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Response to antiviral therapy in liver transplant recipients with recurrent hepatitis C viral infection: a single center experience

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Abstract: Introduction: Recurrence of hepatitis C virus (HCV) in hepatic allograft is a major concern after successful liver transplant (LTx).
Aim: To examine the response rate to pegylated interferon (PEG–IFN) and ribavirin in post-LTx patients with HCV recurrence.
Patients and methods: Between January 2003 and September 2006, 60 patients with biopsy proven HCV recurrence (46 males and 14 females) received PEG–IFN 2a (n = 40) or IFN 2b (n = 20) with ribavirin.
All patients were followed until July 2007.
Results: Fourteen patients (23.3%) tolerated antiviral therapy for less than six months and 10 (16.7%) discontinued therapy between six and 11 months. PEG–IFN dose was reduced in 21 (35%) patients and ribavirin dose was reduced in 16 (26.7%) patients. Overall, 55% patients achieved end of treatment response (EOT) and 35% sustained virological response (SVR). Mean Hepatitis Activity Index and Fibrosis Score pre-therapy was 5.8 ± 1.9 and 1.7 ± 1.3 and post-therapy, it was 4.4 ± 2.1 and 2.4 ± 1.6, respectively. Overall, three yr patient and graft survival was 73.9% and 69.2%, respectively. The patients with SVR had significantly lower viral load compared with other groups (p = 0.028).
Conclusion: PEG–IFN and ribavirin therapy achieved 55% EOT and 35% SVR; 60% patients tolerated therapy. Biochemical response was observed in all groups of patients irrespective of virological response.

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Key words: hepatitis C virus – interferon – liver transplant – recurrence – ribavirin – viral hepatitis

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Hepatitis C virus (HCV) infection related end-stage liver disease is the most common cause of liver transplantation (LTx) in the Western world. Virological and histological recurrence of HCV infection after transplant is universal. Fifty percent of patients will have histological changes within one yr and 15–30% will develop cirrhosis by five yr (1–3). Patient and graft survival with HCV infection is inferior compared with patients without HCV infection (4–6). Antiviral therapy that is currently available requires a long course of treatment consisting of subcutaneous (s.c.) weekly administration of pegylated interferon (PEG–IFN) alfa-2a or -2b with ribavirin (7–9). These drugs are not without side effects. Also, sustained virological response rate (SVR) is about 54–56% (42.5% with genotype 1) and the therapy withdrawal rate is up to 35% (10, 11). Response to therapy in cirrhotic patients is lower and withdrawal rate is higher (12, 13). Post-transplant progression of disease is accelerated as a result of immunosuppression (14, 15). End of therapy response rate (EOT) and SVR are also lower (16–19) compared with immunocompetent pre-LTx patients. Currently, there are no large multi-center data available on post-LTx patients with HCV infection. The majority of the

information is from a single center in a small number of cases with retrospective analysis.

The aim of the present study is to examine the outcome of patients who received antiviral therapy for HCV recurrence after LTx at our institution in last four yr and to analyze the response rate, survival rate, and adverse events at our institution and compare with the available data in literature.

Patients and methods

Between January 2003 and September 2006, 60 HCV positive patients (46 male and 14 female) with known histological recurrence were retrospectively studied according to an Institutional Review Board approved protocol. The mean age was 56.8 ± 6.1 yr, and the patients were 28.6 ± 27.6 months post-LTx. They received a combination of PEG–IFN alfa-2a or -2b with ribavirin. Mean donor age was 47.6 ± 17.9 yr and mean follow up was 37.5 ± 13.2 months. Twelve patients had genotype 1, 27 had genotype 1a, 17 had genotype 1b, one had genotype 2b, two had genotype 3a, and one patient's genotype was unknown. Forty patients were started on PEG–IFN alfa-2a (180 μg/wk, s.c. injection) and 20 patients received PEG–IFN alfa-2b (1–1.5 μg/kg/wk, s.c.). In addition, ribavirin, 400 mg twice a day was given orally. Ribavirin dose adjustments were made depending on renal dysfunction from the outset. All patients with biochemical abnormality and HAI ≥ 4 with or without fibrosis (in the absence of anatomical changes) were offered antiviral therapy. The biopsies were read by an experienced transplant pathologist who had no prior knowledge of clinical events, including antiviral therapy, and for accurate fibrosis staging all slides were stained with Gomori trichrome stain (20).

