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Increasing Adherence to Therapy for Recurrent Hepatitis C After Liver Transplantation by Starting at Lower Drug Doses and Adding Growth Factors

by Nazir Rahim, Colette Prosser, Christopher Bowlus, Natalie Török, Christoph Troppmann, Rajen Ramsamooj, Michael O'Brien, and Lorenzo Rossaro

The aim of the study was to determine if the use of escalating doses of interferon and ribavirin along with growth factors increases adherence to therapy in patients with recurrent hepatitis C (HCV). Ten patients with HCV genotype 1 following liver transplant were enrolled. Post-treatment liver biopsies showed stable or improved disease in six out of nine patients. Our findings suggest that in patients with recurrent HCV after liver transplantation, starting low doses of interferon and ribavirin along with use of growth factors allows for $\geq 80\%$ drug dose adherence. By using pegylated interferons, or possibly the new polymerase or protease inhibitors, we can expect better results. Transplant patients with recurrent HCV remain a clinical challenge with suboptimal response and tolerance to current antiviral therapy.

SUMMARY

The aim of our study was to determine if the use of escalating doses of interferon and ribavirin along with growth factors increases adherence to therapy in patients with recurrent hepatitis C (HCV). Ten

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consecutive patients (9M/1F, mean age 47 years, 6/10 with HCV genotype 1, mean viral load ≥ 2 Million IU/cc) with recurrent HCV on liver biopsy following liver transplant were enrolled. Seven patients (70%) tolerated 48 weeks of combination therapy, two discontinued due to decompensation of cirrhosis and one due to depression. Most patients received $\geq 80\%$ of the expected doses of interferon and ribavirin and 70%-80% required growth factors in order to avoid worsening anemia or neutropenia. Four patients (40%) had negative qualitative HCV-RNA at the end of treatment with combination interferon and ribavirin and were continued on ribavirin monotherapy for an additional 24 weeks. Two of the four responders subsequently relapsed and discontinued ribavirin monotherapy. The other two remained HCV-RNA negative throughout the treatment period and after 24 weeks of follow-up

(20% sustained virological response). Discontinuation of therapy due to hematological toxicity or acute cellular rejection was not observed. Post-treatment liver biopsies showed stable or improved disease in six out of nine patients. Our findings suggest that in patients with recurrent HCV after liver transplantation, starting low doses of interferon and ribavirin along with use of growth factors allows for $\geq 80\%$ drug dose adherence. By using pegylated interferons, or possibly the new polymerase or protease inhibitors, we can expect better results. Transplant patients with recurrent HCV remain a clinical challenge with suboptimal response and tolerance to current antiviral therapy.

INTRODUCTION

Hepatitis C virus (HCV) recurs in virtually all patients after liver transplantation (LT) and cirrhosis is present in 10%–28% of patients five years following LT (1). In addition, mean time to cirrhosis is nine to 12 years, less than half the time compared to the immunocompetent population (1). Once cirrhosis is established, decompensation is rapid, and risk of death or retransplantation is high (2). In fact, the one-year actuarial risk of decompensation is as high as 42%, compared with 28% at 10 years for non-transplant patients (2). Graft failure occurs in approximately one third of patients within the first seven years following LT (1). Treatment of recurrent HCV after LT has not been as successful as in the non-transplanted immunocompetent patients with reported sustained virological response (SVR) rates using standard interferon (IFN) of about 20% (3–9). Adherence to IFN and ribavirin (RBV) has been shown to play a crucial role in response to therapy (10); however, adherence in post-transplant recipients has been disappointing (~40%) (11), primarily due to hematological toxicity. The aim of our study was to determine if starting at low doses of IFN and RBV along with early use of growth factors in patients with recurrent HCV increases adherence to therapy.

METHODS

From November 2000 to May 2002 we enrolled 10 consecutive patients with recurrent HCV after LT in an open label prospective trial. Eligible patients met the

following criteria: liver biopsy confirming the histological diagnosis of recurrent HCV, LT at least six weeks prior to enrollment, and compensated liver disease. At entry visit, the following laboratory parameters were required: hemoglobin ≥ 11 gm/dL for females or ≥ 12 gm/dL for males, white blood count (WBC) $\geq 3,000/\text{mm}^3$, absolute neutrophil count (ANC) $\geq 1,500/\text{mm}^3$, platelets $\geq 70,000/\text{mm}^3$, Albumin ≥ 3.0 g/dL, serum creatinine ≤ 1.5 mg/dL, thyroid stimulation hormone (TSH) within normal limits or thyroid disease under control.

