieved in 37% of patients with recurrent hepatitis C after LT. Similar to non-LT patients, those with lower pretreatment HCV RNA, a week 12 virological response, and pegylated IFN and RBV dose adherence were more likely to achieve SVR. ***Liver Transpl 13:1100-1108, 2007.*** **© 2007 AASLD.**

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Hepatitis C is the major indication for liver transplantation (LT) in western countries. Reinfection with hepatitis C virus (HCV) after LT is a universal phenomenon and is characterized by accelerated histological progression, with 6-23% of patients developing cirrhosis after a median of 3-4 years after LT.[1-5] Currently, there is no consensus on the optimal timing for initiation of antiviral therapy, duration of treatment, or dose regimen for patients with recurrent hepatitis C. Results of preemptive antiviral therapy initiated within the first few weeks after LT to prevent or ameliorate recurrent hepatitis C have been disappointing, with sustained virologic response (SVR) rates ranging 10-20% and as many as 50% of patients discontinuing treatment as a result of adverse events.[6-9] Therefore, most investigators have focused on the treatment of established recurrent hepatitis C.

Abbreviations: HCV, hepatitis C virus; LT, liver transplantation; IFN, interferon; SVR, sustained virological response; HAI, histological activity index; EVR, early virologic response; RBV, ribavirin; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

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More recent studies that used the combination of pegylated interferon (IFN) and ribavirin (RBV) have reported higher SVR rates of 25-40% in LT recipients with recurrent HCV.[10-13] However, most of these studies included small numbers of patients (range 12-54 patients), and the duration of posttreatment follow-up was short (6 months). Furthermore, adverse events that are unique to LT recipients and the use of growth factors were not described in detail. Retrospective analyses of treatment trials in nontransplant patients have demonstrated a strong correlation between SVR rate and dose adherence,[14] but the importance of dose adherence and treatment outcomes in LT recipients has not been described. The aim of our study was to evaluate the efficacy and safety of the combination of pegylated IFN and RBV in LT recipients with histological recurrence of hepatitis C. In addition, we set out to identify baseline and treatment related factors associated with SVR.

METHODS

Patient Population and Data Collection

Medical records of all adult patients (≥18 years) who underwent LT for chronic HCV at the University of Michigan Health System were reviewed. Patients with recurrent HCV and received pegylated IFN and RBV combination therapy for recurrent HCV between January 2000 and February 2005 were included. Patients who received standard IFN with or without RBV or pegylated IFN monotherapy were excluded. Recurrent hepatitis C was defined by the presence of histological features of hepatitis C and Ishak fibrosis score >1 in patients with detectable HCV RNA and abnormal liver biochemistries after LT and the absence of rejection or biliary obstruction at biopsy and imaging.[15] Pretreatment biopsies were performed in all patients. Liver biopsies were repeated during antiviral treatment in patients who had worsening liver biochemistries to exclude rejection or other etiologies. All biopsy samples were subsequently reviewed in a blinded fashion by a single pathologist (J.K.G.). Pretreatment biopsy samples were graded for inflammation and fibrosis with the classification of Ishak et al.[16] Data were censored in March 2006.

Data on demographics (age, gender, race/ethnicity) and Model for End-Stage Liver Disease score at the time of transplant, history of IFN-based treatment before LT, and donor age were recorded. Information collected between LT and initiation of pegylated IFN and RBV therapy included calcineurin inhibitor use, dose and duration of corticosteroids, use of mycophenolate mofetil, episodes of rejection, and rejection treatment. Pretreatment liver histology, HCV RNA level, HCV genotype, blood counts (hemoglobin, white blood cells, absolute neutrophil count [ANC], platelet count), liver biochemistries (albumin, aspartate and alanine aminotransferase [AST and ALT], alkaline phosphatase [ALP], total bilirubin, creatinine), and prothrombin time expressed as international normalized ratio were also recorded. The cumulative dose of pegylated IFN and RBV received, and the timing and reasons for dose reductions and discontinuations, occurrence of adverse events, and use of growth factors and antidepressants were reviewed.

Immunosuppression

Standard immunosuppression at our institution consisted of triple therapy with tacrolimus or cyclosporine, mycophenolate mofetil, and corticosteroids. Prednisone was discontinued at month 6 in patients with recurrent HCV.