The data were analyzed as intent to treat, and the population was divided into three groups based on their response to antiviral therapy: Group I patients achieved EOT but relapsed, group II patients achieved EOT and maintained SVR, and group III patients who did not respond to treatment. All patients were followed until July 2007 for EOT, SVR, toxicity, withdrawal rate, biochemical changes, histological changes, and patient and graft survival.

Baseline immunosuppression consisted of tacrolimus in 56 (93.3%) patients and micro-emulsion formulation of cyclosporine in four (6.6%) patients. The mean tacrolimus dose was 3.8 ± 2.7 mg/d with a trough level of 7.8 ± 3.7 ng/mL. Twelve patients (20%) were on prednisolone (four on 5 mg every other day, five on 5 mg daily, and two on 10 mg/d), mean dose 4.8 ± 2.7 mg/d. In addition, 12 patients (20%) were on mycophenolate mofetil (MMF) with a mean dose of 958 ± 380 mg/d. Forty patients (66.6%) were on monotherapy with tacrolimus or cyclosporine, 15 patients (25%) were on dual therapy, and five patients (8.3%) were on triple therapy at the start of antiviral therapy (Table 1).

Statistical analyses

Values are presented as mean and standard deviation. Mean were compared using t-test and analysis of variance, and response rates between the groups were analyzed using Pearson's chi-squared test. Patient and graft survival was calculated using Kaplan–Meier method and compared using log-rank test. A value of $p < 0.05$ was considered significant. The statistical analyses were performed using the SPSS software, Windows based version 15.0 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA).

Results

Tolerability

All patients were offered therapy for 48 wk. However, 14 patients (23.3%) received antiviral therapy for ≤ 6 months, of which five (8.3%) were

Table 1. Immunosuppression in relation to response

	Immunosuppression at start of treatment							
	Mean Tacro dose (mg/d; n = 55)	Mean Tacro level (ng/mL)	Mean MMF dose (mg/d; n = 12)	Mean Pred dose (mg/d; n = 12)	Monotherapy (CNI)	CNI + Pred	CNI + MMF	CNI + Pred + MMF
Overall (n = 60)	3.8 ± 2.7	7.8 ± 3.7	958 ± 380	4.8 ± 2.7	40 (66.7)	7 (11.7)	8 (13.3)	5 (8.3)
Group I (n = 12)	4.3 ± 2.4	8.2 ± 3.0	750 ± 359	3.8 ± 1.8	8 (66.7)	2 (16.7)	2 (16.7)	0 (0.0)
Group II (n = 21)	4.2 ± 3.2	8.7 ± 4.9	1062 ± 417	3.8 ± 1.4	13 (61.9)	0 (0.0)	4 (19.0)	4 (19.0)
Group III (n = 27)	3.2 ± 2.3	7.0 ± 2.8	833 ± 289	5.8 ± 3.4	19 (70.4)	5 (18.5)	2 (7.4)	1 (3.7)

Tacro, tacrolimus; Pred, prednisolone; MMF, mycophenolate mofetil; CNI, calcineurin inhibitor. Values in parentheses are expressed in terms of percentage.

for less than three months. Another 10 patients (16.7%) discontinued therapy between six and 11 months. Ribavirin dose reduction was made in 16 (26.7%) patients and dose reduction of PEG–IFN was made in 21 (35%) patients; four (6.7%) of these were commenced on half the dose of PEG–IFN alfa-2a. Withdrawal of antiviral therapy or dose reduction of IFN and/or ribavirin was highest in non-responder group.

In group I, two patients were withdrawn from therapy, one for fatigue and irritability, and the other for end stage renal disease post-LTx. In group II, six patients were withdrawn from therapy, one for retinal changes, one for generalized rash, one for generalized weakness, insomnia and body aches, another two for myelosuppression, and one for renal failure. In group III, 16 patients were withdrawn from therapy, four for myelosuppression, one each for stroke, migraine, cholestasis, and chronic renal failure, and one for financial reasons. Two patients were withdrawn from therapy for depression, one for headache and dyspnea, one for fatigue and insomnia, one for nausea dizziness and abdominal pain, one for leg cramping, easy fatigability, and dyspnea, and one for severe backache, vomiting, headache, and fever.

Erythropoietin was used (40 000 U s.c. weekly) when hematocrit (Hct) decreased by more than 15% of initial Hct. If the decrease was more than 15%, the reduction in ribavirin dose was also made. In all, 26 patients (43.3%) received erythropoietin, and ribavirin dosage reduction was made in 16 patients (26.7%).

