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ORIGINAL ARTICLE

# Pre-emptive antiviral therapy in living donor liver transplantation for hepatitis C: observation based on a single-center experience

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## Summary

Reports of large series in living donor liver transplantation (LDLT) for hepatitis C virus infection (HCV) are scarce. Between 1996 and 2008, 105 LDLTs were performed at the University of Tokyo for HCV. Rapid induction of antiviral treatment with interferon (IFN) and ribavirin (RBV) was attempted per protocol regardless of the clinical presentation of recurrent HCV (pre-emptive treatment approach). Treatment was continued for 12 months after serum HCV-RNA became negative (ETR: end-of-treatment response) and judged as a sustained viral response (SVR) after another 6 months of negative results without treatment. A fixed treatment period was not defined unless an ETR was achieved (no-stopping approach). Flexible dose adjustments were allowed. Ninety-five patients were eligible for pre-emptive therapy. Forty-three (45%) patients experienced an ETR, and 32 (34%) achieved SVR. Nonadherence to full-dose INF and RBV had little impact on the viral response. Evaluation using the Kaplan–Meier method to incorporate the cumulative time-dependent nature of the no-stopping approach estimated SVR rate at 53% by the fifth year. Survival rate at 5 years was 79% for the HCV recipients and did not differ significantly from our non-HCV series. In LDLT for HCV, pre-emptive IFN–RBV-based treatment with the application of no-stopping approach is feasible and effective.

## Introduction

Hepatitis C virus (HCV) is the major cause of chronic liver disease resulting in cirrhosis and liver failure in developed countries [1–3], including Japan [4]. It has become the leading indication for liver transplantation and will continue to be an important challenge [5–9]. Unfortunately, liver transplantation is not a cure for HCV infection. Re-infection is universal [10–12], and the histologic progression of HCV seems to be accelerated in comparison to that in nontransplant patients [13–15]. Large studies have demonstrated poorer survival outcomes in liver transplant recipients with HCV [16–19]. Although results of re-transplantation following graft failure in this patient group have been demonstrated with acceptable rate of success [20], this remains a challenging option in the era of organ shortage. Treatment of HCV recurrence generally follows the strategy for treating HCV in non-transplant patients. Experience with interferon (IFN)-based combination therapy has accumulated in liver transplant settings [21–23].

Earlier Western experiences have raised concerns that living donor liver transplantation (LDLT) might be disadvantageous for HCV-positive patients, leading to

more rapidly progressive recurrence of HCV after transplantation [24,25]. Recent studies suggest that the HCV kinetics is accelerated in LDLT as compared with deceased donor liver transplantation (DDLT). Schiano *et al.* [26] compared 11 LDLT patients with 15 DDLT patients; HCV-RNA levels rose more rapidly in the LDLT with greater biochemical changes. Another study by the Barcelona group focusing on the histologic aspects of HCV recurrence with a protocol biopsy reported more severe progression in LDLT as compared with DDLT [27]. Although this remains controversial [28–30], the concern has affected the decision-making process with regard to treating HCV in many transplant centers in the Far East where LDLT is predominantly performed, and where there is little hope for DDLT or re-transplantation.

The rationale for the early initiation of combined IFN-based treatment regardless of the clinical symptoms of recurrent HCV following transplantation (pre-emptive therapy) is to strike at a time when the total HCV viral load is relatively low and histologic damage is minimal [11,12]. Despite this theoretical advantage, the efficacy of pre-emptive therapy has not been determined in Western experience where DDLT is predominant [31–33]. The number of reports on the treatment of HCV in LDLT from high-volume Eastern centers is also limited [34,35]. Much remains to be elucidated regarding the form of application of INF-based treatment as well as its overall outcome in an LDLT setting. We herein report the results of our experience with the application of a pre-emptive therapy approach in LDLT.