HCV RNA Assays

Quantitative polymerase chain reaction assays were performed to detect HCV RNA at weeks 0, 12, and 24, then every 24 weeks during treatment and at months 6 and 12, and annually after completion of treatment. Before 2004, the Cobas Amplicor Monitor (Roche Molecular Diagnostics, Pleasanton, CA) with a lower limit of detection of 600 IU/mL was used; thereafter, the Taqman system (Roche Molecular Diagnostics) with a lower limit of detection of 50 IU/mL was used.

Treatment Protocol

All patients received a combination of pegylated IFN (alfa 2a [α2a] or alfa 2b[α2b]) and RBV. The intended dose of pegylated IFN-α2b was 1.5 μg/kg/week, and the intended dose of pegylated IFN-α2a was 180 μg/week, whereas the intended dose of RBV was 800 mg/day in 2 divided doses. Seventeen patients (49%) initiated treatment at 50% of pegylated IFN dose with escalation to intended dose as tolerated over a 4-6-week period. The intended duration of treatment was 48 weeks regardless of HCV genotype. The cumulative dose of pegylated IFN and RBV received was expressed as a percentage of the total intended dose. End-of-treatment response was defined as undetectable HCV RNA at the end of treatment and SVR as undetectable HCV RNA 24 weeks after the completion of treatment. Early virologic response (EVR) was defined as ≥2 log drop or undetectable HCV RNA at week 12 of treatment.

Blood counts and liver biochemistries were monitored at weeks 0, 1, 2, 4, 6, and 8 and every 4 weeks until the end of treatment and at follow-up weeks 12 and 24. Thyroid-stimulating hormone and HCV RNA levels were tested before treatment and every 12 weeks during treatment, and at follow-up weeks 12, 24, and 48, and annually thereafter. Adverse events and laboratory values were reviewed by transplant nurses in consultation with a transplant hepatologist every 2-4 weeks, and the patients were reassessed in clinic by a transplant hepatologist every 12 weeks.

Between 2000 and 2003, pegylated IFN and RBV were initiated at 50% or 75% of intended doses, and cytopenias were managed by dose reduction and/or discontinuation of pegylated IFN and/or RBV according to recommendations in the package insert. Growth factors

were rarely administered, and when they were, it was mostly in patients with persistent anemia or neutropenia despite dose reductions. During the last 2 years, treatment was initiated at full dose in most patients, and growth factors (i.e. granulocyte colony-stimulating factor, erythropoietin) were usually used before dose reduction. For analysis of cytopenias, anemia was defined as ≥2 g drop in hemoglobin from pretreatment value or hemoglobin <10 g/dL. Neutropenia was defined as ANC <1,000 mm^3 and thrombocytopenia as platelet count <50,000/mm^3. Emotional side effects were managed expectantly with dose reductions and/or antidepressants as clinically needed.

Statistical Analysis

All patients were included in the analysis of response. Patients who discontinued treatment early and had detectable HCV RNA when treatment was withdrawn were considered to have disease nonresponsive to therapy. Patients who had undetectable HCV RNA at the end of treatment and did not have HCV RNA available at the end of 6-month follow-up were considered as not achieving SVR. Continuous variables were expressed as median and range and categorical variables were expressed as proportions. The Mann-Whitney test was used to compare the continuous variables, and the χ^2 and Fisher exact tests were used to compare categorical characteristics of patients with and without SVR. P value of < 0.05 was considered significant. Multivariable analysis was performed with baseline log HCV RNA, EVR (week 12 response), cumulative dosages of pegylated IFN and RBV received, and use of growth factors as predictors of SVR by logistic regression analysis.

TABLE 1. Characteristics of Patients

Variable	Value
Age (yr)	48.5 (36-62)
Male gender	27 (77%)
White	31 (89%)
Time from LT to start of antiviral therapy (weeks)	64 (6-518)
Pre-LT HCV treatment	11/17 (64.7%)
Immunosuppression at start of antiviral therapy	
Tacrolimus	21/35 (58.3%)
Cyclosporine	15/35 (41.7%)
Mofetil mycophenolate	10/35 (29%)
Corticosteroids	4/35 (11.4%)
Rejection episodes before antiviral therapy	10/35 (28.6%)
Hemoglobin (g/dL)	14.7 (11.6-18.2)
ANC (k/mm^3)	2.5 (1.2-7.6)
Platelets (k/mm^3)	130 (53-255)
INR	1 (0.8-1.2)
HCV RNA (log_{10}) (IU/mL)	6.4 (4.4-7.6)
Genotype 1 (%)	77
AST (IU/mL)	150 (43-1,433)
ALT (IU/mL)	209 (62-633)
Total bilirubin (mg/dL)	1.0 (0.4-15.1)
Alkaline phosphatase (IU/mL)	132 (71-520)
Serum creatinine (mg/dL)	1.0 (0.7-1.6)
Calculated creatinine clearance (mL/minute)	95.6 (68-128)
HAI	7 (4-12)
Ishak fibrosis	2 (1-6)

Abbreviations: LT, liver transplantation; ANC, absolute neutrophil count; INR, international normalized ratio; HCV, hepatitis C virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAI, histological activity index. Values are presented as median (range), n/n (%), or n (%).