Granulocyte colony stimulating factor (GCSF; 300 μg s.c. once or twice a week) was used when absolute neutrophil count was <1000/mL. This was required in 30 (50%) patients. A dose reduction in PEG–IFN was made if there was an associated decrease in platelet count (<50/μmL) or other systemic causes.

Virological response. With "intent to treat analysis," EOT (undetectable HCV RNA $<$ 50 copies/mL) was achieved in 33 (55%) patients (group I + II) of whom 21 (35%) maintained SVR (group II) (Table 2). Mean donor age was 48.1 ± 15.1, 41.8 ± 17.4, and 51.6 ± 18.8 in groups I, II, and III ($p = 0.199$), respectively. Of the 27 patients (group III) who did not clear the virus, 10 (37%) were withdrawn from antiviral therapy in less than six months and 17 (62.9%) had dose reduction of either ribavirin (n = 4) or IFN (n = 13) or both (n = 6) (Table 2). Twenty-nine (87.9%) out of 33 patients in group I + II received antiviral therapy for more than six months, most for 11 months (n = 19).

There was a significant difference in the viral load before antiviral therapy between groups ($p = 0.028$). It is interesting to note that patients in group I had the lowest viral load at the initiation

Table 2. Response to therapy

		Group I[a] (N = 12)	Group II[b] (N = 21)	Group III[c] (N = 27)
Age (mean)		55.4	54.2	54.7
HCV genotype		1 (1); 1a (6); 1b (4); 2b (1)	1 (5); 1a (6); 1b (7); 3a (2); unknown (1)	1 (6); 1a (15); 1b (6)
Viral load (mean copies/mL)		492 474.6	3 944 704.8	924 281.1
Pegylated IFN	IFN type (alfa-2a/alfa-2b)	IFN alfa-2b (3) IFN alfa-2a (9)	IFN alfa-2b (6) IFN alfa-2a (15)	IFN alfa-2a (16) IFN alfa-2b (11)
	Start dose (μg/wk)	90 (2); 120 (2); 180 (8)	90 (2); 120 (1); 150 (2); 180 (16)	60 (1); 80 (4); 90 (2); 120 (3); 150 (1); 180 (16)
Months (mean) from Txp to start IFN		36.0	21.4	27.6
Duration of IFN in months (mean)		11.1	10.6	9.2
Mean ribavirin dose (mg/d)		666.7	723.8	718.5
Required neupogen		Yes (8); No (4)	Yes (10); No (11)	Yes (12); No (15)
Required epogen		Yes (6); No (6)	Yes (11); No (10)	Yes (10); No (17)
Mean pre-IFN	HAI	5.3	6.3	5.7
	Fibrosis	1.8	1.5	1.8
Mean post-IFN	HAI	3.5	3.7	5.3
	Fibrosis	2.2	1.8	3.0

HCV, hepatitis C virus; IFN, interferon; Txp, transplant; HAI, Hepatitis Activity Index. [a]Two patients were withdrawn from therapy; [b]One patient was withdrawn from therapy; [c]16 patients were withdrawn from therapy. Values in parentheses denote number of patients (n).

of antiviral therapy, while patients in group II had the highest viral load at the initiation of therapy ($p = 0.002$). Patients in group III had a viral load more than group I but less than group II at the start of antiviral therapy (Fig. 1).

Response rate in relation to genotype. Genotype was available in all patients except one. Surprisingly, HCV genotype 1a had the poorest EOT (44.5%) and SVR (22.2%) when compared with HCV genotype 1 (EOT: 50% and SVR: 41.6%) and HCV genotype 1b (EOT: 64.7% and SVR: 41.1%).

Response rate in relation to pre-LTx therapy. Seventeen patients (28.3%) received antiviral therapy pre-transplant; 12 patients continued treatment for >6 months. Only two patients cleared the virus but both relapsed post-LTx. Both received antiviral therapy again, one of whom did not respond (case #54, discontinued therapy for migraine) while the other achieved SVR. In all, seven out of 17 patients who received antiviral therapy pre-LTx achieved EOT. Incidentally, all seven patients maintained SVR.

