

Telaprevir-based triple therapy for hepatitis C null responders among living donor liver transplant recipients

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Summary

Telaprevir (TVR), a direct -acting protease inhibitor, was recently reported to improve treatment efficacy when used in combination with peg-interferon (PEG-IFN) and ribavirin (RBV) as triple therapy for HCV in non-transplant patients. The aim of the present study was to investigate the feasibility of TVR-based triple therapy among Japanese living donor liver transplant (LDLT) recipients who had been resistant to dual treatment with PEG-IFN and RBV. Among 133 HCV-positive LDLT recipients, 8 null responders during or after dual treatment with PEG-IFN and RBV were finally indicated for TVR-based triple therapy after treatment. All 8 patients had been resistant to dual treatment with PEG-IFN and RBV. While the cyclosporine trough level was well controlled with an 80% dose reduction during TVR administration, the end - of - treatment response rate was only 25% (2/8), with 63% (5/8) of patients developing anemia that required a blood transfusion and 50% (4/8) of patients developing leukopenia that required filgrastim. Dose reduction or treatment discontinuation was required in all cases. Based on the poor efficacy and the unacceptable high rate of cytopenic events, TVR-based triple therapy is not indicated for those resistant to dual treatment with PEG-IFN and RBV.

Keywords: Hepatitis C, Telaprevir, living donor liver transplantation, Japanese, null responder

1. Introduction

Hepatitis C virus (HCV) infection is the leading indication for liver transplantation in both Western countries and Japan. Unfortunately, liver transplantation does not cure HCV-infected recipients, and re-infection of HCV universally occurs with accelerated disease progression compared with that in the nontransplant population, resulting in poor outcomes for HCV-infected recipients. Graft and patient survival could be improved with successful antiviral treatment, but the efficacy of the standard antiviral treatment with peginterferon (PEG-IFN) and ribavirin (RBV)

is unsatisfactory and poorly tolerated for recurrent hepatitis C in the posttransplant setting compared with nontransplant patients, with sustained virologic response (SVR) rates ranging from 0% to 56% (median: 33%) (1).

Telaprevir (TVR), a direct acting protease inhibitor, was recently approved for clinical use, and the administration of TVR in combination with PEG-IFN/RBV substantially improves SVR rates in comparison with standard treatment using PEG-IFN/RBV in nontransplant HCV-positive patients, including treatment-naïve patients, null-responders to previous treatment, and even relapsers after previous treatment. Triple combination therapy with TVR/PEG-IFN/RBV is now a standard treatment for patients with genotype 1 chronic hepatitis C (HCV) (2).

Validation of the triple therapy for recurrent hepatitis C after liver transplantation is urgently needed, but there are significant concerns regarding the safety and efficacy of TVR administration for posttransplant

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recipients due to the severe side effects and potentially strong drug-drug interaction with calcineurin inhibitors (CNI). Several preliminary reports regarding triple therapy for deceased donor liver transplantation (DDLTL) in Western countries were recently published (3,4). However, efficacy and safety was not well describe in a living donor liver transplant (LDLT) setting in an Japanese population (5). Here we report the preliminary experience of TVR-based triple therapy in Japanese living donor liver transplant recipients who had been resistant to dual treatment with PEG-IFN and RBV.

2. Patients and Methods

Between January 1996 and July 2013, 133 adult-to-adult LDLTs were performed for HCV-positive recipients at the University of Tokyo Hospital. The transplantation procedures, including donor selection criteria, surgical procedures, and postoperative management, are described elsewhere (6). As previously reported (7), preemptive PEG-IFN /RBV treatment was administered for 119 of our 133 HCV-positive LDLT recipients, excluding cases of early death (within 3 months) after LDLT ($n = 4$), cases with spontaneous SVR ($n = 5$), and cases without antiviral treatment due to clinical decision ($n = 5$). Briefly, preemptive treatment was initiated just after the recipient's condition stabilized (approximately 1 month after LDLT) with low-dose IFN alpha 2b and RBV (400 mg/day), followed by escalation to PEG-IFN (1.5 $\mu\text{g}/\text{kg}$ per week) and RBV (800 mg/day) depending on the patient's tolerance. The treatment duration was not predetermined, and continued for 12 months more after the serum HCV-RNA became negative. The response was considered to be SVR if the serologic results were negative for another 6 months after therapy was discontinued. That is, a continuous peg-IFN/RBV approach was applied for null-responders. SVR was achieved in 42 patients, and 27 patients discontinued preemptive treatment due to patient death, clinical reasons, intolerance, or refusal of treatment.

