Influence of IL28B of Donors and Recipients on Liver Transplantation Due to End Stage HCV Related Liver Disease

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Abstract

Background: Recent studies have described a major impact of the IL28B gene polymorphism on graft survival post liver transplantation. Our study aims to investigate the impact of IL28B of donors and recipients on the natural course and outcome of liver transplantation due to end stage HCV related liver disease.

Aim of Study: This study aims to investigate SNP of IL28B gene in Egyptian patients with end stage HCV related liver disease. Correlating the prevalence of IL-28b-alleles with patient and graft survival and with the progression of fibrosis for HCV-induced (graft) liver disease after liver transplantation. Also to correlate IL28B genotype with the outcome after liver transplantation.

Patients and Methods: Donor and recipient IL28B rs12979860C>T single nucleotide genotype was determined in 24 patients who had undergone LT for HCV-induced end stage liver disease and received regular follow-up evaluations for two years post liver transplantation.

Results: We found that the CC genotype frequency was reduced among patients with HCV related end stage liver disease while, in contrast, the frequency of CT & TT increased. No association was noted between IL 28B polymorphism of donors and recipients regarding fibrosis progression or patient and graft survival, as well as liver outcomes.

Conclusions: No impact of IL 28B polymorphism on fibrosis progression, liver outcomes or patient and graft survival.

Key Words: IL28B – Gene polymorphism – Liver transplantation – Fibrosis – Graft survival.

Introduction

HEPATITIS C is one of the most common liver diseases worldwide; it is often complicated by the development of cirrhosis and hepatocellular carcinoma [1]. For patients with end-stage chronic liver disease, liver transplantation is currently the treatment of choice [2]. Recurrence of infection with HCV is one of the most important graft diseases that may occur after liver transplantation (LT) [3]. The course of hepatitis C in a graft is usually more severe than that of hepatitis C occurring in non-transplanted patients [4]. HCV-induced fibrosis in a liver graft is an important determinant of morbidity and mortality in patients after LT; the mode of presentation varies from minor symptoms in a clinically stable patient to rapid loss of graft function leading to graft failure. In some patients re-transplantation may be indicated despite persistent antiviral treatment [5].

Relevant risk factors for the development of graft fibrosis have been identified; they include high levels of viremia in the early post-transplant period, HCV-genotype 1b, multiple episodes of rejection, the regimen of immunosuppression, and donor age [6]. However, appreciable variations in graft inflammation and fibrosis, susceptibility to HCV-infection, spontaneous viral clearance and response to antiviral therapy suggest the existence of endogenous risk factors that influence the evolution of graft disease after LT. Recently, in several trials notable associations between IL-28B gene single nucleotide polymorphisms (SNPs) and (i) spontaneous clearance of HCV and (ii) favorable response to standard antiviral therapy of HCV infection with pegIFN-RBV have been demonstrated [7].

The IL-28B gene encodes the antiviral protein, IFNy, which exhibits antiviral properties in response to IFNa; it is upregulated by peripheral blood mononuclear cells and hepatocytes during infection with HCV [8]. The SNP with the strongest association, rs12979860, is located on chromosome 19. As there are similarities between re-infection of a
Influence of IL28B of Donors & Recipients on Liver Transplantation

graft with HCV after LT and the pretransplant course of infection with HCV, we postulated that genetic variants of IL-28B may play a role in the development of HCV-related graft disease and its response to treatment. The best baseline predictors of response to HCV therapy are infection with HCV genotypes 2 or 3, low baseline serum HCV RNA level, and null-minimal liver fibrosis [9]. Once treatment has been initiated, the best predictor of cure is the achievement of undetectable serum HCV RNA level at week 4 [10].

Patients and Methods

This study was conducted on 24 Egyptian patients with end stage liver disease caused by HCV genotype 4 and their donors that had underwent living donor liver transplantation at liver transplantation Unit at El Manial, Cairo University Hospital October 2012 to October 2015.

