Pattern of Recurrent Hepatitis C in Deceased vs Living Donor Liver Transplantation: An Egyptian Experience

Mai Ismail Mehrez, Araf Ibrahim Farrag, Medhat Hassan El Sahhar, Shereen Shoukry Hunter, Mohamed El Beshlawy, Dalia Omran, Magdi Amin El Seragy

ABSTRACT

Introduction: Hepatitis C virus (HCV) is the leading cause for liver transplantation (LT) and viral recurrence.

Objective: Whether HCV recurrence occurs earlier and severer for living donor liver transplantation (LDLT) than for deceased donor liver transplantation (DDLT).

Design: We evaluated preoperative and postoperative clinical, laboratory, and histological outcomes of 180 patients with LT (65 DDLT and 115 LDLT) since 1998 till 2006. Patients diagnosed for recurrence histologically were treated by combination therapy of pegylated interferon (IFN) and ribavirin (RBV).

Results: The LDLT group was significantly younger. CTP score was insignificant, while MELD score was higher in LDLT than DDLT. The mean preoperative (p = 0.012) and postoperative HCV-RNA (p = 0.027) count was significantly lower in DDLT group than LDLT group. At onset of recurrence, laboratory data included levels of aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, serum creatinine, hemoglobin level and platelet count. Fibrosis and activity scores were significantly higher in the LDLT group (p ≤ 0.01) compared to DDLT group. The response to treatment was higher in DDLT group.

Conclusion: HCV recurrence rates and severity of reinfection remain comparable for living and deceased organs. However, LDLT significantly increase the risk and severity of HCV recurrence than DDLT.

Keywords: Living donor liver transplantation, Deceased donor liver transplantation, HCV recurrence, Interferon therapy.


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Conflict of interest: None

INTRODUCTION

End-stage liver disease secondary to chronic hepatitis C virus (HCV) infection is the most common indication for liver transplantation (LT) worldwide. Over the last decade, living donor liver transplantation (LDLT) has been embraced as an alternative option to increase the availability of organs and address the needs of patients who cannot await deceased donor liver transplantation (DDLT).

Unfortunately, HCV reinfection of the graft occurs universally, and is associated with an aggressive course in a proportion of patients, which leads to graft cirrhosis in 10 to 30% of recipients within 3 to 5 years. This in turn results in clinical decompensation in a significant proportion of HCV recipients who have developed cirrhosis of the allograft, with 40% developing clinical decompensation at 1 year, and up to 60% will suffer a decompensation episode 3 years after the diagnosis of cirrhosis. This unfortunately significantly affects patient survival, with an estimated survival rate of less than 10% at 3 years.

Early reports have indicated that recurrence of HCV infection in LDLT recipients had an earlier and more aggressive clinical course compared to recurrence in the DDLT recipient. This phenomenon had been attributed to rapid graft regeneration and inflammation accompanied by poor graft function in the early postoperative period. The clinical practice in many programs had been significantly modified by their initial experience. However, significant conflicting evidence had also surfaced.

In the present study, we compared the pattern of recurrent hepatitis C, including the possible risk factors, onset, severity and the efficacy of HCV treatment in DDLT versus LDLT recipients.

MATERIALS AND METHODS

This study was conducted in the period from January 1998 till January 2006. One hundred and eighty patients were included in the study. All patients suffered HCV-related end-stage liver disease or HCC complicating HCV-related cirrhosis. A total of 115 patients were subjected to LDLT in Dar Al Fouad Hospital, Cairo, Egypt, while 65 patients were subjected to DDLT in Leeds Hospital in England, Boukham Hospital in Germany and Tianjin Hospital in China. Clinical, laboratory and imaging data were collected for all patients’ pretransplantation. After transplantation, adverse events in the form of bouts of rejection, pulse steroid therapy, cytomegalovirus (CMV) infection, biliary complications and type of immunosuppression during this period were reported. Patients were then followed up from January 2006 till December 2008 in Police Hospital, Agouza.

The study variables included patient and donor demographics, pretransplant and post-transplant viral load, the results of synthetic liver function tests before and after living-donor liver transplant, histologic data. The laboratory data included levels of aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, serum creatinine, hemoglobin level and platelet count. Fibrosis and activity scores were significantly higher in the LDLT group compared to DDLT group. The response to treatment was higher in DDLT group.
albumin, and alkaline phosphatase, as well as prothrombin concentration, all of which were evaluated before transplant and daily after transplant during the first postsurgical month, then twice weekly until the end of the third postsurgical month, then monthly, and then on longer intervals thereafter. HCV RNA in serum was detected by PCR assay (Cobas AmpliCor HCV test version 2.0; Roche Molecular system; lower limit of detection 50 IU/ml) before transplant, 3 months after transplant, and then whenever there is clinical indication.