2.1. Patient selection for triple therapy

Inclusion criteria for TVR-based triple therapy in this study were null responders during or after the preemptive treatment described above. Consequently, candidates for triple therapy had already undergone our preemptive antiviral treatment regimen for at least 12 months, except for 2 patients: 1 with early recurrent hepatitis C and high aspartate transaminase and alanine transaminase levels during preemptive treatment at 5 months after liver transplantation, and the other with fibrosing cholestatic hepatitis during preemptive treatment at 2 months after liver transplantation. Patient selection is shown in the flowchart in Figure 1. A total of 8 patients (6 men, 2 women) were enrolled in this study. The study protocol was approved by the

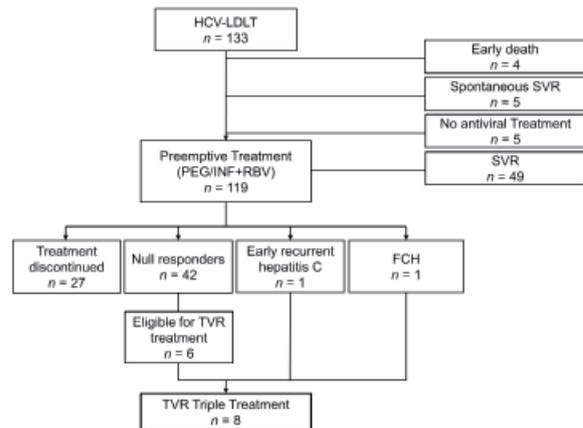


Figure 1. Flow diagram of the patients enrolled in the Telaprevir (TVR)-based triple therapy. Abbreviations: HCV-LDLT, living donor liver transplantation for hepatitis C; SVR, sustained virological response; PEG/INF, peginterferon; RBV, ribavirin; FCH, fibrosing cholestatic hepatitis.

University of Tokyo Ethics Committee (No. 2140) and registered in the UMIN-clinical trials registry (UMIN000013628, <https://center.umin.ac.jp/ctr/index.htm>). Informed consent was obtained from all patients. The follow-up period was 13 month in all participants.

2.2. The triple therapy regimen and immunosuppression

The protocol for TVR-based triple therapy comprised TVR (Telaprevir, Mitsubishi Tanabe Pharma Corp. Osaka, Japan), PEG-IFN (Pegintron, peginterferon Alfa-2b, MSD K.K., Tokyo, Japan), and RBV (Rebetol, MSD K.K.) for 12 weeks without a lead-in phase. After triple therapy for 12 months, treatment with PEG-IFN/RBV was continued for at least 36 weeks more, and even further in cases without viral eradication. TVR was administered orally at 1,000 to 1,500 mg/day, PEG-IFN was administered subcutaneously at 0.8 to 1.7 $\mu\text{g}/\text{kg}/\text{week}$, and RBV was administered orally at 200 mg/day. Dose adjustments were made based on patient tolerance, side effects, and laboratory results.

Our regimen for postoperative immunosuppression is described in detail elsewhere (8). Basically, dual immunosuppression with tacrolimus and methylprednisolone was used, and conversion from tacrolimus to cyclosporine (CsA) was performed without delay if patients developed adverse events due to tacrolimus (9). Considering the strong drug-drug interaction between TVR and CNI (10), especially tacrolimus, tacrolimus was converted to CsA before initiating the triple therapy in all cases, and all patients were admitted to the hospital for 7 to 14 days to measure blood trough levels of CsA and to adjust the CsA dose. On the first day of triple therapy, the CsA dose was reduced to 20% of the original daily dose, and adjusted according to therapeutic monitoring. Close monitoring with daily measurement of the trough levels of CsA was performed during hospitalization, and once a week for

12 weeks at the outpatient clinic. After the completion of TVR, the original daily dose of CsA was resumed.