## Patients and methods

### Patients

Between January 1996 and March 2008, 411 LDLTs were performed at the University of Tokyo. Of the 411 LDLTs, 336 were performed in adults, among whom 105 underwent LDLT for HCV. The clinical courses of these patients were studied prospectively. The median age of the patients was 55 years (range 23–66). The majority of patients were male subjects (76 men and 29 women), and the HCV genotype was 1b in 84 cases (80%). The median Model for End-Stage Liver Disease (MELD) score was 14 (range 6–48). Six patients were co-infected with HIV and 60 patients had hepatocellular carcinoma (HCC), 50 of whom were within the Milan criteria. As for 231 patients that underwent adult-to-adult LDLT for other indications, the median age of the patients was 55 years (range 18–67). The majority of patients were female subjects (110 men and 121 women). The median MELD score was 14 (range 6–41). Forty patients had HCC, 37 of whom were within the Milan criteria.

Our surgical technique for LDLT and the process of donor selection and evaluation are described elsewhere [36–39]. Splenectomy was performed at the time of LDLT to prevent the progression of thrombocytopenia under IFN-based antiviral therapy [40]. In line with the practice at majority of liver transplantation centers worldwide [41], tacrolimus-based immunosuppression regimen had been administered in our program for all indications including HCV. All patients initially received the same immunosuppressive regimens with tacrolimus (Prograf; Astellas Pharmaceutical Corporation, Tokyo, Japan) and methylprednisolone [42]. In brief, tacrolimus was administered by continuous intravenous infusion at a dose of 2.5 μg/kg/h just after the operation. After the whole blood level of tacrolimus reached 17–18 ng/ml, the dose was adjusted to maintain this level during the first week after the operation. Intravenous methylprednisolone was started during the operation (20 mg/kg/day), and was gradually tapered afterwards. When gastrointestinal function returned, tacrolimus and steroid were given orally. Steroid treatment was not discontinued in any of the patients. Conversion from tacrolimus to cyclosporine was performed in 34 patients (32%), mostly as a result of adverse events [43,44].

Before transplantation, the HCV genotype was determined [45]. After initiation of the combined therapy, blood counts and liver function tests were performed every 2 weeks for the first month, and at up to 4-week intervals thereafter. Serum samples were collected once per month for quantitative HCV-RNA detection. HCV-RNA was measured quantitatively immediately before and after liver transplantation by reverse-transcriptase polymerase chain reaction (Amplicor HCV; Roche Molecular Systems, Pleasanton, CA, USA). Serum HCV-RNA was considered negative when test results were negative (sensitivity <50 IU/ml).

### IFN-based combination treatment for HCV

The current study includes patients from our previous pilot study describing the feasibility of our approach for the early initiation of antiviral treatment in HCV recipients [46]. In brief, treatment was initiated with low-dose IFN alpha2b and ribavirin (RBV) 400 mg/day promptly after improvement in general condition following liver transplantation, especially recovery of hematologic and renal function was recognized. More specifically, initiation was considered when the leukocyte number was ≥4000/ml, the platelet count was ≥50 000/ml, the hemoglobin was ≥8 g/l, and serum creatinine <2 mg/dl. Thereafter, the dosage was gradually increased as tolerated. Finally, pegylated (PEG)-IFN 1.5 μg/kg/week and RBV 800 mg/day are administered, depending on patient compliance.

The treatment is continued for 12 months after serum HCV-RNA becomes negative, which is defined as the end-of-treatment response (ETR). The response was considered to be a sustained viral response (SVR) after another 6 months of negative serologic results without antiviral treatment (Fig. 1). Serologic monitoring for HCV-RNA was consecutively performed on a monthly basis even after SVR was achieved to avoid unrecognized episodes or delayed diagnosis of relapse.

Flexible dose adjustments were made accordingly to avoid serious adverse events and to prevent any lapse in treatment. Actual levels of the given dosage at the time of data collection or final administration was recorded, represented by percentile, with 100% being the full target dose described above (i.e., PEG-IFN 0.5 μg/kg/week is represented as 33%, or RBV 200 mg/day is represented as 25%).