Most of the patients received tacrolimus as postoperative immunosuppressant (63.08% in DDLT patients and 70.43% in LDLT patients), while 18.46% of DDLT patients and 3% only among LDLT patients received sirolimus. Regarding cyclosporine, it was taken by 13.85% of DDLT patients and 26.09% of LDLT patients.

At first a liver biopsy was done according to protocol biopsy at 1, 3 and 12 months. After 2002, liver biopsies were performed if there were unexplained elevations in liver enzymes. The biopsy was performed with ultrasonographic guidance and a conventional automatic 16-gauge Tru-cut needle. The coagulation profile was determined before the biopsy to ensure the safety of the patient.

The histopathologic diagnosis for the recurrence of HCV infection was based on the pattern of inflammatory infiltrate and a histologic activity index (an 18-point scale). The stage of fibrosis was assessed with a 6-point scale according to the Ishak modification of the Knodell classification. Other possible diagnoses (particularly cellular rejection or drug-induced liver injury) were excluded.

All patients positive for HCV RNA by real-time PCR and showed histological evidence of recurrent HCV infection. They received IFN-α2a (180 μg/week) or IFN-α2b (1.5 μg/kg/week) + RBV (1.3-1.5 mg/kg/day) for 48 weeks. Therapy was started at least 1 year post-transplantation.

The patients had on-treatment complete blood count and liver function tests assessed weekly in the first 4 weeks, then every 2 or 4 weeks thereafter.

RBV dose was reduced if hemoglobin levels decreased below 10 g/dl and discontinued if hemoglobin levels were <8.5 g/dl despite erythropoietin therapy. Erythropoietin was started in patients with hemoglobin levels below 9.5 g/dl.

PEG-IFN dose was reduced to two-thirds the dose per week for platelet counts between 50,000 and 65,000/mm³ and for leukocyte counts between 1,700 and 2,000/mm³ and halved for platelet counts less than 50,000/mm³ and for leukocyte counts less than 1,700/mm³. PEG-IFN was discontinued in cases of platelet counts <25,000/mm³ or white blood cell counts <1,000/mm³.

Treatment was continued for a period of 48 weeks in responders. Response was defined as at least two log decrease of the initial viral load (as estimated by quantitative PCR of HCV RNA) at week 12 and no viremia at week 24.16

Follow-up PCR was done every 3 months during the first year, then twice yearly in the second year, then once in the third year to ensure sustained virological response or detect any recurrence. HCV RNA was measured also whenever, clinically indicated (persistently elevated or any increase in serum ALT during therapy).

STATISTICAL ANALYSIS

Patients’ data was tabulated and processed using SPSS (15.0) statistical package for Windows XP. The following patients’ data were compared: before transplantation, follow-up after transplantation, at time of diagnosis of recurrence. Quantitative variables were expressed by means and standard deviation, while qualitative data were expressed by frequency and percent. Qualitative variables were analyzed using Chi-square or Fisher’s exact test when appropriate. Quantitative variables were analyzed using student’s t-test or Friedman’s test when appropriate. In all tests, p-value was significant when <0.05.

RESULTS

Demographic data of LDLT and DDLT recipients are presented in Table 1.

The preoperative viral load was 373967.58 ± 577388.37 IU/ml in DDLT group, compared with 1018282.44 ± 2197587.20 IU/ml in LDLT group, the mean count was significantly lower in DDLT group (t = -1.887; p = 0.012), and 66.3% of LDLT group had significantly high viremia, in comparison with 36.9% in DDLT group (χ²= 9.176, p-value = 0.00102) (Graph 1).

The mean postoperative viral load was significantly higher in LDLT (760341.62 ± 871713.61 IU/ml) compared to DDLT group (484766.58 ± 668721.41 IU/ml) (t = 2.207, p = 0.027). More than half (64.62%) of DDLT group had
no viremia, while 18.46% had low viremia and 16.92% had high viremia, compared to 44.35, 34.78 and 20.87% in LDLT group respectively. This may be due to the use of preoperative interferon (IFN) therapy in some patients who underwent transplantation in Leeds Hospital (London). On comparison using Chi-square, it was found that the level of viremia was significantly higher in LDLT group ($\chi^2 = 8.097$, p-value = 0.017).

Recurrence of HCV was universal in terms of viremia. The time taken for clinical recurrence (indicated by evidence of viral replication shown via PCR after transplant, elevated levels of transaminases, and necroinflammatory changes) ranged from 3 to 38 months after transplantation among the DDLT group with a mean of 13.89 ± 7.169 months, while in LDLT group, it ranged from 1 to 39 months after transplantation with a mean of 10.94 ± 9.491 months. On comparing the time taken for HCV recurrence between both patients following DDLT and 31 patients following LDLT. Various risk factors for clinical HCV recurrence after DDLT and LDLT were studied (Tables 2 and 3).