These patients received regular follow-up evaluations for two years post liver transplantation, which include clinical and serum biochemical assessments. The study was approved by the Institutional Ethics Committee of Cairo University. Written informed consent was obtained from each patient before the enrollment.

Study population:

Patients undergoing living donor liver transplantation (LDLT) for end stage liver disease due to HCV infection and normal adult donors, at liver transplantation Unit at El Manial, Cairo University Hospital.

Inclusion criteria:

Patients undergoing living donor liver transplantation (LDLT) for end stage liver disease due to HCV infection and Normal adult donors.

Exclusion criteria:

Patients undergoing living donor liver transplantation (LDLT) for end stage liver disease due to any etiology other than HCV infection or patients with co-infection with HBV or HIV.

Preoperative laboratory data:

LTX Recipient Step I:

- Renal Profile: S.creatinine/blood urea/uric acid/Na/K.
- Blood grouping, CBC & ESR.
- PT, PC, INR & PTT.
- HCV Ab. HBsAg & HbcAb total.
- Abdominal ultrasound.
- Anti Schistosomal antibody.

LTX Recipient Step II:

- Bleeding time, Prothrombin time.
- Cholesterol, TG, FBS.
- Tumors markers: CA19.9, CA125, Alpha fetoprotein & CEA.
- Viral profile: HAV IgM/HAV total/HBs Ab/Hbc IgM/HBe Ab/Hbc Ag/HCV PCR (Quantitative) /HIV I, HIV II/EBV IgM/EBV IgG/CMV IgM/CMV IgG/Herpes I IgG/Herpes II IgG.

Post liver transplantation evaluation:

During the hospital stay, the patients were assessed daily by:

- Complete liver profile.
- Alpha-fetoprotein level.
- Kidney profile.
- Coagulation profile.
- CBC, Fasting blood sugar.
- CRP.
- Immunosuppressant drug level in the blood.
- Chest X-ray.
- Abdominal ultrasound and Hepatic Doppler.

All patients received 1 g of intravenous methylprednisolone intra operatively. Tacrolimus was initiated immediately after transplantation, and trough levels were maintained at approximately 8 to 10ng/mL. Subjects who displayed Tacrolimus toxicity (e.g, neuro-toxicity) were converted to cyclosporine. Recipients routinely received steroids (with an initial dose of 200mg/day on postoperative day 1 that was tapered to 20mg/day on day 6) and was weaned off them after 3 months.

After obtaining consent for genotyping, venous blood was collected from the donors and the recipients for genomic DNA extraction from peripheral blood leucocytes for IL28B genotyping by PCR and restriction fragment length polymorphism analysis.

After LDLT, all the patients were followed-up for a period of 3 months for mortality, graft rejection, number of clinically significant infective episodes requiring systemic antibiotics or antiviral therapy, length of hospital stay (ward and intensive care unit [ICU]) and graft failure or dysfunction, by using postoperative serum total bilirubin, liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) levels and international normalized ratio (INR).
During the 2-year post operative, the patients were assessed monthly by:
- Complete liver profile.
- Alpha-fetoprotein level.
- Kidney profile.
- Coagulation profile.
- CBC, Fasting blood sugar.
- CRP.
- Immunosuppression drug level in the blood.
- Chest X-ray.
- Abdominal ultrasound and Hepatic Doppler.

Half of the patients in our study had post transplant biliary complications (strictures ± leakage), and had to do MRCP and ERCP.

**Histological evaluation:**

Liver biopsy was done when clinically indicated (eg, a rise in transaminases), and a protocol biopsy was performed 1 year after transplantation. Percutaneous liver biopsies were fixed in 10% formalin, processed then embedded in paraffin, and cut at 5 microns thickness. Histological sections were stained with haematoxylin and eosin for grading of activity, and Masson trichrome stains for staging of fibrosis. The degree of inflammatory reaction and the stage of fibrosis were evaluated according to the Metavir scoring system:

A = histological activity (A0 = no activity, A1 = mild activity, A2 = moderate activity and A3 = severe activity). F = fibrosis (F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with rare septa, F3 = numerous septa without cirrhosis, and F4 = cirrhosis) [1].