A fixed overall treatment period length was not defined and cessation resulting from adverse events was considered temporary unless an ETR was achieved. Poor virologic response alone was not considered an indication for discontinuation. Treatment was temporarily discontinued when there was significant leukopenia (<1500/ml), thrombocytopenia (<50 000/ml) despite administration of granulocyte colony-stimulating factor (Gran, Sankyo, Co. Ltd., Tokyo, Japan), hemolytic anemia (hemoglobin <8 g/l), renal dysfunction (serum creatinine <2 mg/dl), depressive psychologic status, or general fatigue affecting quality of life. Erythropoietin was given when recovery from anemia remained poor following cessation of antiviral treatment.

### Treatment of acute cellular rejection

During the period of observation, biopsy-proven mild-to-moderate acute cellular rejections were confirmed in 27 (26%) patients and treated with a 20-mg/kg bolus of methylprednisolone intravenously with subsequent tapering of the dosage, which was decreased by 50% on each of the following days.

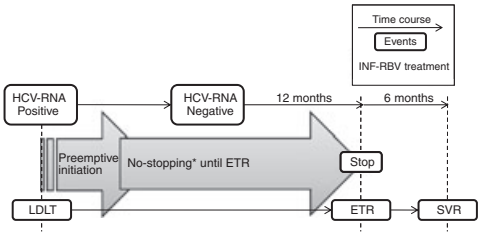


**Figure 1.** Diagram of combined interferon and ribavirin treatment following living donor liver transplantation at Tokyo University. HCV-RNA, status of hepatitis C virus RNA in the serum; IFN RBV, interferon and ribavirin therapy; LDLT, living donor liver transplantation; ETR, end of treatment response; SVR, sustained viral response. *Treatment with interferon and ribavirin was put on hold when serious adverse events occurred.

### Statistical analysis

To clarify whether tolerability affected the outcome, tolerated rates of doses of INF and RBV were studied in accordance with the viral response and eradication. To clarify the time-dependant response, the cumulative rate of negative HCV-RNA, and of the ETR and SVR statuses were studied using the Kaplan–Meier method. The survival curves and cumulative viral response rates were compared using the log-rank test. Various clinical factors, including recipient and donor age and gender, MELD score, presence of HIV, HCV genotype, HCV-RNA viral titer prior to LDLT, occurrence of acute cellular rejection, and use of cyclosporine, were analysed for their effect on achieving an SVR and survival. A multivariate analysis was performed using the Cox proportional hazards model and a forward stepwise procedure. Continuous data were compared between groups using the Mann–Whitney *U*-test. Creation of figures including Kaplan–Meier curves, density-contour plots, box-and-whisker plots, and statistical calculations were performed using SAS software (SAS Institute, Cary, NC, USA). A $P$ value of <0.05 was considered statistically significant.

## Results

### Applicability of IFN-based treatment using a pre-emptive approach

Among the 105 recipients with HCV who underwent LDLT during the observation period, 95 patients (90%) received IFN-based combination therapy with RBV, according to our early treatment regimen. Ten patients were not eligible for our pre-emptive approach; in the case of two patients, the reason was attributable to early death, in case of six attributable to lack of consent, and in case of one patient, attributable to negative HCV-RNA after transplantation. One other patient was excluded because of poor condition, including multi-organ failure, during the immediate post-transplant period, which resulted in subsequent renal failure necessitating maintenance hemodialysis. This patient eventually received IFN monotherapy for recurrent HCV, resulting in viral eradication 23 months after LDLT, but died from the progression of pulmonary hypertension before achieving the ETR. For the remaining 95 patients, the median period from LDLT to IFN/RBV initiation was 26 days (range 10 days–6 months). The median follow-up period was 45 months (range 1–122 months).