Biochemical response. There was an overall reduction in all biochemical parameters post-antiviral therapy. The overall mean total bilirubin (TBili), alkaline phosphatase (ALK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (GGT) before antiviral therapy were 1.3 ± 1.9 mg/dL, 182.9 ± 86 IU/L, 91.7 ± 74.2 IU/L, 100 ± 73.4 IU/L, and 316.9 ± 440.3 IU/L, respectively. Post-antiviral therapy mean TBili, ALK, AST, ALT, and GGT were 0.9 ± 0.7 mg/dL, 150.7 ± 62.3 IU/L, 51.1 ± 40.5 IU/L, 53.1 ± 43.7 IU/L, and 173 ± 133.4 IU/L, respectively. This biochemical response was observed in all groups of patients irrespective of the status of viremia at the end of therapy. When patients were examined individually, biochemical response (decrease in ALT) was obtained in 51 patients (85%); there was no difference in the rate of biochemical response in various groups; 10 patients (83.3%) in group I, 19 patients (90.4%) in group II, and 22 patients (81.5%) in group III (Table 3).

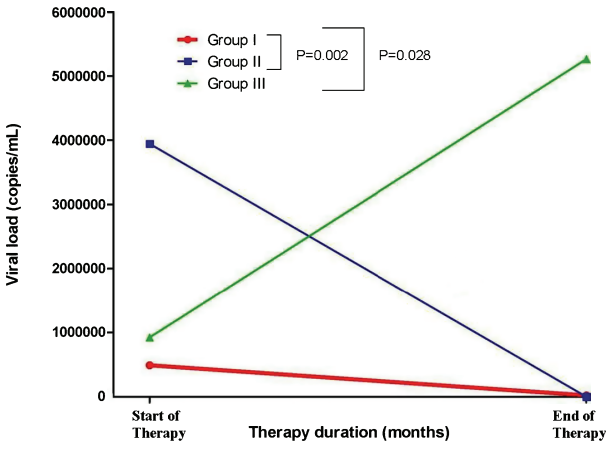

Fig. 1. Pre- and post-therapy viral load in all groups.

Histological response. All 60 patients underwent liver biopsy before the start of antiviral therapy and 55 (91.6%) after the completion of therapy. The mean overall Hepatitis Activity Index (HAI), as per Ishak scoring (21), was 5.8 ± 1.9 and fibrosis score was 1.7 ± 1.3 before antiviral therapy. There was a mean decrease in HAI of 1.4, whereas a mean increase of 0.7 was observed in the fibrosis score. When the individual groups of patients were examined, the mean decrease in HAI score was 1.8 ± 1.4 in group I, 2.6 ± 2.0 in group II, and 0.4 ± 2.8 in group III. The mean fibrosis score increased by 0.4 ± 1.4 in group I, 0.3 ± 1.1 in group II, and 1.2 ± 1.6 in group III (Table 4).

Response in relation to antiviral therapy. Nine (45%) out of 20 patients who received PEG–IFN alfa-2b with ribavirin had EOT with six (30%) patients maintaining SVR, whereas in PEG–IFN alfa-2a with ribavirin, 24 (60%) patients had EOT and 15 (37.5%) maintained SVR ($p = 0.534$). Rate of dose reduction was 25% ($n = 5$) for PEG–IFN alfa-2b and 42.1% ($n = 16$) for PEG–IFN alfa-2a. The rate of early withdrawal was 60% ($n = 12$) for PEG–IFN alfa-2b and 30% ($n = 12$) for PEG–IFN alfa-2a.

Rejection

None of the patients experienced acute cellular rejection during antiviral therapy. One patient in group II, who responded to antiviral therapy experienced severe steroid-resistant rejection after due completion of antiviral therapy, despite adequate baseline immunosuppression (case #63). She received another LTx.

Patient and graft survival. During the follow-up period, 14 patients (23.3%) expired. The most common cause of death (Table 5) was sepsis ($n = 6$, 10%) followed by metastatic cancer ($n = 4$, 6.7%). Other causes of death were adult respiratory distress syndrome ($n = 1$, 1.7%), stroke ($n = 1$, 1.7%), recurrent HCV with liver failure ($n = 1$, 1.7%), and variceal bleed ($n = 1$, 1.7%). The three-yr actuarial survival was 73.9% from the time of start of antiviral therapy. This was

Table 3. Biochemical changes before and after antiviral therapy in relation to response rate