RESULTS

Baseline Characteristics

Table 1 shows the baseline characteristics of the 35 patients that were eligible for this study. All the patients had increased AST and ALT before antiviral treatment. Most of the patients were men (77%) and white (89%). The median age at the time of LT was 48.5 years (range 36-62 years). All patients received deceased donor liver allograft, and the median donor age was 31 years (range 15-64 years). The median interval from LT to start of pegylated IFN and RBV therapy was 64 weeks (range 6-518 weeks). Three patients began treatment within the first 6 months after LT, 10 between 6-12 months, 13 in year 2 after LT, and 9 after year 2 after LT. Nine patients experienced a single episode of rejection each, and 1 additional patient had 2 episodes of rejection. All patients with rejection responded to corticosteroid pulses except the last patient, who required monoclonal antibody for the second episode of rejection. None of the patients had a rejection episode within 3 months before initiation of antiviral therapy. At the time pegylated IFN and RBV therapy was started, 15 patients were receiving cyclosporine, and the remaining 20 were receiving tacrolimus. Ten patients were also receiving mycophenolate mofetil, and 4 patients were still receiving prednisone at the beginning of antiviral therapy. All the patients with rejection or autoimmune hepatitis on antiviral treatment were receiving cyclosporine; their trough levels during treatment were similar to those who did not have rejection or autoimmune hepatitis.

Most patients (77%) had HCV genotype 1 infection, and median pretreatment HCV RNA was 6.4 log IU/mL (range 4.4-7.6 log IU/mL). Although most patients had compensated liver disease and preserved renal function, 2 patients had total bilirubin >5 mg/dL, and 5 had a pretreatment serum creatinine >1.2 mg/dL. Liver biopsy was performed on all patients within a median of 97 days (range 20-1,063 days) before treatment. Twenty-two patients (63%) underwent a liver biopsy within 6 months before the initiation of antiviral treatment. The median necroinflammatory score was 7 (range 4-12) and Ishak fibrosis score was 2 (range 1-6). One patient had cholestatic recurrent hepatitis C.

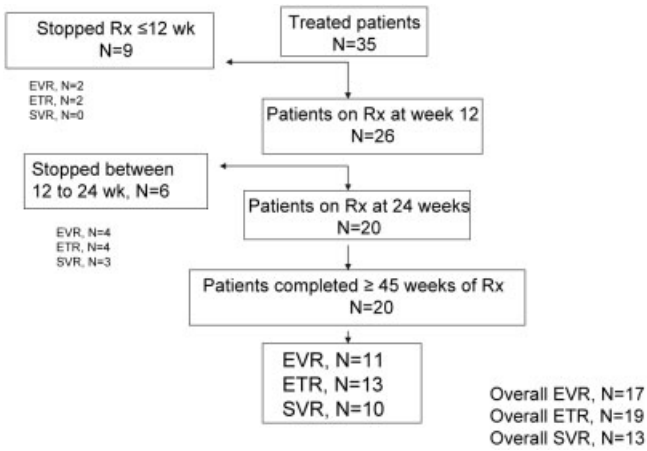

Figure 1. Outcomes of patients receiving antiviral therapy. EVR, early virological response; ETR, end-of-treatment response; SVR, sustained virological response.

Dose and Duration of Treatment Received

The outcomes of the patients are summarized in Figure 1. The median duration of treatment was 46 weeks (range 3-126 weeks). Twenty patients (57%) completed >80% of intended treatment duration, and 15 (43%) discontinued treatment early as a result of adverse effects. Eleven patients (31.4%) received >80% of intended pegylated IFN dose, 13 patients (37%) received >80% of intended RBV dose, and 9 patients (26%) received >80% of intended pegylated IFN and RBV dose. Fourteen (40%), 17 (49%), and 12 (34%) patients received ≥60% of pegylated IFN, RBV, and combination of pegylated IFN and RBV doses. The RBV dose received did not correlate with baseline creatinine clearance ($r = -0.2$, $P = 0.18$).