<table>
<thead>
<tr>
<th>Table 1: Demographic comparison between LDLT and DDLT</th>
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<tbody>
<tr>
<td>DDLT (65)</td>
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</tr>
<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<td>Age</td>
</tr>
<tr>
<td>Diabetes</td>
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<tr>
<td>Hypertension</td>
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<td>HBV coinfection</td>
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<tr>
<td>HCC</td>
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<tr>
<td>Child A</td>
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<tr>
<td>Child B</td>
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<tr>
<td>Child C</td>
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<tr>
<td>MELD score</td>
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<td>CTP score</td>
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NS: not significant; HCC: hepatocellular carcinoma; MELD: model for end-stage liver disease; CTP score: Childs-Turcotte-Pugh score

<table>
<thead>
<tr>
<th>Table 2: Factors affecting recurrence in DDLT group</th>
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<tr>
<td>Recurrence (n = 28)</td>
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<tr>
<td>CMV coinfection</td>
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<tr>
<td>Pulse steroids therapy</td>
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<tr>
<td>Tacrolimus</td>
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<td>Cyclosporine</td>
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<tr>
<td>Diabetes mellitus</td>
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</table>

Preoperative viral load (7 missing values)

<table>
<thead>
<tr>
<th>Recurrence (n = 24)</th>
<th>No recurrence (n = 34)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No viremia</td>
<td>3 (12.50%)</td>
<td>5 (14.71%)</td>
</tr>
<tr>
<td>Low viremia</td>
<td>11 (45.83%)</td>
<td>15 (44.12%)</td>
</tr>
<tr>
<td>High viremia</td>
<td>10 (41.67%)</td>
<td>14 (41.18%)</td>
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S: significant; NS: not significant

<table>
<thead>
<tr>
<th>Table 3: Factors affecting recurrence in LDLT group</th>
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<tbody>
<tr>
<td>Recurrence (n = 31)</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>CMV coinfection</td>
</tr>
<tr>
<td>Pulse steroids therapy</td>
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<tr>
<td>Tacrolimus</td>
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<tr>
<td>Cyclosporine</td>
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<tr>
<td>Diabetes mellitus</td>
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</tbody>
</table>

Preoperative viral load (23 missing values)

<table>
<thead>
<tr>
<th>Recurrence (n = 31)</th>
<th>No recurrence (n = 61)</th>
<th>p&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>No viremia</td>
<td>1 (3.23%)</td>
<td>5 (5.95%)</td>
</tr>
<tr>
<td>Low viremia</td>
<td>7 (22.58%)</td>
<td>18 (21.43%)</td>
</tr>
<tr>
<td>High viremia</td>
<td>23 (74.19%)</td>
<td>38 (45.24%)</td>
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</table>

NS: not significant
As regard factors affecting HCV recurrence in DDLT group, the only significant factor was pulse steroid therapy ($\chi^2 = 4.46; \text{p-value} = 0.034$). CMV coinfection showed statistically significant difference ($\chi^2 = 7.773; \text{p-value} = 0.005$) in the LDLT group. In the DDLT group, nine patients showed low viremia, and 19 patients showed high viremia versus 11 and 20 patients respectively in the LDLT group.

On histopathological examination, the fibrosis score and the activity score were significantly higher in the LDLT group than the DDLT group ($t = 2.755, \text{p-value} < 0.01; t = 3.121, \text{p-value} < 0.01$ respectively) (Table 4).

Among the patients diagnosed to have hepatitis C recurrence, 21/28 (75%) and 17/31 (54.84%) patients agreed to have treatment in DDLT and LDLT groups respectively. In the DDLT group, one (3.57%) patient and in LDLT group, two (6.45%) patients discontinued treatment due to severe side effects. On comparing end of treatment response among patients who received IFN, it was found that 14 (70%) patients were responders in the DDLT group, compared to six (40%) patients in the LDLT group, which was found statistically insignificant ($\chi^2 = 2.0449, \text{p-value} > 0.05$).

**DISCUSSION**

The Egyptian National Committee on Viral Hepatitis stated that 9.8% of the Egyptians are HCV infected, whereas other researchers claim that the figure is between 15 and 20%. As DDLT being still not a valid option in Egypt, LDLT seemed to be the only choice to save many patients in desperate need for LT.18

The current study was conducted to compare the pattern of recurrent hepatitis C, including the possible risk factors, onset, severity and the efficacy of HCV treatment in DDLT versus LDLT candidates.