Episode of biopsy-proven acute cellular rejection was confirmed in 21 of the 95 patients. Episode of rejection

took place prior to, or after the initiation of IFN-based combination therapy in nine (9%), and 12 (13%) patients respectively. The median period from LDLT to the initiation of antiviral treatment in the nine patients was 28 days (range 21–59 days), whereas the median interval from LDLT to rejection episodes was 11 days (range 5–29 days). In the 12 patients in whom rejection took place after the initiation of IFN-based combination therapy, the median period from LDLT to the initiation of antiviral treatment was 17 days (range 12–52 days), and the median period to rejection episode from LDLT was 44 days (range 18–577 days).

### Viral response

Among the 95 recipients that underwent IFN-based therapy, 51 (54%) patients had negative HCV-RNA results at least once, among whom 43 patients experienced a sustained response for 12 months (ETR). Six patients who reached the ETR eventually presented with a viral relapse, and did not achieve an SVR. At the time of data collection, 32 (34%) achieved an SVR. None of the recipients that achieved SVR have presented with a viral relapse during the observed period. The median time to achieve a negative HCV-RNA, ETR, and SVR under the treatment regimen was 12 months (range 2–63 months), 25 months (13–79 months), and 28 months (19–67 months) respectively.

Consistent with the nature of a treatment protocol without a defined time endpoint, the response rate tended to increase over time. At 3 years, negative HCV-RNA status was obtained in 63%, ETR in 48%, and SVR in 34%. By the fifth year, negative HCV-RNA status was obtained in 70%, ETR in 68%, and SVR in 53% (Fig. 2a).

Hepatitis C virus infection genotype 1b, use of cyclosporine, and a lower rate of tolerated RBV dose presented with significantly poorer outcomes (Table 1). Multivariate analysis revealed HCV genotype 1b as the only independent factor resulting in a significantly poorer viral

**Table 1.** Sustained viral response in patients with combined treatment and clinical factors.

| | Factors | No. | %SVR at 5 years | *P* |
|---|---|---|---|---|
| R-age | ≤55 | 50 | 58 | 0.85 |
| | > | 45 | 47 | |
| R-gender | Male | 68 | 57 | 0.39 |
| | Female | 27 | 40 | |
| MELD | <15 | 49 | 54 | 0.75 |
| | ≥ | 46 | 51 | |
| HIV | Positive | 4 | 67 | 0.17 |
| | Negative | 91 | 52 | |
| HCC | Positive | 55 | 41 | 0.08 |
| | Negative | 40 | 66 | |
| Genotype | 1b | 78 | 43 | <0.0001 |
| | Non-1b | 17 | 85 | |
| HCV-RNA titer | ≤250 K IU/ml (5.4 log)* | 40 | 49 | 0.29 |
| | > | 55 | 53 | |
| ACR | Yes | 21 | 37 | 0.27 |
| | No | 74 | 56 | |
| D-age | ≤35 | 46 | 47 | 0.35 |
| | >35 | 49 | 61 | |
| D-gender | Male | 59 | 45 | 0.59 |
| | Female | 36 | 71 | |
| CyA | Yes | 64 | 35 | 0.02 |
| | No | 31 | 61 | |
| INF dosage† | ≥60% | 48 | 55 | 0.36 |
| | <60% | 47 | 58 | |
| RBV dosage† | ≥50% | 54 | 69 | 0.02 |
| | <50% | 41 | 33 | |

No., number of patients; %SVR, percentage of patients achieving sustained viral response; R-age, age of the recipient at the time of transplantation; R-gender, gender of the recipient; MELD, Model for end-stage liver disease score; HIV, human immunodeficiency virus; HCC, hepatocellular carcinoma; HCV-RNA, hepatitis C viral ribonucleic acid; ACR, acute cellular rejection; D-age, age of the donor at the time of transplantation; D-gender, gender of the donor; CyA, cyclosporine A.
*During the study period, quantification of real-time RT-PCR introduced for linear quantification and detection of HCV-RNA.
†Actual levels of the given dosage at the time of data collection or final administration was recorded represented by means of percentile, 100% being the per-protocol full target dose.