2.3. Monitoring for hepatitis C virus and adverse events

The HCV genotype was determined before liver transplantation. The nucleotide sequences of the core and non-structural 5A (NS5A) regions of genotype 1b were determined using a direct sequencing method, as described previously (11). The interleukin 28B (IL28B) genotype was examined using the Invader assay (Third Wave Technologies, Madison, WI, USA) (12). Liver biopsy was performed before initiating the triple therapy and evaluated by a pathologist according to the Ishak score for assessing the stage of fibrosis and the degree of necroinflammatory activity (13). HCV-RNA was measured by reverse-transcriptase polymerase chain reaction (TaqMan HCV; Roche Diagnostics Japan K.K., Tokyo, Japan) before starting the treatment and monthly after that. Serum HCV-RNA was considered negative when the results were below the lower limit of quantification (15 IU/mL).

After initiating the triple therapy, blood counts, and liver and renal function were examined every day during admission, and once a week for 12 weeks until the end of TVR administration. Thereafter, these were measured every 4 weeks. The estimated glomerular filtration rate (eGFR; mL/min/1.73 m²) was calculated using the following formula: $194 \times \text{serum creatinine} (-1.094) \times \text{age} (-0.287) \times 0.739$ (if female), Japanese equation (equation 4) (14).

Filgrastim (75 µg; Gran, Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan) was administered subcutaneously to patients with neutrophil counts below 1,000/mm³. Packed red blood cell transfusion was performed when the hemoglobin level dropped below 8 g/dL.

2.4. Ethics statement

All LDLTs were performed after individually obtaining informed consent from recipients and donors. LDLT program at The University of Tokyo Hospital has been approved by its Institutional Review Board, and all aspects of the procedures have been conducted

according to the principles expressed in the Declaration of Helsinki. The current human subject research was approved as project number G3515 by Graduate School of Medicine and Faculty of Medicine, the University of Tokyo Research Ethics Committee and Human Genome, Gene Analysis Research Ethics Committee. All subjects have been properly instructed and participated by signing the appropriate informed consent paperwork. In the preparation of this manuscript, all efforts have been made to protect patient privacy and anonymity.

2.5. Statistical analysis

CsA levels and eGFR before initiating therapy were compared with those at 1 week after initiating the triple therapy by Student's *t* test using GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA). Data are expressed as mean and ± standard deviation (S.D.). A *p* value less than 0.05 was considered statistically significant.

3. Results

The patient characteristics of the eight recipients are summarized in Table 1. The time from LDLT to initiation of the triple therapy was 4.4 ± 3.6 y. Mean recipient age was 59 ± 5.3 y. The HCV genotype was 1b in all patients except for one with a 2a genotype. All eight patients were null-responders to preemptive treatment. Among them, two patients with early recurrent hepatitis C and fibrosing cholestatic hepatitis were switched to triple therapy during preemptive treatment with conventional dual drugs.

3.1. Immunosuppressant modification

Among the eight patients, six had already been converted to CsA before the induction of triple therapy. Consequently, two patients were newly changed from tacrolimus to CsA as a maintenance immunosuppressant before initiating TVR. The CsA trough levels before (81 ± 45 ng/mL) and 1 week after (82 ± 30 ng/mL) initiating the triple treatment did not differ significantly (*p* = 0.54 ; Table 2). The maintenance dose of CsA after

Table 1. Patient characteristics

Patient No.	Sex	Age	Weight	Time from LT (Y)	Previous treatment	HCV genotype	NS5A	IL-28B polymorphism	Liver biopsy
1	M	56	65	9.5	NR	1b	intermediate	T/C	A2F3
2	M	64	52	7.8	NR	1b	wild	T/C	-
3	F	55	46	0.4	NR	1b	wild	T/C	A1F1
4	M	66	63	6.3	NR	1b	NA	C/C	A1F1
5	M	61	60	4.0	NR	1b	intermediate	T/C	A2F0
6	M	60	59	6.2	NR	1b	NA	T/T	A1F1
7	M	50	63	0.6	NR	1b	mutant	T/T	A1F1
8	F	63	36	0.2	NR	2a	mutant	T/T	A2F0

Abbreviations: LT, liver transplantation; NR, null responder, HCV, hepatitis C virus; NS5A, non-structural 5A; IL-28B, interleukin 28B.