Interferon alpha-2b was started at one Million International Units (MIU) three times a week and incrementally increased by 0.5 MIU biweekly to a maximum of three MIU three times a week. RBV was started at 200 mg bid and incrementally increased by 200 mg biweekly to a maximum of 1000–1200 mg/day depending on body weight. Patients who achieved end of treatment virological response (ETVR) also took an additional 24 weeks of RBV monotherapy. Filgrastim was started at 300 mcg three times a week if the ANC decreased to $\leq 1,500/\text{mm}^3$. Erythropoietin was started at 40,000 Units (U) weekly if hemoglobin dropped ≤ 10 g/dL or symptoms of anemia were present. Patients were evaluated and had laboratory monitoring done at weeks two, four, eight, 12, and every four weeks thereafter until the completion of treatment and throughout the 24 weeks of follow-up. HCV-RNA was measured every three months by quantitative methods. If negative, a qualitative test was performed. Liver biopsy was performed at baseline and at the end of therapy. Two independent pathologists blindly evaluated and scored the pre- and post-biopsies and their scores were averaged. Primary outcomes were (1) SVR, defined as loss of detectable HCV-RNA by PCR 24 weeks after the completion of 48 weeks of combination IFN and RBV plus an additional 24 weeks of RBV monotherapy, and (2) therapy discontinuation rate. Secondary outcomes included (1) ETVR, defined as loss of detectable HCV-RNA by PCR at the end of combination therapy with or without additional RBV monotherapy, (2) use of $\geq 80\%$ of target dose of IFN and RBV, (3) histological changes, and (4) hematological toxicities.

Written informed consent, which was approved by the Human Subjects Review Committee, was obtained on all patients prior to entry.

Increasing Adherence to Therapy for Recurrent Hepatitis C

VIRAL HEPATITIS, SERIES #1

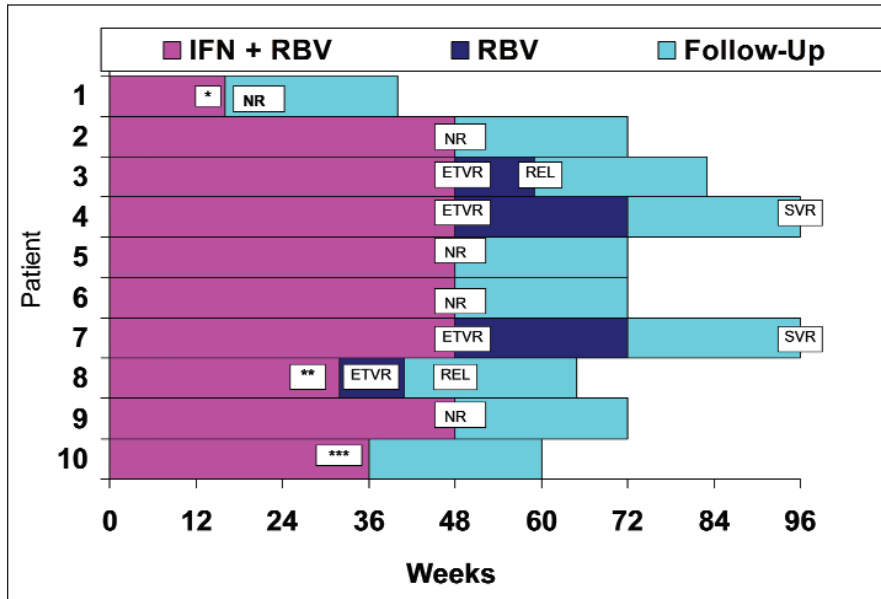


Figure 1. Duration of therapy and reasons for discontinuation. Three patients discontinued treatment: * at 16 weeks (variceal bleeding), ** at 32 weeks (depression), and *** at 36 weeks (ascites). Four patients, who had negative HCV RNA at the end of combination treatment (ETVR), received an additional 24 weeks of ribavirin monotherapy. Two of them relapsed (REL) during monotherapy and two achieved a sustained virological response (SVR). (IFN = interferon, RBV = ribavirin).