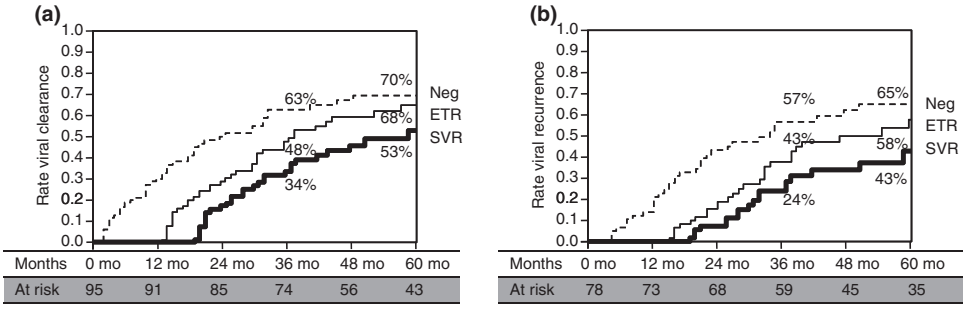


**Figure 2.** (a) Cumulative overall viral response depicted by Kaplan-Meier method. (b) Cumulative overall viral response of recipients with HCV genotype 1b depicted by Kaplan-Meier method. Neg, negative HCV-RNA; ETR, end of treatment response; SVR, sustained viral resposne; mo, months.

response (hazard ratio 0.263, 95% confidence interval 0.127–0.545, $P = 0.0003$). Of the recipients with an HCV genotype 1b, negative HCV-RNA status was obtained in 57%, ETR in 43%, and SVR in 24% at 3 years. By the fifth year, negative HCV-RNA status was obtained in 65%, ETR in 58%, and SVR in 43% (Fig. 2b).

### Tolerability of IFN-based treatment

At the time of final data collection, a total of 24 (25%) patients had tolerated the full dose of INF, and eight (8%) patients had tolerated the planned full dose of RBV. The average dosage of INF tolerated among the 95 patients was 68% (SD 26%) of the full dose, and that of RBV was 41% (SD 24%, Fig. 3).

Tolerability in terms of rates of dosage of INF or RBV did not differ significantly between those with a viral response and those without (Fig. 4a–c). Lack of adherence to the planned target dose was common, but had no significant impact on the viral response within the observation period.

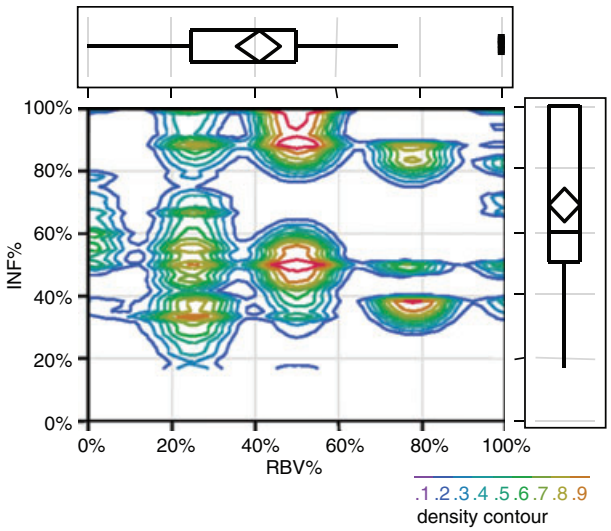


**Figure 3.** Actual tolerated rates of dosages of interferon (IFN) and ribavirin (RBV) by density contour plot. Box-and-whisker plots accompanying the vertical and horizontal axis represent the summery of IFN and RBV tolerated rates of dosages.

### Survival

The overall mid-term rates of survival were not statistically different between HCV and non-HCV recipients (Fig. 5a). The short-term outcomes, however, were poorer in HCV recipients. At 2 years after transplantation, recipients with HCV presented with a significantly lower survival rate compared to non-HCV recipients (82% vs.