Biopsy-proven Acute Cellular Rejection (ACR) was treated by modifying the doses of immunosuppressant or with a steroid bolus. CMV infections were monitored by CMV polymerase chain reaction, and pre-emptive treatment with intravenous ganciclovir (10mg/kg/day) or oral valganciclovir (900mg twice a day) was given when indicated.

**Follow-up and monitoring response to antiviral therapy:**

Quantitative HCV RNA by polymerase chain reaction (PCR) was performed after 12 weeks of therapy to determine Early Virological Response (EVR) (>2-log drop or loss of HCV RNA) upon which the decision to continue treatment after 12 weeks is obtained then after 24 weeks, 48 weeks to determine End of treatment response (ETR) and finally 24 weeks after stoppage of treatment to find out those who develop Sustained virological response (SVR) or those who relapse (Relapsers). For those who received DAA agents, SVR was considered if HCV PCR done 12 weeks after end of treatment proved to be negative.

**DNA extraction & IL28 B genotyping:**

Peripheral blood on EDTA was withdrawn from all subjects and genomic DNA was extracted from the whole blood sample using genomic DNA extraction kits QIAamp ® DNA Blood Mini Kit. DNA samples were subjected to DNA quantitation and purity assessment using the NanoDrop® (ND)-1000 spectrophotometer (NanoDrop Technologies, Inc. Wilmington, USA). Recipient DNA and donor DNA were genotyped for the DNA polymorphism rs12979860 near the IL-28B gene with a custom TaqMan® single-nucleotide polymorphism SNP Genotyping Assays (Applied Biosystems) in Qiaplex thermal cycler.

**Statistical analysis:**

Data will be coded and entered using the statistical package SPSS version 17.0 Data will be summarized using mean, standard deviation and range (minimum and maximum) for quantitative variables and number and percent for qualitative variables. Comparisons between groups will be done using Chi-square test and Fisher’s exact test for qualitative variables while, independent sample. t-test for normally distributed quantitative variables and non parametric Mann Whitney test will be used for quantitative variables which are not normally distributed. p-values less than or equal to 0.05 were considered as statistically significant. Logistic regression to control the effect of other variables that are associated with treatment response will be done.

**Results**

All 24 subjects underwent liver transplantation as they suffered from end stage liver disease due to HCV infection. They all underwent liver transplantation between the years 2007 and 2014. The 24 recipients were 22 males and 2 females, while
the 24 donors were categorized into 19 males and 5 females. (Table 1).

Mean age of recipients was 50 years at the date of transplantation. (Table 1). All the patients had Child Pugh score "C". The mean MELD score was 18.45 (Table 1). Biliary complications due to anastomotic strictures occurred in 12 patients (50%) and resolved by ERCP & stenting. Acute graft rejection occurred in 2 patients (8.33%), and they received pulse steroids. Late cellular rejection occurred in 2 patients (8.33%) and treated by increasing baseline immunosuppressive drugs.

Genotype frequencies among recipients were 3/24 (12.5%), 20/24 (83.3%) and 1/24 (4.2%) for CC, CT and TT genotypes respectively (Table 2).

Genotype frequencies among donors were 10/24 (41.6%), 13/24 (54.2%) and 1/24 (4.2%) for CC, CT and TT genotypes respectively (Table 2).

The distribution of IL28B genotypes differed between recipients and donors (CC: 12.5% vs. 41.6%; and non-CC: 87.5% vs. 58.4%; respectively; \( p = 0.08 \) for CC vs. non-CC). Although it did not reach statistical significance, but it was well observed in our study that the CC genotype frequency was reduced among patients with HCV end stage liver disease while, in contrast, the frequency of CT + TT increased.