Table 2. Characteristics of the 8 patients during treatment

Patient No.	Pretreatment		CsA dose during study		CsA trough level (ng/mL)		MP (mg/d)	MMF (mg/d)	TVR (mg/d)	RBV (mg/d)	PEG-IFN (µg/kg/w)	BT	Filgrastim use	Therapy Discontinue	Infection	eGFR (mL/min/1.73 m ²)		HCV-RNA (Log ₁₀ IU/mL)		Outcome
	CsA dose (mg/day)	CsA dose (mg/day)	Pre	1w after	pre	end of study										0w	12w	48w		
1	60	10	36	50	1500	1500	200	0.8	+	-	-	13 w	-	-	32	6	5.3	0.0	6.8	NR
2	60	10	33	49	1500	1500	200	1	+	-	-	13 w	-	-	42	37	5.5	0.0	7.5	NR
3	100	20	141	116	-	-	200	1.7	+	-	-	-	-	-	68	79	6.6	0.0	5.7	NR
4	100	10	74	104	-	-	200	0.8	+	-	-	-	-	-	48	52	6.4	1.2	7.0	NR
5	50	10	30	40	1500	1000	200	1.4	+	-	-	6 w	CMV	-	43	44	6.8	1.2	6.9	NR
6	100	10	92	89	1000	1500	200	1.5	-	-	-	-	pneumonia	-	44	45	5.4	0.0	0.0	ETR
7	120	20	138	110	-	-	200	1.5	-	-	-	-	-	-	62	89	2.7	0.0	7.1	NR
8	120	30	104	94	-	-	200	1.5	+	-	-	-	-	-	87	28	7.8	3.2	0.0	ETR

Abbreviations: CsA, cyclosporine A; MP, methylprednisolone; MMF, mycophenolate mofetil; TVR, Telaprevir; RBV, ribavirin; BT, packed red blood cell transfusion; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; NR, null responder; ETR, end of treatment response.

the adjustment was 17% (range 10-25%) of the original daily dose (Table 2).

3.2. Efficacy of the triple treatment

At 4 weeks after initiating TVR-based triple therapy, all 8 patients had HCV-RNA levels under 200 IU/mL, and HCV-RNA was undetectable in 50% (4/8) of patients showing a rapid virologic response (undetectable serum HCV at 4 weeks after treatment). At the end of the treatment period (48 weeks), 38% (3/8) of patients showed a partial response (> 2 log HCV decrease) and 25% (2/8) of patients had become HCV-negative, achieving the end-of-treatment response, but re-elevation of HCV-RNA titer occurred in 50% (4/8) of the patients during the subsequent dual therapy period. Changes in the HCV-RNA levels in all patients treated with TVR-based triple therapy are shown in Figure 2.

One patient who did not achieve negative-HCV status at all through the treatment period had a C/C IL-28B polymorphism.

One patient (Patient No.8) developed fibrosing cholestatic hepatitis 2.4 months after liver transplantation. The total bilirubin level was 2.6 mg/dl. Liver biopsy revealed no acute rejection, but A2/F0 was noted. After initiating TVR-based triple therapy for this patient, aspartate transaminase, alanine transaminase, and total bilirubin levels returned to the normal range.

3.3. Tolerance to the treatment and adverse events

TVR-based triple therapy was discontinued in one patient at 6 weeks due to cytomegalovirus infection. TVR was temporally discontinued in another two patients at 4 and 10 weeks, respectively, due to elevated transaminase levels, and subsequently resumed. PEG-IFN and RBV were discontinued in two patients at 13 weeks due to severe fatigue with anemia. Other adverse events were as follows: requiring PEG-IFN dose reduction, 50% (4/8); leukopenia with filgrastim use, 50% (4/8); anemia with packed red blood cell transfusion, 63% (5/8); symptomatic skin rashes, 13% (1/6); and infectious complications, 38% (3/8).