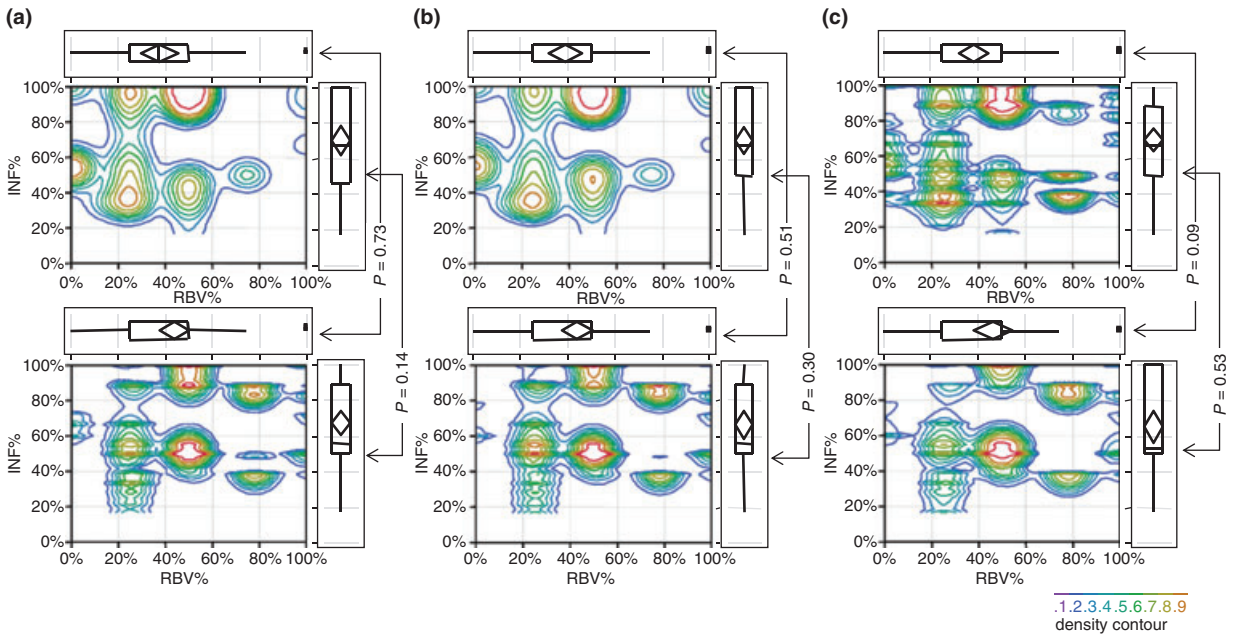


**Figure 4.** Actual tolerated rates of dosages of interferon (IFN) and ribavirin (RBV) by density contour plot according to viral response. Box-and-whisker plots accompanying vertical and horizontal axis represent the summery of IFN and RBV tolerated rates of dosages, respectively. Diamond in the box-plot represents the mean and 95% confidence interval. (a) Above: outcomes of patients that remained positive for HCV-RNA during the studied period. Below: outcomes of patients that demonstrated negative HCV-RNA results at least once during the studied period. (b) Above: outcomes of patients that did not achieve end-of-treatment (ETR). Below: outcomes of patients that achieved ETR. (c) Above: outcomes of patients that did not achieve sustained viral response (SVR). Below: outcomes of patients that achieved SVR (*P*-values by Mann-Whitney *U*-test).