Virologic and Biochemical Responses

After 12 weeks of antiviral treatment, 15 patients had undetectable HCV RNA, and 2 additional patients had >2 log decrease in HCV RNA level, giving an EVR rate of 49% (17 of 35). Nineteen patients (54%) had end-of-treatment virologic response, and 13 (37%) achieved SVR. Of the 13 patients with SVR, 11 (85%) had EVR.

Normalization of AST and ALT was observed in 19 patients (54%) and 13 patients (37%), respectively, at the end of treatment and in 11 patients (31%) and 8 patients (23%), respectively, after 24 weeks of post-treatment follow-up.

Four patients had moderately increased pretreatment liver biochemistries (AST 332-1,433 IU/mL, ALT 291-633 IU/mL, ALP 270-520 IU/mL) and were jaundiced (total bilirubin 2.4-15.1 mg/dL). One patient received treatment for 50 weeks with normalization of AST, ALP, and total bilirubin at the end of treatment. This patient had a >2 log decrease in HCV RNA at week 12; however, HCV RNA remained detectable throughout the course of treatment. Despite persistent viremia, AST and ALT remained normal >1 year after treatment was stopped. Another patient had marked reduction in AST (594 to 111 IU/mL), ALT (536 to 81 IU/mL), ALP (520 to 226 IU/mL) and total bilirubin (3.9 to 1.5 mg/dL). However, treatment was discontinued at week 8 because of disabling myalgias and fatigue with persistently detectable HCV RNA. The other 2 patients had increased ALP despite some improvement in AST, ALT, and total bilirubin during treatment. However, treatment was stopped after 6 and 10 weeks in these 2 patients as a result of induction of autoimmune-like hepatitis.

Factors Associated With SVR

Table 2 compares the characteristics of patients with and without SVR. Univariate analysis showed that patients with SVR had significantly lower levels of pretreatment HCV RNA level ($P = 0.003$), and had received significantly higher median doses of pegylated IFN (77% vs. 33% of intended dose, $P = 0.029$) and RBV (90% vs. 26% of intended dose, $P = 0.016$) compared with patients without SVR. In addition, patients with SVR tended to have longer median duration of treatment (48 vs. 20 weeks, $P = 0.072$) compared with patients without SVR. Patients who received ≥60% of the intended dosage of both pegylated IFN and RBV dose had higher rates of SVR (8 of 12, 67%, vs. 5 of 23, 22%, $P < 0.037$) than those who received <60% of one or both medications. Patients with SVR were also more likely to have EVR (85% vs. 27%, $P < 0.0009$), anemia (92% vs. 59%, $P = 0.049$), and use of erythropoietin (38% vs. 9%, $P = 0.04$) than those without SVR. However, none of these factors remained significant on multivariable analysis.

Long-Term Outcomes of Patients Who Completed Antiviral Therapy

Nine patients (69%) with SVR were followed for a median of 25.2 months (range 14.4-40.8 months) after completion of treatment, and none of them had late virological relapse. One of these 9 patients developed an abrupt increase in aminotransferases 2 years after successful completion of treatment with liver histology suggestive of autoimmune hepatitis. Azathioprine and prednisone were added to the immunosuppression regimen, resulting in improvement of aminotransferases. This patient was receiving cyclosporine, azathioprine, and 7.5 mg/day prednisone and had normal aminotransferases and undetectable HCV RNA at the last follow-up visit, 30 months after completion of pegylated IFN and RBV treatment, and 12 months after reinitiation of prednisone and azathioprine.

Another patient, who discontinued treatment after 17 weeks as a result of severe neutropenia and myalgias, had undetectable HCV RNA at the end of treatment underwent retransplantation for severe cholestasis due to an unidentified cause 13 months after completion of treatment. This patient had undetectable HCV RNA 2 years after retransplantation.