Table (1): Baseline characteristics of studied population.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Recipient: M 22 F 2</th>
<th>Donor: M 19 F 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Age (Mean &amp; SD.)</td>
<td>Hepatic focal lesions</td>
</tr>
<tr>
<td></td>
<td>50 (±5.9)</td>
<td>4/24</td>
</tr>
<tr>
<td>HCC confirmed</td>
<td>3/24 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>MELD (Mean &amp; SD.)</td>
<td>18.45 (±3.27)</td>
<td></td>
</tr>
<tr>
<td>Biliary complications</td>
<td>12/24 (50%)</td>
<td></td>
</tr>
<tr>
<td>Acute rejection</td>
<td>2/24 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Number of cases received</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>PEG IFN and SVR</td>
<td>SVR: 5/10</td>
<td></td>
</tr>
<tr>
<td>Number of cases received</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>DAA and SVR</td>
<td>SVR: 14/14</td>
<td></td>
</tr>
<tr>
<td>Number of cases who did liver biopsy &amp; Fibrosis score</td>
<td>19 F0-F1 = 11/19 (58%) ≥F2 = 8/19 (42%)</td>
<td></td>
</tr>
</tbody>
</table>

Table (2): Distribution of IL-28B gene polymorphism in recipients & Donors.

<table>
<thead>
<tr>
<th></th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipients</td>
<td>3 (12.5%)</td>
<td>20 (83.3%)</td>
<td>1 (4.2%)</td>
<td>24</td>
</tr>
<tr>
<td>Donors</td>
<td>10 (41.6%)</td>
<td>13 (54.2%)</td>
<td>1 (4.2%)</td>
<td>24</td>
</tr>
</tbody>
</table>

\( p\)-value = 0.08

We also compared the IL-28B SNP combination or chimerism of the donor liver and the recipient. The frequency of recipient non-CC genotype with donor non-CC genotype was 12/24 (50%) in our study, the highest of all the pair groups. Patients with CC genotype who also received CC genotype donor livers represented only 1/24 (4%) of the patients in our study.

The distribution of IL28B polymorphisms in the pairs donor-recipients according to CC and non-CC genotype is shown in Table (3).

Table (3): The frequency of CC vs. non-CC genotype in pairs donors-recipients.

<table>
<thead>
<tr>
<th>Recipients - donors</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC - CC</td>
<td>1/24 (4%)</td>
</tr>
<tr>
<td>Non CC - CC</td>
<td>9/24 (38%)</td>
</tr>
<tr>
<td>CC - non CC</td>
<td>2/24 (8%)</td>
</tr>
<tr>
<td>Non CC - non CC</td>
<td>12/24 (50%)</td>
</tr>
</tbody>
</table>

Fibrosis was assessed one year after liver transplantation for 19 patients through either liver biopsy or Fibroscan of the liver, whereas 4 didn't do and one died at 3 months from time of transplantation. Out of the 19 patients whom fibros was assessed, 11 had a fibrosis score F0-F1 (58%), and 8 patients had a score of ≥F2 (42%). (Metavir scoring system). (Tables 4,5).

In the 19 Recipients whose fibros was assessed; 2 patients had CC genotype and 17 had non-CC genotype, in the two patients with CC genotype, one patient had F0/F1 score and the other a fibrosis score of ≥F2. In the 17 patients with non-CC genotype 10/17 (59%) had a fibrosis score F0/F1 and 7/17 ≥F2. (41 %) (Table 4).

Table (4): Fibrosis & IL 28B in Recipients.

<table>
<thead>
<tr>
<th>IL 28b Rec.</th>
<th>F0/F1</th>
<th>≥ F2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>2</td>
</tr>
<tr>
<td>Non-CC</td>
<td>10 (59%)</td>
<td>7 (41%)</td>
<td>17</td>
</tr>
</tbody>
</table>