	Mean LFT: pre-antiviral therapy					Mean LFT: post-antiviral therapy					Mean difference (decrease)				
	Tbili	ALK	AST	ALT	GGT	Tbili	ALK	AST	ALT	GGT	Tbili	ALK	AST	ALT	GGT
Overall (n = 60)	1.3	182.9	91.7	100	316.9	0.9	150.7	51.1	53.1	173	0.4	32.2	40.5	46.9	143.9
Group I (n = 12)	1.3	164.2	63.2	76.4	191.2	0.8	131.7	32.1	42.7	160	0.5	32.5	31.1	33.7	31.2
Group II (n = 21)	1.5	198.5	127.4	135.8	398.8	0.9	157.2	55.8	58.4	144.8	0.6	41.3	71.6	77.4	254
Group III (n = 27)	1.2	179.1	76.6	82.7	310.7	1	154.1	56	53.7	200	0.2	25	20.6	29	110.7

Tbili, total bilirubin (mg/dL); AST, aspartate aminotransferase (U/L); ALT, alanine aminotransferase (U/L); ALK, alkaline phosphatase (U/L); GGT, γ-glutamyl transpeptidase (U/L); LFT, liver function tests; IFN, interferon.

Table 4. Histological changes before and after antiviral therapy in relation to response rate

	Mean HAI: pre-antiviral therapy	Mean HAI: post-antiviral therapy	Mean fibrosis: pre-antiviral therapy	Mean fibrosis: post-antiviral therapy	Mean HAI difference	Mean fibrosis difference
Overall (n = 60)	5.8 ± 1.9	4.4 ± 2.1	1.7 ± 1.3	2.4 ± 1.6	−1.4	+0.7
Group I (n = 12)	5.3 ± 1.7	3.5 ± 1.7	1.8 ± 1.4	2.2 ± 1.3	−1.8	+0.4
Group II (n = 21)	6.3 ± 1.8	3.7 ± 1.6	1.5 ± 1.1	1.8 ± 1.2	−2.6	+0.3
Group III (n = 27)	5.7 ± 2.0	5.3 ± 2.3	1.8 ± 1.5	3.0 ± 1.8	−0.4	+1.2

IFN, interferon; HAI, Hepatitis Activity Index.

83.3% for group I, 81.5% for group II, and 64.1% for group III. Although survival was poor in non-responders, it did not reach statistical significance (p = 0.251) (Fig. 2a).

Three patients underwent retransplant (Table 5) during the follow-up period. Three patients had a retransplant. The causes of retransplant were post-therapy rejection (n = 1, 1.7%), recurrent HCV (n = 1, 1.7%), and late hepatic artery thrombosis (n = 1, 1.7%). Overall graft survival at three yr was 69.2% from start of antiviral therapy, 83.3% from group I, 75% from group II, and 57.8% from group III (Fig. 2b).

Table 5. Causes of death and retransplant

Cause	n	%
Death		
Sepsis	6	10
Metastatic cancer[a]	4	6.7
Adult respiratory distress syndrome	1	1.7
Cerebrovascular accident	1	1.7
Recurrent hepatitis C viral infection	2	3.4
Total	14	23.3
Retransplant		
Rejection (post-antiviral therapy)	1	1.7
Recurrent hepatitis C viral infection	1	1.7
Late hepatic artery thrombosis	1	1.7
Total	3	5

[a]Four patients had metastatic cancer; esophageal, gastric, cholangiolar and hepatic origin (one each).

Discussion

Efficacy of IFN alfa-2b in viral hepatitis (both hepatitis B viral infection and HCV) was shown in

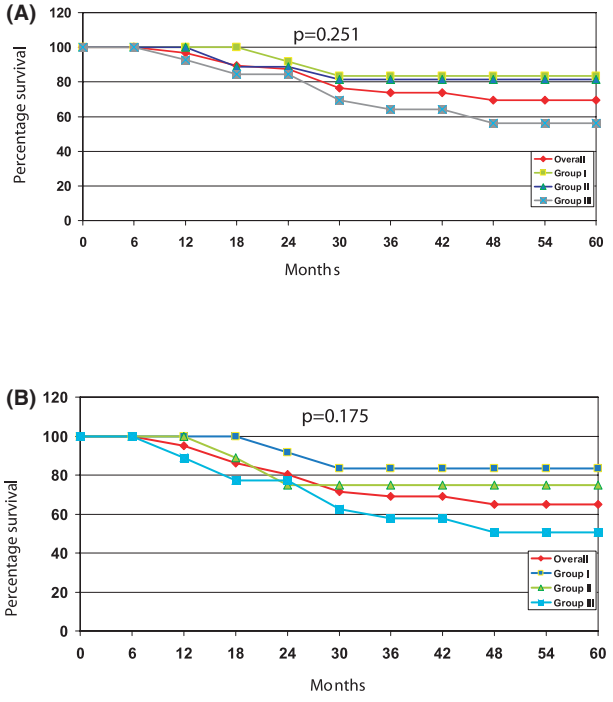

Fig. 2. (A) Patient survival in relation to antiviral therapy response. (B) Graft survival in relation to antiviral therapy response.