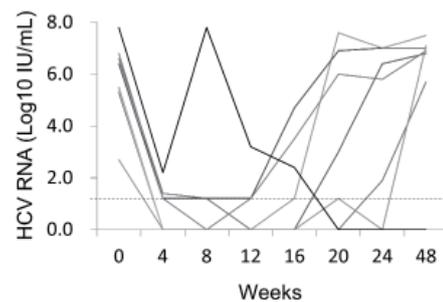


Figure 2. Changes in HCV-RNA level in all patients treated with the TVR-based triple therapy. Each solid gray to black line represents an individual patient. The dotted line represents the lower limit of quantification (15 IU/mL).

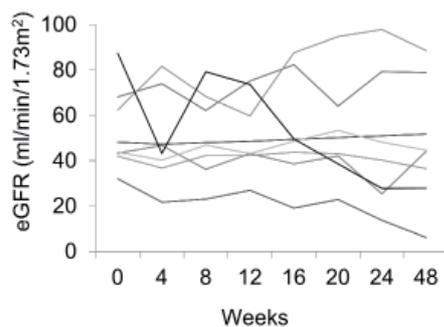


Figure 3. Changes in the estimated glomerular filtration rate (eGFR; mL/min/1.73 m²) during TVR-based triple therapy. Each solid gray to black line represents an individual patient.

In contrast, we observed no acute rejection, hepatic decompensation, or treatment - related mortality among the eight recipients.

3.4. Renal function

In 63% (5/8) of patients, eGFR decreased during the initial 4 weeks, but there was no significant difference between the eGFR level before (53 ± 18 mL/min/1.73 m²) and at the end (47 ± 27 mL/min/1.73 m²) of the treatment ($p = 0.53$). One patient developed end-stage renal disease at end of the study, eventually requiring hemodialysis. Changes in the eGFR during TVR-based triple therapy in each patient are shown in Figure 3.

4. Discussion

The present report describes our initial experience treating recurrent hepatitis C with TVR-based triple therapy in Japanese LDLT recipients. In contrast to several Western reports of the triple therapy demonstrating moderate success for genotype 1 recurrent hepatitis C after DDLT (3,15,16), the present results were discouraging, with an end-of-treatment response rate of only 25% (2/8). It is important to note, however, that all eight recipients indicated for the triple therapy in our study had been resistant to standard dual treatment with PEG-IFN and RBV. In the aforementioned Western reports (3,15,16), triple therapy was used as the initial antiviral treatment for recurrent disease after liver transplantation. Unlike this report, Ikegami and colleagues reported that 82% of patients achieved SVR after LDLT, however, 18% (2/11) of patients did not have previous IFN treatment history (5). Thus, based on the present study: 1) TVR-based triple therapy provided disappointing results for HCV-positive recipients who did not respond to standard dual therapy, 2) TVR-based triple therapy could be performed safely in Japanese LDLT recipients but requires meticulous CNJ management and will result in a high incidence of cytopenic events.