 

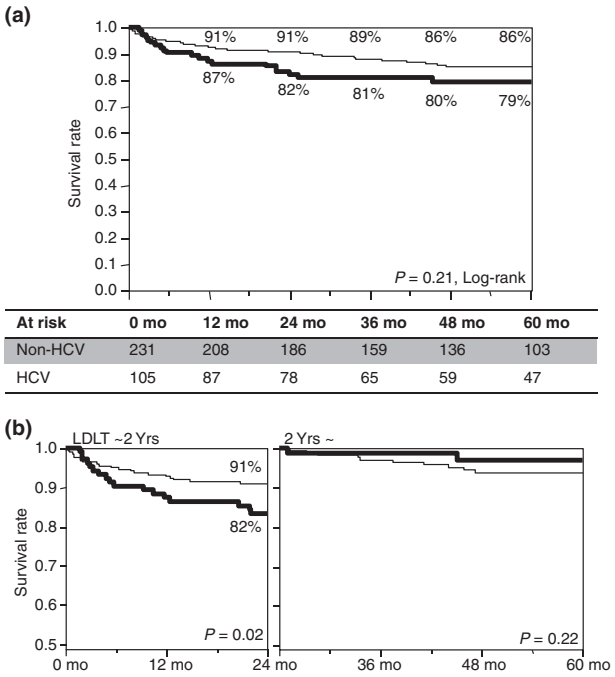


**Figure 5.** (a) Comparison of overall survival between hepatitis C virus infection (HCV) ($n$ = 105) and non-HCV ($n$ = 231) adult-to-adult LDLT recipients. Median follow up period of HCV, and non-HCV patients were 45 and 55 months, respectively. (b) Comparison of overall survival between HCV and non-HCV adult-to-adult LDLT recipients at 2 years post-LDLT and thereafter (bold lines indicate HCV patients). LDLT, living donor liver transplantation; mo, months.

91%, $P = 0.02$). Survival rate after the second year did not differ between HCV and non-HCV recipients (Fig. 5b).

Analysis of factors affecting the short-term survival rates indicated that viral titer prior to transplantation, viral response to treatment, acute cellular rejection, donor age, and donor gender were significant factors affecting the survival at 2 years (Table 2). Multivariate analysis revealed that a higher viral titer prior to transplantation, poor response to antiviral treatment, occurrence of acute cellular rejection, and older donor age were independently significant factors associated with poor survival (Table 3).

## Discussion

In this study, as also considering the experience gained in the above-mentioned pilot series, data of a total of 105 adult patients with HCV that underwent LDLT at our institution over the past decade were collected and evaluated to validate our approach of pre-emptive treatment. Ninety-five patients were eligible and received pre-emptive antiviral therapy. The rate of complete viral eradication identified by an SVR within the observed follow-up period was comparable to a reported series of DDLT recipients with responsive treatment approaches (32 of 95 recipients, 34%). Unlike the outcome in the previously reported series with a fixed treatment period, however,

**Table 2.** Survival at 2-year after living donor liver transplantation and clinical factors.

| | Factors | No. | %OS at 24 months | *P* |
|---|---|---|---|---|
| R-age | ≤55 | 54 | 79 | 0.35 |
| | > | 51 | 86 | |
| R-gender | Male | 76 | 82 | 0.98 |
| | Female | 29 | 82 | |
| MELD | <15 | 56 | 80 | 0.52 |
| | ≥ | 49 | 85 | |
| HIV | Positive | 6 | 67 | 0.23 |
| | Negative | 99 | 83 | |
| HCC | Positive | 60 | 79 | 0.39 |
| | Negative | 45 | 86 | |
| Genotype | 1b | 84 | 82 | 0.85 |
| | Non-1b | 21 | 81 | |
| HCV-RNA titer | ≤250 K IU/ml (5.4 log) | 49 | 92 | 0.02 |
| | > | 56 | 73 | |
| Response to INF-RBV Tx | Yes | 51 | 94 | 0.0005 |
| | No | 44 | 69 | |
| ACR | Yes | 27 | 63 | 0.0009 |
| | No | 78 | 89 | |
| D-age | ≤35 | 53 | 96 | 0.0002 |
| | >35 | 52 | 67 | |
| D-gender | Male | 67 | 89 | 0.009 |
| | Female | 38 | 69 | |
| CyA | Yes | 34 | 76 | 0.29 |
| | No | 71 | 85 | |

No., number of patients; %OS, percentage of overall survival of patients; R-age, age of the recipient at the time of transplantation; R-gender, gender of the recipient; MELD, Model for end-stage liver disease score; HIV, human immune deficiency virus; HCC, hepatocellular carcinoma; HCV-RNA, hepatitis C viral ribonucleic acid; Response to INF-RBV Tx, Response to interferon ribavirin combination therapy indicated by negative serum HCV-RNA at one point or more; ACR, acute cellular rejection; D-age, age of the donor at the time of transplantation; D-gender, gender of the donor; CyA, cyclosporine A.