| Total       | 11 | 8 | 19 |

Among the donors; 8 subjects had CC genotype and 11 had non-CC genotype, in recipients of the 8 CC genotype grafts, 5/8 had F0/F1 score (63%) and 3/8 ≥F2 (37%). In the 11 patients receiving non-CC genotype grafts, 6/11 had a fibrosis score F0/F1 (55%) and 5/11 ≥F2 (45%). (Table 5).
We also compared the IL-28B SNP combination or chimerism of the donor liver and the recipient. Among 19 patients who underwent liver biopsy, the frequency of recipient non-CC genotype with donor non-CC genotype was 10 cases, of them 6/10 showed a fibrosis score F0/F1 (60%) and 4/10 had a score of \( \geq F_2 \) (40%). The frequency of recipient non-CC genotype with donor CC genotype was 7 cases, of them 4/7 showed a fibrosis score F0/F1 (57%) and 3/7 had a score of \( \geq F_2 \) (43%). One case with CC genotype in recipient and donor also showed F0/F1. One case having recipient CC and the donor has non-CC genotype that had a score of \( \geq F_2 \). (Table 6). No association between IL 28B polymorphism of recipients or donors and in recipient/donor genotypes combined on fibrosis progression post liver transplantation was noted in our study.

Table (5): Fibrosis & IL 28B in Donors.

<table>
<thead>
<tr>
<th>IL 28b Don.</th>
<th>F0/F1</th>
<th>( \geq F_2 )</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>5 (63%)</td>
<td>3 (37%)</td>
<td>8</td>
</tr>
<tr>
<td>Non-CC</td>
<td>6 (55%)</td>
<td>5 (45%)</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>8</td>
<td>19</td>
</tr>
</tbody>
</table>

We also compared the IL-28B SNP combination or chimerism of the donor liver and the recipient. Among 19 patients who underwent liver biopsy, the frequency of recipient non-CC genotype with donor non-CC genotype was 10 cases, of them 6/10 showed a fibrosis score F0/F1 (60%) and 4/10 had a score of \( \geq F_2 \) (40%). The frequency of recipient non-CC genotype with donor CC genotype was 7 cases, of them 4/7 showed a fibrosis score F0/F1 (57%) and 3/7 had a score of \( \geq F_2 \) (43%). One case with CC genotype in recipient and donor also that showed F0/F1. One case having recipient CC and the donor has non-CC genotype that had a score of \( \geq F_2 \). (Table 6). No association between IL 28B polymorphism of recipients or donors and in recipient/donor genotypes combined on fibrosis progression post liver transplantation was noted in our study.

Table (6): Fibrosis & IL 28B in Recipient/Donors pairs.

<table>
<thead>
<tr>
<th>IL 28b Recipient-Donor</th>
<th>F1/F0</th>
<th>( \geq F_2 )</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CC-Non CC</td>
<td>6 (60%)</td>
<td>4 (40%)</td>
<td>10</td>
</tr>
<tr>
<td>Non-CC-CC</td>
<td>4 (57%)</td>
<td>3 (43%)</td>
<td>7</td>
</tr>
<tr>
<td>CC-CC</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CC-Non CC</td>
<td>–</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>8</td>
<td>19</td>
</tr>
</tbody>
</table>

During the 2 years time of our study, only one patient died 3 months after the operation due to non-liver related graft loss (HCC recurrence), whereas 23 patients survived the 2 years time of our study. The IL 28B genotype of this case’s recipient was CC and the donor was CT.

In our study we relied only on the Prothrombin concentration (P.C. %) and Albumin levels (Alb) of the patients in the first 3 months post operative and at one and 2 years post operative to assess the graft function.

Bilirubin levels and liver function tests were excluded as 12 patients included in our study had biliary anastomotic strictures with elevated bilirubin levels and transaminases and underwent multiple sessions of ERCP with stenting.

The progress of P.C% levels showed no significant difference between CC vs. non-CC IL 28b genotypes in recipients and donors. (Graphs 1,2). There were also no significant difference when compared as recipient/donor pairs (non-CC/non CC) vs. (non-CC/CC). (Graph 3).

The progress of Albumin levels showed no significant difference between CC vs. non-CC IL 28b genotypes in recipients and donors. (Graphs 4,5). There were also no significant difference when compared as recipient/donor pairs (non-CC-non CC) vs. (non-CC-CC). (Graph 6).

There is no significant difference between both groups concerning the parameters indicative of graft function in our study.