late 1980s and early 1990s in several prospective trials in non-transplant patients (22–26). The introduction of ribavirin with IFN and PEG–IFN with ribavirin further improved the response rate in non-transplant viral hepatitis patients (27, 28). However, in post-LTx patients, a combination of IFN with ribavirin resulted in dose reduction rate of ribavirin in >60% of patients and a withdrawal rate of up to 50%, because the dose adjustment for nephrotoxicity was not made (29–32). The need for dose reduction in ribavirin with renal dysfunction was first demonstrated in a large population in 2002 (33). Since then, there have been several published reports of combination of PEG–IFN and ribavirin (with dose modification for renal dysfunction). Most of the studies are on a small number of cases. However, response rate to antiviral therapy in post-LTx patients as predicted by Wright (19) were lower compared with immunocompetent patients. This is a large series of patients from a single institution that is carefully conducted by the same group of physicians in a separate dedicated clinic for post-LTx HCV positive patients.

Picciotto et al. (34) reported an SVR of 28% and treatment failure of 72% in their report of 61 patients. They observed a significantly better survival in patients who achieved SVR. Similarly, Carrion et al. (35) in their report of 81 patients of whom only 54 received antiviral therapy found that antiviral therapy slows disease progression, particularly in patients who achieve SVR. Other authors have reported similar results (17, 36).

In the present study, 55% of patients had EOT and 35% maintained SVR; 93.3% of patients were of HCV genotype 1, where response rate is shown to be lower in pre-transplant population (27, 28). The dose reduction in IFN was made in 35% of cases and dose reduction in ribavirin was made in 26.7%. Five cases (8.3%) discontinued antiviral therapy within three months, another nine (15%) patients between three and six months, and 10 patients (16.7%) between six and 11 months, with an overall withdrawal rate of 40% (n = 24) before 11 months completion of therapy. This is consistent with most of the cited reports (17, 34, 35, 37, 38).

As mentioned in the study by Oton et al. (38), the baseline immunosuppression is an important parameter for success. In our study also, we tried to get the majority of patients (67%) on monotherapy. The remaining patients (33%) could not be maintained on monotherapy to preserve renal function; 48 (80%) of our patients were off steroids altogether and the remaining nine (15%) patients were on 2.5–5.0 mg/d only. Two patients were on 10 mg for previous history of rejection. Also, 20% patients were on small doses of MMF and only five (8.3%) patients were on triple therapy. At our institution, the majority of our patients waited three to six months before starting antiviral therapy to reduce baseline immunosuppression very gradually which may influence EOT or SVR rate.

The most surprising finding in our study was biochemical response irrespective of virological response. While there was an improvement in HAI, the improvement in fibrosis score was disappointing as reported by others (39, 40). It is interesting to note that some authors have reported a high rate of sampling error on needle liver biopsy in patients with diffuse parenchymal liver diseases (41). Like in many reports from the Western world, the majority of our patients (93.3%, n = 56) were infected with genotype 1, of which 30.3% were genotype 1b. None of our patients received preemptive therapy post-LTx. All of them had proven histological recurrence, with biochemical abnormality before starting antiviral therapy. Contrary to reports in our series, genotype 1b had a better EOT (64.7%) and SVR (41.1%) compared with genotype 1 and 1a (42).

Despite the introduction of PEG–IFN with ribavirin, the management of recurrent HCV hepatitis post-LTx remains a challenging problem. Tolerability of the drug, withdrawal of the drug and frequent dose reduction has remained a major problem in the vast majority of cases. In the present series, 23% patients were withdrawn from antiviral therapy consisting of PEG–IFN with ribavirin; 93% of patients were genotype 1. EOT was 55% and SVR was 35%. Patients with SVR had significantly lower HCV viral load before initiation of therapy; 48% of patients required GCSF and 43% required erythropoietin factor. Overall three-yr actuarial patient and graft survival was 73.9% and 69.2%, respectively, which was better for patients who responded to therapy but did not reach statistical significance.