TABLE 2. Comparison of Patients With and Without Sustained Virological Response

Variable	No SVR (N = 22)	SVR (N = 13)	*P* value
Recipient and donor factors			
Recipient age at LT (yr)	48 (42-62)	51 (36-62)	0.52
MELD at LT	16 (11-28)	15 (10-20)	0.29
Donor age (yr)	42.5 (15-64)	25 (17-56)	0.37
Pretreatment histology and laboratory results			
HAI	7 (5-12)	5 (3-11)	0.2
Ishak fibrosis	2 (1-5)	2 (1-3)	0.3
Genotype 1 (%)	85%	71%	0.4
Log_{10} HCV RNA (IU/mL)	6.5 (5.5-7.6)	5.6 (4.4-7)	0.003
ALT (IU/mL)	225 (63-633)	168 (62-490)	0.24
AST (IU/mL)	155 (43-1,433)	110 (52-352)	0.09
ALP (IU/mL)	136 (71-520)	106 (72-226)	0.2
Total bilirubin (mg/dL)	1 (0.3-15)	0.9 (0.7-2.2)	0.19
Creatinine (mg/dL)	1 (0.9-1.6)	1.1 (0.8-1.4)	0.6
Treatment-related factors			
Treatment duration (weeks)	20 (3-126)	48 (13-102)	0.072
Peg IFN received (%)	33 (4-180)	75 (20-130)	0.029
RBV received (%)	26 (6-114)	90 (14-160)	0.016
Early virologic response (week 12)	6 (27%)	11 (85%)	0.0009
Anemia	13 (59%)	12 (92%)	0.049
Use of erythropoietin	2 (9%)	5 (38%)	0.04
Neutropenia	12 (57%)	9 (69%)	0.4
Use of granulocyte colony-stimulating factor	3 (14%)	3 (24%)	0.25

Abbreviations: SVR, sustained virological response; MELD, Model for End-Stage Liver Diseases; HAI, histological activity index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; IFN, interferon; RBV, ribavirin. Upper limit of normal: AST 40 IU/mL; ALT 40 IU/mL; ALP 120 mg/dL; total bilirubin 1.2 mg/dL; creatinine 1.0 mg/dL. Values are presented as median (range), n/n (%), or n (%) unless indicated otherwise. Mann-Whitney test and χ^2/Fisher exact were used to compare the continuous and categorical variables in 2 groups.

Adverse Events

Cytopenias

Cytopenias were the most common adverse event that necessitated dose adjustments, treatment discontinuation, and/or use of growth factors. Neutropenia was observed in 21 (60%) of 35 patients, and 10 patients (48%) required dose reduction of pegylated IFN, despite the use of granulocyte colony-stimulating factor in 6 (29%) of these 21 patients. Anemia was observed in 25 (71%) of 35 patients, and 13 patients (52%) required dose reduction of RBV despite the use of erythropoietin in 7 (28%) of these 25 patients.

Two patients developed thrombocytopenia. One patient had platelet counts $<5{,}000/mm^3$ and developed spontaneous subdural hematoma that resulted from idiopathic thrombocytopenic purpura; this patient's course has been reported previously.[17] The other patient's platelet count varied between 49,000 and $57{,}000/mm^3$, and the patient did not experience any bleeding or dose adjustment.

Other adverse effects

Fifteen patients (42%) experienced depression requiring antidepressants. Treatment was discontinued in 2 patients who required psychiatric hospitalization for suicidal ideation in one and suicidal attempt in the other. Both patients improved and have remained emotionally stable 21 and 36 months after discontinuation of treatment.

Three patients developed infections during the course of treatment. Two patients had uncomplicated urinary tract infection and were managed as outpatients with antibiotic therapy. ANC at the time of diagnosis of infection were 1.8 k/mm^3 and 3.8 k/mm^3. One patient with genotype 3 developed a dilated cardiomyopathy that led to bowel ischemia with gastrointestinal bleeding, renal failure, and sepsis at week 12 of antiviral therapy. After a 3-month hospitalization, this patient's cardiac function recovered. She remained HCV RNA negative with good synthetic function of the allograft 15 months after discontinuation of antiviral therapy.

Rejection and autoimmune hepatitis

Four patients experienced worsening liver biochemistries with features of rejection/autoimmune hepatitis on repeat liver biopsies, which led to early discontinuation of antiviral therapy. Patient 1 was a 45-year-old man who initiated antiviral therapy 76 weeks after LT. Trough cyclosporine level during the course of treatment varied between 72 and 90 ng/mL. The pretreatment liver biopsy results revealed a histological activity index (HAI) of 6 and Ishak fibrosis score of 2. Serum AST, ALT, and bilirubin levels increased markedly within 6 weeks of starting pegylated IFN and RBV treatment (Fig. 2a). Analysis of liver biopsy samples showed