In our study, IL-28B gene polymorphism showed no impact on graft function or survival till 2 years post liver transplantation. These results were demonstrated in our study among recipients and donors, and also in recipient/donor combined.
Graph (3): Progress of P.C % levels in Recipient/donor pairs (non-CC/non-CC) vs. (non-CC/CC).

<table>
<thead>
<tr>
<th></th>
<th>1 month post-operative PC</th>
<th>2 month post-operative PC</th>
<th>3 month post-operative PC</th>
<th>1 year post Ltx follow-up Pc</th>
<th>2 year post Ltx follow-up PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>90.50</td>
<td>89.867</td>
<td>90.90</td>
<td>89.60</td>
<td>88.400</td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Non-CC - CC N=9

<table>
<thead>
<tr>
<th></th>
<th>1 month post-operative PC</th>
<th>2 month post-operative PC</th>
<th>3 month post-operative PC</th>
<th>1 year post Ltx follow-up Pc</th>
<th>2 year post Ltx follow-up PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>85.11</td>
<td>82.667</td>
<td>89.22</td>
<td>86.11</td>
<td>90.567</td>
</tr>
<tr>
<td>N</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Graph (4): Progress of Albumin levels in CC vs. non-CC IL 28b genotypes in recipients.

Graph (5): Progress of Albumin levels in CC vs. non-CC IL 28b genotypes in donors.
Discussion

The distribution of IL28B genotypes differed between recipients and donors (CC: 12.5% vs. 41.6%; and non-CC: 87.5% vs. 58.4%; respectively; \( p = 0.08 \) for CC vs. non-CC). Although it did not reach statistical significance, but it was well observed in our study that the CC genotype frequency was reduced among patients with HCV end stage liver disease while, in contrast, the frequency of CT & TT increased in end stage liver disease. This is consistent with previous findings that reported a significantly lower prevalence of CC genotype in HCV infected liver transplantation (LT) recipients [12,13]. An explanation for this distribution could be that the favorable genotype CC is associated with a higher spontaneous clearance rate and that more HCV patients with genotype CT and TT will develop chronic HCV and cirrhosis, eventually leading to end-stage liver disease and liver transplantation [14,15].

We then examined the impact of IL-28B on histopathology of the liver biopsies of grafted livers. In our study neither the recipient or donor IL-28B gene polymorphism had an impact on fibrosis in the 1-year routine liver biopsy. On studying the impact of IL-28B on fibrosis in pairs of recipients and donors combined, there were no association between fibrosis and polymorphism of IL-28B genotype. In accordance with our findings, [12] found no significant association of either the donor or recipient IL28B genotype with the occurrence of allograft cirrhosis, three- and five-yr graft survival, three- and five-yr overall survival, or time to hepatic decompensation.

On the contrary very few available data suggest that the IL-28B polymorphism may determine the severity of the histological recurrence of HCV [15]. Charlton et al., [13]. Reported that the recipient IL-28B genotype (but not the donor IL-28B genotype) was significantly predictive of the fibrosis stage, with the T/T genotype being associated with more rapid fibrosis Charlton et al., [13] also suggested that the recipient IL-28B genotype may influence fibrosis progression by regulating the HCV-specific, human leukocyte antigen-independent adaptive
immune response through the activation of dendritic cells, T lymphocytes, or plasma cells. The favorable histology with CC genotype is consistent with other studies that showed that recipients with CC genotypes had less fibrosis than the non-CC genotypes [13,16,17]. In a recent paper by Duarte-Rojo et al., [18], recipient IL28B CC genotype was associated with lower frequency of F >_2 on liver biopsy at 1 year after LT, when compared with the non-CC genotype. Firpi et al., [19] demonstrated that both recipient and donor CC genotype is a favorable biomarker for liver histopathology and treatment response to IFN therapy after liver transplantation [18,19].