All HCV positive patients with proven histological recurrence (HAI ≥ 4, with or without fibrosis) and a biochemical abnormality should be offered antiviral therapy and the baseline immunosuppression should be gradually reduced prior to initiation of therapy. However, with yearly protocol liver biopsy irrespective of biochemical abnormality, one may be able to treat more patients earlier.

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Self.

Conflict of Interest

None.

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References

1. Berenguer M, Ferrell L, Watson J et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. J Hepatol 2000: 32: 673.
2. Feray C, Caccamo L, Alexander GJ et al. European collaborative study on factors influencing outcome after liver transplantation for hepatitis C. European Concerted Action on Viral Hepatitis (EUROHEP) Group. Gastroenterology 1999: 117: 619.
3. Gane E. The natural history and outcome of liver transplantation in hepatitis C virus-infected recipients. Liver Transpl 2003: 9: S28.
4. Ghobrial RM, Farmer DG, Baquerizo A et al. Orthotopic liver transplantation for hepatitis C: outcome, effect of immunosuppression, and causes of retransplantation during an 8-year single-center experience. Ann Surg 1999: 229: 824.
5. Paik SW, Tan HP, Klein AS, Boitnott JK, Thuluvath PJ. Outcome of orthotopic liver transplantation in patients with hepatitis C. Dig Dis Sci 2002: 47: 450.
6. Sanchez-Fueyo A, Restrepo JC, Quinto L et al. Impact of the recurrence of hepatitis C virus infection after liver transplantation on the long-term viability of the graft. Transplantation 2002: 73: 56.
7. Berenguer M, Palau A, Fernandez A et al. Efficacy, predictors of response, and potential risks associated with antiviral therapy in liver transplant recipients with recurrent hepatitis C. Liver Transpl 2006: 12: 1067.
8. Mukherjee S, Lyden E. Impact of pegylated interferon alfa-2a and ribavirin on hepatic fibrosis in liver transplant patients with recurrent hepatitis C: an open-label series. Hepatogastroenterology 2006: 53: 561.
9. Neff GW, O'Brien CB, Cirocco R et al. Prediction of sustained virological response in liver transplant recipients with recurrent hepatitis C virus following combination pegylated interferon alfa-2b and ribavirin therapy using tissue hepatitis C virus reverse transcriptase polymerase chain reaction testing. Liver Transpl 2004: 10: 595.
10. Bacon BR. Managing hepatitis C. Am J Manag Care 2004: 10(2 Suppl.): S30.
11. Camma C, Licata A, Cabibbo G, Latteri F, Craxi A. Treatment of hepatitis C: critical appraisal of the evidence. Expert Opin Pharmacother 2005: 6: 399.
12. Everson GT, Hoefs JC, Seeff LB et al. Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: lessons from the HALT-C trial. Hepatology 2006: 44: 1675.
13. Crippin JS, McCashland T, Terrault N, Sheiner P, Charlton MR. A pilot study of the tolerability and efficacy of antiviral therapy in hepatitis C virus-infected patients awaiting liver transplantation. Liver Transpl 2002: 8: 350.
14. Neuberger J. Treatment of hepatitis C virus infection in the allograft. Liver Transpl 2003: 9: S101.
15. Teixeira R, Menezes EG, Schiano TD. Therapeutic management of recurrent hepatitis C after liver transplantation. Liver Int 2007: 27: 302.
16. Firpi RJ, Abdelmalek MF, Soldevila-Pico C et al. Combination of interferon alfa-2b and ribavirin in liver transplant recipients with histological recurrent hepatitis C. Liver Transpl 2002: 8: 1000.
17. Lavezzo B, Franchello A, Smedile A et al. Treatment of recurrent hepatitis C in liver transplants: efficacy of a six versus a twelve month course of interferon alfa 2b with ribavirin. J Hepatol 2002: 37: 247.
18. Rodriguez-Luna H, Khatib A, Sharma P et al. Treatment of recurrent hepatitis C infection after liver transplantation with combination of pegylated interferon alpha2b and ribavirin: an open-label series. Transplantation 2004: 77: 190.
19. Wright TL. How can we identify better those with recurrent hepatitis C who will respond to therapy? What are the optimal treatment regimen and treatment duration? Liver Transpl 2003: 9: S109.
20. Gomori G. A rapid one-step trichrome stain. Am J Clin Pathol 1950: 20: 661.
21. Ishak K, Baptista A, Bianchi L et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995: 22: 696.
22. Bosch O, Tapia L, Quiroga JA, Carreno V. An escalating dose regime of recombinant interferon-alpha 2A in the treatment of chronic hepatitis C. J Hepatol 1993: 17: 146.
23. Di Bisceglie AM, Martin P, Kassianides C et al. Recombinant interferon alfa therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. N Engl J Med 1989: 321: 1506.
24. Perrillo RP, Schiff ER, Davis GL et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. The Hepatitis Interventional Therapy Group. N Engl J Med 1990: 323: 295.
25. Saez-Royuela F, Porres JC, Moreno A et al. High doses of recombinant alpha-interferon or gamma-interferon for chronic hepatitis C: a randomized, controlled trial. Hepatology 1991: 13: 327.
26. Picciotto A, Varagona G, Valle F, Coviello DA, Lapertosa G, Celle G. Interferon therapy in chronic hepatitis C. Evaluation of a low dose maintenance schedule in responder patients. J Hepatol 1993: 17: 359.
27. Fried MW, Shiffman ML, Reddy KR et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002: 347: 975.
28. Manns MP, McHutchison JG, Gordon SC et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001: 358: 958.
29. Dumortier J, Scoazec JY, Chevallier P, Boillot O. Treatment of recurrent hepatitis C after liver transplantation: a pilot study of peginterferon alfa-2b and ribavirin combination. J Hepatol 2004: 40: 669.
30. Ross AS, Bhan AK, Pascual M, Thiim M, Benedict Cosimi A, Chung RT. Pegylated interferon alpha-2b plus ribavirin in the treatment of post-liver transplant recurrent hepatitis C. Clin Transplant 2004: 18: 166.
31. Shakil AO, McGuire B, Crippin J et al. A pilot study of interferon alfa and ribavirin combination in liver transplant recipients with recurrent hepatitis C. Hepatology 2002: 36: 1253.