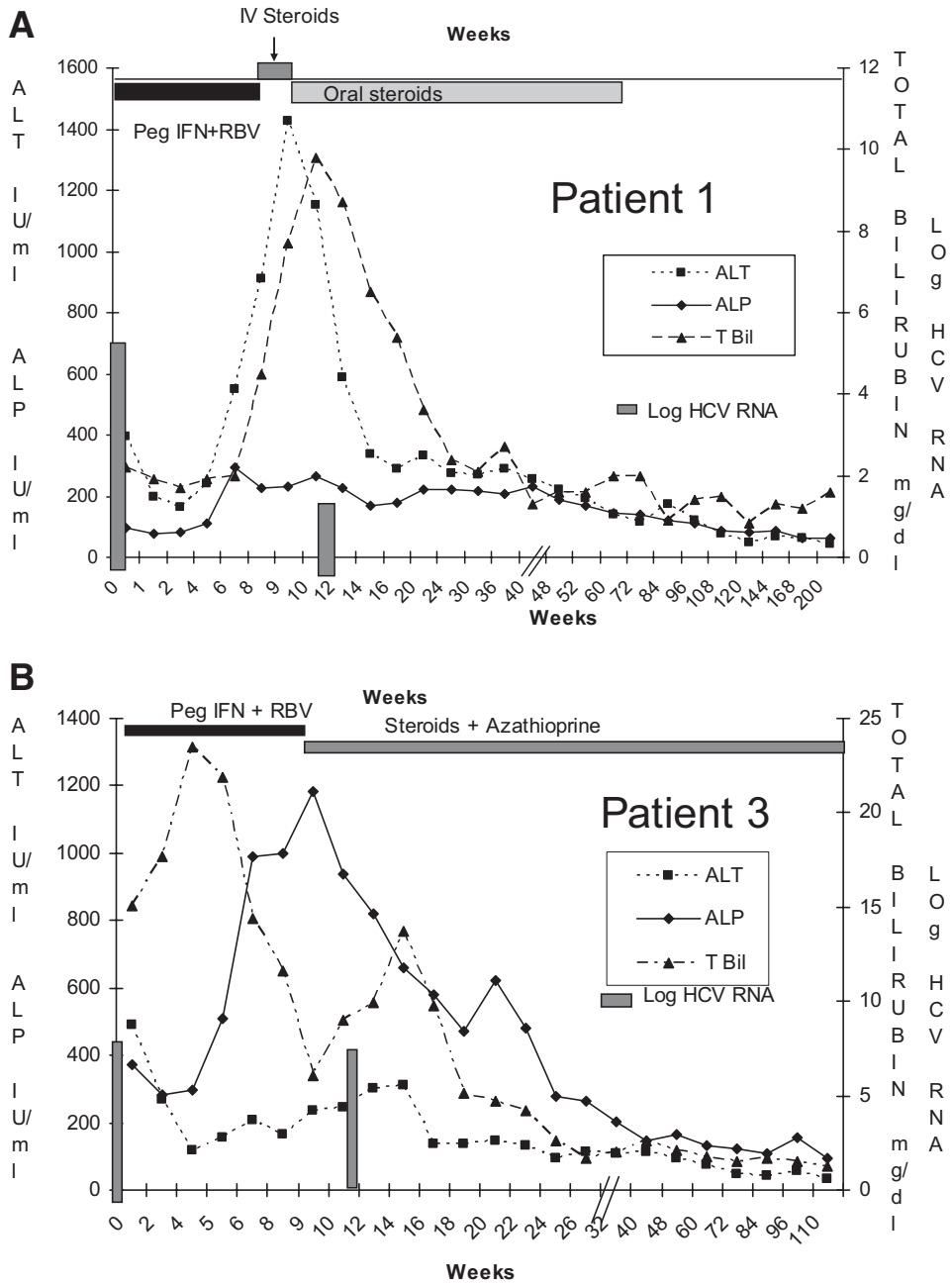

Figure 2A and B. Serial changes in liver chemistries in patients 1 and 3 with rejection and autoimmune hepatitis after initiation of antiviral therapy.

features of acute cellular rejection; antiviral therapy was stopped, and rejection was treated with pulse intravenous corticosteroids. Results of a subsequent liver biopsy 2 weeks later showed resolution of rejection, but there were persistent features of lobular and interface hepatitis with prominent plasma cell infiltrates. This patient was switched from cyclosporine to tacrolimus and was maintained on corticosteroids for 1 year, resulting in normalization of AST and total bilirubin.