Absence of recipients with CC genotype in our study, may be a potential explanation for this discrepancy between our results and others regarding the impact of recipients IL-28B on fibrosis progression. The impact of IL28B genotypes on fibrosis progression could be explained by the effect on treatment outcome, but a specific effect on fibrosis progression remains speculative. We can only speculate about the mechanism underlying the association between the recipient IL-28B polymorphism and fibrosis progression through the severity of HCV recurrence. Also due to the combined effect of treatment response and IL-28B CC genotype on fibrosis progression, recipients with genotype CC tended to respond better to treatment and seemed to have less pronounced progression of the fibrosis post-transplant than recipients with non-CC.

In our study no significant association of either recipient or donor IL28B genotype in 2-year graft or patient survival was observed. In agreement with this result Charlton et al., [13]. Studied 189 HCV infected LT patients in the U.S. of whom one third were treated for recurrent HCV. While the IL28B genotype of the donor and recipient were strongly and independently associated with higher rates of SVR, there was no significant difference in overall graft survival [13]. In accordance with previous reports, the recipient and donor IL-28B genotypes did not show any impact on graft or patient survival [12,17]. Also no association was found between the recipient or donor IL28B genotype and adverse clinical outcomes [20]. In agreement with this data Cisneros et al., [21] did not find an association between donor IL28B genotype and liver outcomes. No difference in patient survival was present at any time point according to recipient IL-28B polymorphism [19,21].

This was in contrast to reports suggesting an important influence of the donor IL28B genotype in HCV infected recipients [23]. In addition, others found that a favorable donor IL28B CC genotype was only noticeable after antiviral therapy [18]. Allam et al., [23] showed that recipient IL28B polymorphism was linked with outcomes in patients with HCV undergoing LT. He found that while donor IL28B genotype was not associated with graft survival, the recipient IL28B TT genotype, compared to CC/CT genotypes, was associated with early and clinically relevant HCV recurrence and inferior graft survival. He also found that the detrimental effect of the TT genotype on HCV recurrence and graft survival was independent of antiviral treatment [23]. Graziaedi et al., [17] demonstrated an association between the recipient IL-28B genotype and cholestatic recurrent HCV. Patients with a non-C/C recipient genotype had an almost 3-fold increased risk of developing a severe recurrence of HCV [17]. While one group found an association between the donor IL28B CC genotype and the composite outcome of progression to cirrhosis, liver-related death, and retransplantation. Duarte-Rojo et al., [24] and another group found an association between the donor CC genotype and severe recurrent HCV in a case-control study [18,24], data on the association of IL28B genotype and the clinical course of post-transplant HCV had been inconsistent. Ackefors et al., [14] found a strong association between the IL-28B genotype and clinical long-term outcome, fibrosis progression in liver transplant recipients with hepatitis C recurrence. In particular, the recipient IL-28B CC genotype indicated a more favorable outcome [14].

As donors are often not available, several studies used DNA samples obtained from implanted liver biopsies. The rapid repopulation of the graft with recipient-derived cells can confound the donor genotype determination explaining some of the discrepancies observed among different studies. Also the post-transplant course is complex with AVT, immunosuppressant changes, anastomotic biliary complications and episodic rejection, and it is therefore difficult to attribute outcomes specifically to HCV recurrence [20].

Conclusion:

Our study revealed that the CC genotype frequency was reduced among patients with HCV end stage liver disease while, in contrast, the frequency of CT & TT increased.

No association was noted between IL 28B polymorphism and fibrosis progression or patient and graft survival, and no impact on liver outcomes.
References


تأثير تحوّر جين الانترلوكين 28 على النتائج في عملية زراعة الكبد للمرضى والمبتعرين و المتلقيين

تهدف دراستنا لتحقيق تأثير تحوّر جين الانترلوكين 28 على النتائج في عملية زراعة الكبد للمرضى والمبتعرين و المتلقيين.

تم تحديد نوع جين الانترلوكين 28 في المرضى والمبتعد و المتلقي لدى 44 حالة زرع كبد مع متابعة دورية للمريض على مدى عامين بعد عملية زراعة الكبد.

و قد وجد أنه لا يوجد أي تأثير لتحوّر جين الانترلوكين 28 على النتائج في عملية زراعة الكبد.

1316 Influence of IL28B of Donors & Recipients on Liver Transplantation