In our study, the incidence of hepatitis C recurrence was higher in DDLT (59.57%) than LDLT (41.89%) patients. This was lower than previous studies,7,10,12,19 where a histologically diagnosed recurrence of chronic hepatitis C occurred in 65 to 90% of HCV positive DDLT recipients during the first 2 years after surgery. In the current study, recurrence occurred within a time range from 3 to 38 months in DDLT group, while in LDLT group, it ranged from 1 to 39 months. This comes in agreement with the study done by Guo et al., where histological evidence of recurrent hepatitis occurred at 4 months and reached 90% 1 year post-LT.

In the DDLT group, nine patients showed low viremia, and 19 patients showed high viremia compared to 11 and 20 patients respectively in the LDLT group. The higher level and activity of HCV may be due to rapid regeneration of the liver in LDLT group making the cells more prone to reinfection and their activity enhances the viral introduction and replication.21

Immunosuppression is considered a main factor in the severity of recurrent HCV infection,22,23 because of its effect on viral replication and its suppression of systemic immune responses, both of which can lead to accelerated hepatocellular damage and fibrosis.

In our study, tacrolimus and cyclosporine were not associated with HCV recurrence. Cyclosporine had antiviral properties in vitro and was associated with a significantly lower risk of recurrence of HCV24 and less fibrosis.25 However, no compelling data suggested that there was an advantage to using either tacrolimus or cyclosporine in clinical practice.26,27 In DDLT group, pulse steroid therapy was significantly related to HCV recurrence ($p = 0.034$). This might be due to the increased use of pulse steroid to treat rejection which was encountered more in this group (possibly due to prolonged ischemia time). Our results were similar to previous studies.20 In contrast, Yosry et al.28 suggested that immunosuppressive therapy and pulse steroid therapy were not associated with HCV recurrence.

Due to the fact that CMV has immunomodulating properties, it was presumed that reactivation of CMV could accelerate HCV pathogenesis in critically ill patients.29 This came in agreement with our results that CMV coinfection was significantly correlated with HCV recurrence in LDLT group. On the contrary, a recent study showed that CMV coinfection was not associated with HCV recurrence.30 Moreover, Nebbia et al.31 proved in his study that HCV-infected patients with CMV DNAemia were not at increased risk of liver fibrosis at 1 year post-transplantation.

Severity of recurrence was assessed by fibrosis and activity scores in liver biopsy, where the LDLT group showed significantly higher grade of fibrosis (2.227 ± 1.159) and inflammation (7.982 ± 4.762) than DDLT group (1.669 ± 1.532 and 4.846 ± 2.483 respectively) ($p < 0.001$). This might be due to higher cellular activity in the LDLT group, reflecting the need of the hepatocytes to regenerate so they are more prone to be reinfected by HCV.9,21,32 On the contrary, other studies did not identify LDLT as a risk factor for more intense HCV recurrence.11,12,14,15,20

These discrepancies in the outcomes in different centers could be clarified according to Wiesner et al.23 explanation which was centered on the definition of recurrent hepatitis. He strongly encouraged the wide application of the consensus criteria formulated by the International Liver Transplantation Society. Clarity in definition of recurrent HCV, which should join histological with biochemical.

| Table 4: Grading and staging of HCV recurrence (Ishak score) |
|-------------|-------------|-------------|
|            | DDLT (n = 28) | LDLT (n = 31) | p-value |
| Fibrosis score | 1.669 ± 1.532 | 2.227 ± 1.159 | <0.01 |
| Activity score   | 4.846 ± 2.483 | 7.982 ± 4.762 | <0.01 |
parameters, is of utmost importance until less invasive diagnostic parameters are developed.

In the current study, treatment with pegylated IFN and RBV was started in 75% of DDLT patients and 54.84% of LDLT patients. Patients who did not receive therapy deliberately decided to postpone it and to be followed up.

Three patients (one in DDLT group and two in LDLT group) dropped out during therapy due to serious side effects. This was similar to the results of the study conducted by Iacob et al. where 11 to 37% of patients discontinued the therapy.

Among those who completed the therapy, 70% of DDLT group and 40% of LDLT group achieved end of treatment response (ETR) after 48 weeks of therapy. These results were in agreement with other studies.35

From this study, we could conclude that the incidence of hepatitis C recurrence is higher in DDLT but the severity is more in LDLT. Pulse steroid therapy and CMV were related to recurrence in DDLT and LDLT respectively. While diabetes mellitus, preoperative viral load and the use of tacrolimus or cyclosporine as immunosuppressant did not affect recurrence.

CONTRIBUTORSHIP

All the authors have carried out the study, participated in the design of the study and data collection, performed the statistical analysis and wrote the manuscript. All authors have read and approved the final manuscript.

REFERENCES


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