Previous reports in a DDLT setting demonstrated

the efficacy of TVR-based triple therapy against HCV recurrence after liver transplantation. Pungpapong and colleagues (15) reported that 67% (14/21) of patients receiving TVR-based triple therapy achieved undetectable HCV-RNA levels at 24 weeks after finishing treatment without viral breakthrough. Another study described an SVR rate of 56% (5/9) (17). Coilly and colleagues (16) reported that a complete virologic response was obtained after 12 weeks of TVR-based triple therapy in 58% of patients treated with TVR. The end-of-treatment virologic response rate was 40% (4/10) and 20% (1/5) of the patients achieved an SVR. In the present study, however, only 25% (2/8) of patients achieved HCV-negative status at the end of therapy. Accumulating reports from Western countries in a DDLT setting suggest the efficacy of triple therapy for recurrent hepatitis C with genotype 1b (3,15,16), but the present results demonstrated dismal results for non-responders to standard dual therapy. Documented drug-drug interactions with protease inhibitors have raised concerns about the safety of protease inhibitors in the post-transplant setting. In a previous study, TVR increased the area under the blood concentration time-curve of cyclosporine by 4.6-fold, while tacrolimus led to a 70-fold increase (10). Hence, we, as other institutions, used cyclosporine rather than tacrolimus because of the relatively fewer drug-drug interactions. A key finding of the present study is that Japanese LDLT recipients could safely be managed with an initial 80% reduction of the CsA dose in adjusting the trough level of CsA during TVR administration. The dose reduction necessary to maintain the same trough level of CsA seems comparable to that recommended in Western DDLT populations (15).

As emphasized in other studies using TVR in the treatment of recurrent HCV after liver transplantation (3,15,16), the high frequency of hematologic adverse events is a major concern of TVR-based triple therapy, and is higher than that in the non-transplant population and more severe than that in the standard dual treatment among transplant recipients. In our study, 63% (5/8) of patients developed anemia requiring a blood transfusion and 50% (4/8) of patients developed leukopenia requiring filgrastim. The RBV dose was minimized (200 mg/day) from the beginning of the treatment in our protocol. Pungpapong and colleagues (15) similarly described that 46% (16/35) of patients required a packed red blood cell transfusion, 77% (27/35) required an erythropoiesis-stimulating agent for anemia, and 17% (6/34) required filgrastim for leukopenia. Accumulating preliminary reports (15) confirmed that the dose reductions of PEG-IFN and RBV are universal in triple therapy for posttransplant recipients. Although recent data suggest that the RBV dose can be lowered in nontransplant patients treated with TVR-based triple therapy without a loss of efficacy (18), the optimal doses of RBV and PEG-IFN for transplant recipients

under triple therapy requires further study.

Another concern regarding antiviral treatment with TVR is its impact on renal function. Liver transplant recipients have impaired renal function, mainly due to long-term use of CNIs. In this study, the recipients showed impaired renal function with a mean eGFR of 53 mL/min/1.73 m² at the beginning of the triple therapy. After initiating TVR-based triple therapy, the eGFR decreased in 63% (5/8) of patients within the first 4 weeks with a mean eGFR of 47 mL/min/1.73 m². The pretreatment eGFR and that at the end of TVR-based triple therapy, however, were not significantly different from each other. Similar reversible renal dysfunction during the TVR-based triple therapy was reported by Pungpapong and colleagues (15). Because TVR has never been reported to be nephrotoxic in non-transplant setting trials, the renal impairment could be due to changes in CNI pharmacokinetics during triple therapy, despite strict CNI trough level monitoring and dose adjustment.

There are several limitations to our report. First, the main limitation is that treatment was arbitrarily performed for a small number of cases, which makes the data inadequate to support the findings. Second, in addition to the high rate of treatment discontinuation, the dose of TVR and RBV were unacceptably reduced to appropriately assess the efficacy of TVR. Third, none of the patients were naïve for antiviral treatment after transplant but were resistant to the standard dual treatment, making it difficult to compare the findings with those from other studies. In conclusion, we report our preliminary experience of triple therapy with TVR and PEG-IFN/RBV to treat recurrent HCV resistant to the standard dual treatment among Japanese LDLT recipients. The efficacy of TVR-based triple therapy was disappointing, and associated with difficulty controlling CNI trough levels and an unacceptable high rate of cytopenic events. Therefore, we conclude that TVR-based triple therapy is not indicated for those resistant to standard PEG-IFN and RBV treatment. Recently, simeprevir, a new direct-acting protease inhibitor, was approved for clinical use in both the United States and in Japan. Preliminary reports indicate that simeprevir, when used in association with PEG-IFN/RBV among nontransplant patients, has a more potent effect for achieving SVR with fewer adverse events (19,20), and has no drug-drug interaction with CNIs (21). Triple therapy for recurrent HCV with simeprevir is currently under investigation in our institution.

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