**Table 3.** Factors affecting survival at 2 years after living donor liver transplantation: a multivariate analysis.

| Factors | Ratio | 95% CI | *P* |
|---|---|---|---|
| Response to Tx | 0.12 | 0.04–0.44 | 0.001 |
| ACR | 3.63 | 1.40–9.43 | 0.008 |
| Age of the donor | 8.20 | 1.84–36.6 | 0.006 |
| HCV-RNA titer | 3.30 | 1.04–10.5 | 0.04 |

Response to Tx, response to interferon combination therapy indicated by negative serum HCV-RNA at one point or more; ACR, acute cellular rejection; CI, confidence interval.

 

our current series indicates the possibility of improvement in the rate of viral eradication over a period of time with continued, non-stop application. Viral responses based on the Kaplan–Meier method demonstrate that a continued treatment is related to higher rates of viral response, as high as an expected rate of 70% for clearance of viremia, and 53% for SVR at 5 years post-LDLT (Fig. 2).

Another interesting implication of the results from our approach is the improvement in survival over the longer term. Extensive data on the outcomes of HCV patients after DDLT indicates that outcomes become poorer in later years when compared with non-HCV patients [16,17]. So far, this has not been the case for our LDLT series. The overall rate of survival after the second year following LDLT remains equivalent for HCV and non-HCV recipients (Fig. 5). In contrast to the acceptable mid-to-long term outcomes, however, our current series demonstrated poorer survival rates as compared with non-HCV recipients for the immediate short-term in HCV recipients. Analysis revealed higher viral titer prior to transplantation, poor response to antiviral treatment, occurrence of acute cellular rejection, and older donor age were significant risk factors for poorer short-term survival. This offers important insights for the management during this period.

Finally, our series demonstrated that adherence to the full target dose of INF or RBV is not mandatory. Patients who tolerated the full target dose were in the minority. The majority tolerated <70% of the intended dose of INF and less than half that of RBV (Fig. 3). The low tolerability for the target dose, however, did not have apparent disadvantage (Fig. 4). Reports in the recent literature suggest the benefits of sustained application of antiviral therapy at a lower dosage for normalizing liver function and preventing recurrent HCC in non transplant patients [47–49]. In the most recent report from the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) study, a randomized controlled trial of PEG-IFN alpha-2a at a dosage of 90 μg/week for 3.5 years in the treatment arm indicated that there was no significant difference between groups in the rate of progression of liver disease, defined as death, HCC, or hepatic decompensation [50]. The studied population, however, was predominantly patients with advanced fibrosis who had not had any response to previous therapy with PEG-IFN and RBV. On the other hand, most interestingly, the report described significantly improved serum aminotransferase levels, decreased serum HCV-RNA levels, and improved histologic necroinflammatory scores. Kuo *et al.* [51] reported a reduced risk of fibrosis progression, even among virologic nonresponders who underwent pre-emptive treatment that was limited to 48 weeks. These outcomes may support, in part, the application of prolonged treatment initiated pre-emptively in liver transplant recipients with un-injured liver grafts, and are encouraging to our approach.

In conclusion, pre-emptive antiviral treatment with combined IFN-based therapy is feasible and effective in LDLT for HCV. The application of a non-stopping, flexible dose adjustment approach for further improvement in the outcomes is warranted in the LDLT setting.

## Authorship

ST, YS and MM: designed study. ST, YS, JK, NK, and MM: performed study. ST, YS, NY, JK: collected data. ST and YS: wrote the paper.

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