Table 1
Patient Characteristics at Baseline

Patient No.	Age	Gender	HCV Genotype	HCV RNA †	Yrs after Transplantation	Liver Biopsy *	
						Inflammation	Fibrosis
1	34	F	1A	1.7	13.0	5	2
2	50	M	1B	4.4	2.0	2	1
3	51	M	3A	2.7	4.0	3	0
4	52	M	3A	0.2	2.0	7	3
5	54	M	1A	6.4	5.0	5	2
6	58	M	1A	4.4	4.0	6	3
7	37	M	1A	0.4	1.5	4	2
8	46	M	3A	1.8	0.7	4	1
9	45	M	1B	1.6	0.5	5	1
10	47	M	3A	0.1	6.0	7	6
Mean	47	M		2.4	3.9	4.8	2.1

† Million International Units /mL; * Ishak Score: Inflammation (0-12), Fibrosis (0-6)

RESULTS

Ten consecutive patients were enrolled. The patient characteristics at baseline are summarized in Table 1: one female and nine males, mean age: 47 years, 60% with HCV genotype 1, mean viral load ≥ 2 MIU with recurrent HCV on liver biopsy (grade 2–7, stage 0–6, Ishak score).

Virological Response

Figure 1 shows the duration of treatment with IFN and RBV, monotherapy with RBV, follow-up after the end of therapy and relationship to virological response. Six patients were non-responders. Of these six, two dropped out before completing 48 weeks of treatment secondary
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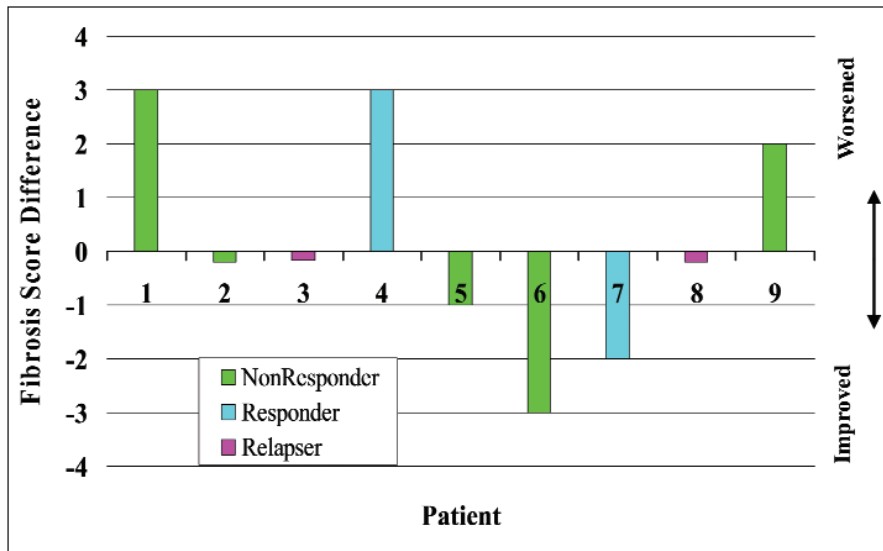


Figure 2. Fibrosis change and viral response. One third of patients had worsening fibrosis (Ishak score, difference between post- and pre-treatment liver biopsies), one third no change, and one third had improvement of fibrosis. (SVR = sustained virological response)

Table 2
Dosages of interferon, ribavirin and percentage of patients on filgrastim and erythropoietin throughout the treatment period

Week	0	4	8	12	24	48	72¶
Number of patients	10	10	10	10	9	7	4
Interferon †	1.0 ± 0	1.5 ± 0.47	2.1 ± 0.25	2.61 ± 0.61	3.0 ± 0.95	2.63 ± 1.45	NA
Ribavirin ‡	400 ± 0	760 ± 84	920 ± 234	1020 ± 289	1044 ± 389	975 ± 456	800 ± 0
Filgrastim (%)	10	40	60	70	67	57	0
Erythropoietin (%)	0	0	10	30	56	71	0

† Dose (mean ± SD) in Million Units three times weekly

‡ Dose (mean ± SD) in mg per day

¶ RBV Monotherapy for those with ETVR at the end of combination therapy

to decompensation of liver disease (patient #1 at 16 weeks for variceal bleeding and patient #10 at 36 weeks for ascites). Patients #3 and #8 responded to treatment (despite patient #8 discontinuing treatment at 32 weeks due to depression). Both patients were placed on RBV monotherapy and relapsed after 12 and 10 weeks, respectively, on RBV monotherapy (relapsers). The remaining two patients (#4 and #7) achieved ETVR at 48 weeks and continued to be virus free during the 24 weeks of RBV monotherapy and subsequent 24 weeks of follow-up (sustained virological responders).

Most patients received 80% of the expected doses of IFN and RBV (Table 2) and 70–80% required growth factors in order to avoid worsening anemia or neutropenia.

Discontinuation of therapy due to hematological toxicity or acute cellular rejection was not observed.