Patient 2 was a 52-year-old woman who initiated antiviral therapy 181 weeks after LT. Her pretreatment biopsy findings revealed an HAI of 9 and Ishak fibrosis score of 2. Serum AST and ALT levels increased after 12 weeks of pegylated IFN and RBV therapy (AST 51-309 IU/mL, ALT 46-194 IU/mL, ALP 117-1,273 mg/dL, and total bilirubin 1-9 mg/dL), and the results of a repeat liver biopsy showed acute cellular rejection with evidence of mildly active recurrent hepatitis C. Trough cyclosporine level during treatment ranged 82-106 ng/mL. Pegylated IFN and RBV were discontinued; the patient was treated with intravenous pulse corticosteroid, and cyclosporine was switched to tacrolimus. Prednisone was tapered off over a period of 10 months with improvement in serum aminotransferase levels.

Patient 3 was a 45-year-old man who began antiviral therapy 6 weeks after LT because of clinical and biochemical features of an acute hepatitis. The pretreatment liver biopsy sample had a HAI of 8 and Ishak fibrosis score of 2. At the beginning of treatment, ALT and total bilirubin were 490 IU/mL and 15 mg/dL,

respectively, while ALP was normal. Total bilirubin peaked at 23 mg/dL at week 4 but dropped to 6.1 mg/dL by week 8. ALT levels also decreased over the first 8 weeks. However, ALP showed a consistent increase. At week 10, ALT started to increase (Fig. 2b). Analysis of repeat liver biopsy samples revealed evidence of severe chronic hepatitis with abundant plasma cells resembling autoimmune hepatitis. Trough cyclosporine levels remained at 80-82 ng/dL during the course of treatment. Antiviral therapy was stopped, prednisone dose was increased from 5 to 15 mg daily, and azathioprine was added with clinical and biochemical improvement.

Patient 4 was a 50-year-old man who initiated antiviral therapy 35 weeks after LT. Analysis of pretreatment liver biopsy samples showed minimal lobular hepatitis and increased portal fibrosis consistent with Ishak fibrosis score of 2. Arteries showed foam cell changes. There was no evidence of acute rejection or ductopenia. AST and ALT remained stable; however, ALP increased from 326 to 544 IU/mL after 4 weeks of treatment, and bilirubin increased from 7.7 to 9.5 mg/dL at week 5. Repeat liver biopsy samples showed cholestasis with bile duct damage consistent with chronic ductopenic rejection. Antiviral treatment was discontinued. Trough cyclosporine levels during treatment were 78-87 ng/mL. Cyclosporine dose was increased, and mycophenolate mofetil and prednisone were continued. Liver biochemistry laboratory values remained high despite discontinuation of antiviral treatment. Prednisone was discontinued after 6 months. This patient was maintained on tacrolimus and mycophenolate mofetil with improvement of liver chemistries.

DISCUSSION

In this single-center study of 35 LT recipients with recurrent HCV treated with pegylated IFN and RBV, 37% achieved SVR despite the need for frequent dose reductions and early discontinuations. To date, there are 7 published studies with >20 patients evaluating the efficacy of pegylated IFN and RBV in the treatment of recurrent HCV after LT. SVR in these studies ranged 31-45%.[10,11,18-22] These results are markedly improved over randomized controlled trials of pegylated IFN monotherapy that reported SVR of 8% and 12% when used preemptively and for treatment of established disease after LT.[23] Recently, a systematic review of IFN-based combination therapy for recurrent HCV showed SVR of 27% (95% confidence interval [95% CI], 23-31) for pegylated IFN and RBV and 24% (95% CI, 20-27) for standard IFN and RBV.[24] Compliance to pegylated IFN and RBV therapy was poor, with only 21% (95% CI, 9%-34%) maintaining the full dose of pegylated IFN and RBV vs. 33% (95% CI, 28%-38%) for standard IFN and RBV.[24]

The rates of early treatment discontinuation and dose reduction of pegylated IFN and RBV varied from 11-37% to 30-60%, respectively. Berenguer et al.[21] reported an early treatment discontinuation rate of 40% as a result of adverse effects in their study of 67 patients who were treated with standard IFN (n = 31) or pegylated IFN (n = 36) and RBV. In our study, 43% patients discontinued antiviral treatment early as a result of adverse events. Fifty-seven percent of the patients were able to complete at least 80% of the intended duration of therapy; however, similar to other reports, only 26% of patients were able to tolerate at least 80% of the desired dose of pegylated IFN and RBV.