32. Narayanan Menon KV, Poterucha JJ, El-Amin OM et al. Treatment of posttransplantation recurrence of hepatitis C with interferon and ribavirin: lessons on tolerability and efficacy. Liver Transpl 2002: 8: 623.
33. Jain AB, Eghtesad B, Venkataramanan R et al. Ribavirin dose modification based on renal function is necessary to reduce hemolysis in liver transplant patients with hepatitis C virus infection. Liver Transpl 2002: 8: 1007.
34. Picciotto FP, Tritto G, Lanza AG et al. Sustained virological response to antiviral therapy reduces mortality in HCV reinfection after liver transplantation. J Hepatol 2007: 46: 459.
35. Carrion JA, Navasa M, Garcia-Retortillo M et al. Efficacy of antiviral therapy on hepatitis C recurrence after liver transplantation: a randomized controlled study. Gastroenterology 2007: 132: 1746.
36. Chalasani N, Manzarbeitia C, Ferenci P et al. Peginterferon alfa-2a for hepatitis C after liver transplantation: two randomized, controlled trials. Hepatology 2005: 41: 289.
37. Kornberg A, Hommann M, Tannapfel A et al. Long-term combination of interferon alfa-2b and ribavirin for hepatitis C recurrence in liver transplant patients. Am J Transplant 2001: 1: 350.
38. Oton E, Barcena R, Moreno-Planas JM et al. Hepatitis C recurrence after liver transplantation: viral and histologic response to full-dose PEG-interferon and ribavirin. Am J Transplant 2006: 6: 2348.
39. Abdelmalek MF, Firpi RJ, Soldevila-Pico C et al. Sustained viral response to interferon and ribavirin in liver transplant recipients with recurrent hepatitis C. Liver Transpl 2004: 10: 199.
40. Bizollon T, Pradat P, Mabrut JY et al. Benefit of sustained virological response to combination therapy on graft survival of liver transplanted patients with recurrent chronic hepatitis C. Am J Transplant 2005: 5: 1909.
41. Regev A, Berho M, Jeffers LJ et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002: 97: 2614.
42. Polyak SJ, Paschal DM, McArdle S, Gale MJ Jr, Moradpour D, Gretch DR. Characterization of the effects of hepatitis C virus nonstructural 5A protein expression in human cell lines and on interferon-sensitive virus replication. Hepatology 1999: 29: 1262.