Nine paired biopsies (baseline and at the end of therapy) showed stable or improved fibrosis scores in six patients (baseline Ishak fibrosis scores of 2.0 ± 1.5 vs. 1.1 ± 0.5 at end of therapy) and worsening fibrosis in three patients (1.6 ± 0.5 at baseline vs. 3.5 ± 1.0 at

end of therapy) (Figure 2). There was no correlation between viral response and histologic change.

DISCUSSION

With the prospect of an increase in the number of patients with recurrent HCV in need of retransplantation, it is becoming more apparent to develop not only more effective but also more tolerable antiviral protocols for graft recipients. Adherence to IFN and RBV has been disappointing, primarily due to hematological toxicity. In the non-transplant setting, achieving $\geq 80\%$ drug dose adherence favorably predicts sustained viral response (3). Unfortunately, similar data in the transplant setting is not robust. In a recent study, 43% of transplant recipients with recurrent HCV discontinued IFN and RBV combination therapy due to hematological toxicity (4). In all studies there was a higher rate of treatment discontinuation than in non-transplant populations, primarily due to poor hematological tolerance (5–12). In another study, 66% of patients treated with IFN and RBV required dose reduction or cessation of therapy mainly due to hematological toxicity (13). Erythropoietin was used in 15% of their patients. Similarly, an Italian study reported dose reduction in 51% of their enrolled patients due to anemia and leucopenia (14).

The use of adjunctive hematologic growth factors has not been extensively studied in the liver transplant setting. Recombinant human erythropoietin has been evaluated in treatment of IFN and RBV-induced hemolytic anemia (15). Greater pre-treatment hemoglobin levels and an absolute hemoglobin level greater than 11.5 g/dL was found to correlate with longer duration of therapy (13). In addition, Gergely, et al have reported beneficial effects of erythropoietin in treating anemia induced by RBV and allowing maintenance of RBV dose (16). However, in that study, the optimal dose and frequency of erythropoietin was not established. A large prospective study had shown favorable efficacy in preventing RBV dose reduction or drug withdrawal using early, adjunctive erythropoietin therapy (17). Likewise, scattered reports have documented the use of granulocyte colony stimulating factor (G-CSF), but formal studies on its use have not been performed (18).

Currently, there is no standard therapy for the treatment of recurrent HCV. RBV, used alone, has been

shown to have suboptimal virological response (19–20). Likewise, IFN monotherapy has shown poor virological response (21–22). Studies using combination of non-pegylated IFNs and RBV have shown a SVR rate of around 20% (5–12,23). SVR rates have ranged from 10%–30% in prior studies (4). Unfortunately, as described above, lack of adherence was often reported as the barrier to better treatment outcomes.

Specifically, bone marrow suppression and hemolytic anemia seem to be the main reasons for drug discontinuation. Studies on use of growth factors and antidepressants in this patient population have been scarce.

Our findings suggest that the use of escalating doses of IFN and RBV along with early use of growth factors and antidepressants does allow for $\geq 80\%$ drug dose adherence, resulting in SVR rate of $\sim 20\%$.

Although the rate of post-transplantation fibrosis progression in untreated subjects has been reported to be 0.3/year, the majority of our patients demonstrated improved or stable fibrosis scores following therapy (24).

An additional six months of RBV monotherapy in patients who had achieved ETVR following combination therapy did not appear to make any significant difference in the final SVR rate (50% of patients relapsed while on RBV monotherapy), although we acknowledge that we are unable to reach any meaningful, statistical conclusions based on our few number of patients.

We did not observe a correlation between viral response and histological improvement. Of note, two of three participants who withdrew from the study had baseline cirrhosis and perhaps should not have been entered in the study from the outset. If we exclude them from our analysis, our histological changes become even more favorable (6/8 vs. 6/9 without worsening fibrosis).

In conclusion, our experience is unique in that drug discontinuation due to hematological toxicity was not observed in our protocol. Cirrhotic patients have poor tolerance to treatment and alternative therapies should be explored (i.e., lower dose of maintenance IFN).

We believe the reasons for our high adherence rate are the use of (1) escalating doses of IFN and RBV and

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(2) aggressive use of hematological growth factors. Our study is primarily limited by few numbers of subjects and use of non-pegylated IFN. In addition, although the total duration of the combination therapy was 48 weeks, only during the latter 40 weeks of the protocol did the patients receive the highest tolerable doses. Perhaps, future studies using pegylated IFN for 56 vs. 48 total weeks (given initial eight weeks for escalation delay) should be performed. ■

Acknowledgement

We would like to thank Yulia Suprun for her editorial assistance. This study was supported in part by Integrated Therapeutics, a subsidiary of Schering Plough Corporation.

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