The target dose of pegylated IFN-α2a 180 μg every week and pegylated IFN-α2b 1.5 μg/kg every week in the present study was similar to that used in the nontransplant setting. The lower target dose for RBV (800 mg/day) was chosen because most LT patients have lower baseline hemoglobin and some degree of renal insufficiency. Only 3 of 20 patients were able to achieve a RBV dosage of 1,000-1,200 mg/dL in a pilot study of treatment of recurrent HCV with pegylated IFN-α2b and RBV.[10]

Factors associated with SVR after IFN and RBV therapy in post-LT patients are not well established because of the limited size of prior studies and the low response rate. In a pilot study of 20 patients, EVR but not dose of pegylated IFN and RBV received was predictive of SVR.[10] In another study of 67 patients treated with combination of standard or pegylated IFN and RBV, >80% dose of RBV, > 80% overall dose and duration (>80/80/80 rule), use of erythropoietin, and EVR were statistically significant predictors of SVR on univariate analysis.[21] However, only EVR was predictive of SVR on multivariate analysis. Similarly, Wang et al.,[24] in their systematic review of IFN-based combination therapy for recurrent HCV, found that genotype 1 and prior antiviral therapy after LT were statistically significantly associated with lack of SVR in univariate analysis of trials on pegylated IFN + RBV, but drug dosage, use of growth factors, interval from LT, and duration of therapy were not associated with SVR. However, patients who received >60% of pegylated IFN and RBV had higher rates of SVR.

In this study, lower pretreatment HCV RNA, EVR, higher cumulative dose of pegylated IFN and RBV, anemia, and use of erythropoietin were associated with SVR on univariate analysis. It should be pointed out that anemia and use of erythropoietin was related to the higher cumulative dose of RBV. However, none of these factors was predictive of SVR by multivariate analysis, presumably as a result of the small sample size and their colinearity.

Although delayed viral relapse after SVR in immunocompetent individuals is rare, there are no data on the durability of response after SVR in immunosuppressed individuals.[25,26] None of the patients in this study experienced viral relapse, including 9 patients followed for >1 year and 5 patients for >2 years after completion of antiviral treatment. These data suggest that durable responses are possible in LT recipients.

IFN treatment is associated with an increased risk of rejection in transplant patients. The risk is higher in renal transplant patients; the risks reported in LT patients vary. Two retrospective studies reported an 11%

and 35% rejection rate in patients with histologically proven recurrent hepatitis C who received IFN-based combination therapy.[27,28] However, 2 prospective randomized controlled trials evaluating pegylated IFN monotherapy in LT patients treated preemptively or for established HCV recurrence reported similar rates of rejection in the treated patients and untreated controls.[23]

Four patients (11%) in the current study had worsening liver biochemistries within 12 weeks of the onset of IFN therapy. Analysis of repeat liver biopsy samples showed acute rejection in 2 patients, autoimmune hepatitis in 1 patient, and chronic ductopenic rejection in 1 patient. All 4 patients responded to corticosteroid treatment. An additional patient with SVR had de novo autoimmune hepatitis 2 years after completion of antiviral therapy, which responded to reintroduction of prednisone and azathioprine without virological relapse. Although none of these patients experienced graft loss, this experience highlights the potential risks of IFN therapy in liver transplant patients and the importance of liver histology in determining the cause of abnormal liver chemistries in LT patients. De novo autoimmune hepatitis has been reported in 0.4-3.4% of transplant recipients without previous autoimmune hepatitis.[29,30] Only 9 cases of de novo autoimmune hepatitis in patients with recurrent HCV after LT had been reported.[12,29-33] Four of them were receiving IFN-based antiviral therapy at the time of diagnosis,[12,32,33] and one patient developed progressive graft failure despite discontinuation of antiviral treatment requiring retransplantation.[29]

The limitations of this study include retrospective design, small number of patients, heterogeneity in the titration of the pegylated IFN and RBV dose up to target dose, and use of growth factors in the management of cytopenias.

In conclusion, this study has shown that combination pegylated IFN and RBV therapy can result in SVR of 37% in patients with recurrent HCV after LT despite the need for dose reductions and early discontinuation in 43% of patients. Patients with low pretreatment HCV RNA and EVR, and those who received higher cumulative dose of pegylated IFN and RBV were more likely to achieve SVR. Once SVR is achieved, the response appeared to be durable. However, serious adverse events were common, which highlights the need for careful laboratory and clinical assessment. Prospective studies are needed to confirm the applicability of the early stop rule on the basis of week 12 virologic response and the cost-effectiveness of prophylactic growth factors in this setting.

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