New era of liver transplantation for HIV-HCV Co-infected patients: A case report

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Case Presentations

A 59-year-old Caucasian male presented in 2013 for liver transplant evaluation as the treatment for hepatocellular carcinoma (HCC), on the background of liver cirrhosis from HIV (on HAART) and HCV infection (without treatment). A routine hepatoma screening; via contrast triple phase CT-Scan demonstrated an arterially enhancing lesion within segment VIII of the liver measuring 1.8x1.7x1.8 cm and the lesion washed out on portal venous and delayed phases (OPTN V). His past medical history

Abstract

Morbidity and mortality of HIV-infected patients have been improved over the last decades with the advent of combined antiretroviral therapy. As a result, other comorbidities such as chronic kidney and chronic liver diseases have emerged in the HIV population. A considerable percentage of end-stage liver disease (ESLD) in HIV population is attributed to hepatitis C co-infection and reactivation, and a growing need for solid organ transplantation has emerged among those patients. On the other hand, several studies on liver transplantations of patients co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) have shown discouraging results both in patient and graft survival rates. As a result, HIV-HCV co-infection has been considered a relative contraindication for liver transplantation. Thankfully, new drugs for HCV treatment have been discovered, acting direct on viral replication of HCV and they have changed the whole clinical course of HCV/HIV co-infected liver transplant recipients. Our case illustrates the long-term efficacy and safety of the new combination of Sofosbuvir/Ledipasvir in HCV/HIV co-infected liver transplant recipients.

Introduction

Widespread implementation of highly active antiretroviral therapy (HAART) has improved dramatically the life expectancy of HIV-infected patients [1] and with this increase in life expectancy, illnesses such as chronic kidney and chronic liver disease constitute a new challenge in HIV-infected patients [2]. Liver disease is now a leading cause of morbidity and mortality in the HIV-infected population [3]. A large proportion of liver diseases originates from HCV co-infection, because of shared routes of transmission. In the USA, 15-30% of HIV-infected patients are co-infected with HCV [4]. HIV infection has been associated with a more rapid progression of the HCV-related liver disease, and the risk of progression to end-stage liver disease (ESLD) in HIV-HCV co-infected patients is six-fold higher, in comparison with HCV mono-infected patients [5]. Additionally, HCV infection is leading cause for inferior outcomes after orthotopic live transplantation (OLT) in the patient with HIV/HCV co-infection [5]. Herein, we present a case report of a HIV-HCV co-infected patient who underwent OLT and had an HCV recurrence, which was treated successfully with a direct-acting antivirus regiment (DAAs) and has excellent two years survival to date.
was significant for anxiety, depression, HIV and HCV infection (HCV genotype 1a) both
diagnosed several years before. The patient had a positive smoking history which was
stopped five years before and positive history for illegal drug abuse which was stopped
ten years before. His past surgical history was significant for right nephrectomy and
cholecystectomy after a gunshot wound. His family history was significant for coronary
disease in both parents.

The patient underwent four sessions of trans-arterial chemoembolization (TACE)
as a bridging maneuver to liver transplantation. After one and a half years from the
initial diagnosis of the lesion, a suitable HCV negative deceased donor became available
and the patient underwent OLT. At the time of transplantation, the patient had MELD
score 34, WBC 6.8 K/MM^3, Hematocrit 39.2%, Platelets: 62 K/MM^3, CD4 199 cells/ul (CD4
percentage 43%). Total Bilirubin 1.7 mg/dL, Alanine Aminotransferase 79 U/L, Aspartate
Aminotransferase 87 U/L and AFP 10.4. The histological examination of the explanted showed
residual hepatocellular carcinoma confined to the liver, status post chemoembolization,
moderate differentiated, with 90% tumor necrosis and without vascular or peri-neural
invasion. The non-neoplastic liver was cirrhotic, stage 6/6, with chronic active hepatitis
and macro-steatosis up to 25%. The postoperative course was uneventful and the patient
was discharged ten days later, with treatment for HIV (Raltegravir, Abacavir, Lamivudine
and Maraviroc) and immunosuppression therapy with Steroids, Mycophenolate Mofetil
and Tacrolimus. Two months after transplantation the patient came back with clinical and
laboratory picture of acute cellular rejection, which was verified with biopsy and treated
appropriately with steroids. After this episode of acute rejection, he was additionally
treated three times with steroids. During the first post-operative months after the liver
transplantation the patient had clinical and laboratory findings compatible with HCV
reurrence (HCV PCR 8,571,687 International Units/mL) and it was proposed to start
treatment for HCV infection, with a combination of Ribavirin, Ledipasvir and Sofosbuvir.
He received 24 weeks of anti-HCV treatment and sustained virologic response (SVR)
was achieved for both 12 and 24 weeks. One year after the completion of HCV
treatment the patient had no detectable levels of HCV and no adverse effects or drug
interactions have been observed. Preoperative and postoperative laboratory findings
are cited in table 1 and the HCV viral load course is cited in figure 1.

**Discussion**

HCV-HIV co-infection is associated with exceedingly poor outcomes after OLT, with
regard to both patient and graft survival rates; mainly due to a higher rate and worse
phenotypes of rejection in that population [5]. The causative factors are primarily
hepatitis C virus recurrence which leads to liver fibrosis/cirrhosis and HIV infection
which accelerates the pathophysiologic process, through immunosuppression [6].
Therefore, in HIV-HCV co-infected liver transplant candidates there are two primary

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**Table 1: Preoperative and Postoperative Laboratories.**

<table>
<thead>
<tr>
<th>Dates</th>
<th>AST</th>
<th>ALT</th>
<th>ALP</th>
<th>T.BILI</th>
<th>HCV RNA (IU/mL)</th>
<th>HIV RNA (Copies/mL)</th>
<th>CD4 (count)</th>
<th>Hb (gm/dL)</th>
<th>WBC (K/MM^3)</th>
<th>PLT (K/MM^3)</th>
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<tr>
<td>Preoperative Values</td>
<td></td>
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<td></td>
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<tr>
<td>Oct 13</td>
<td>62</td>
<td>74</td>
<td>150</td>
<td>0.8</td>
<td>66,721</td>
<td>N/A</td>
<td>N/A</td>
<td>12</td>
<td>3</td>
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<td>Jan 14</td>
<td>147</td>
<td>179</td>
<td>204</td>
<td>1.2</td>
<td>601,785</td>
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<td>12.8</td>
<td>3.5</td>
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<td>22</td>
<td>20</td>
<td>119</td>
<td>0.6</td>
<td>13,293</td>
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<tr>
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<td>562</td>
<td>63</td>
<td>3.1</td>
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<td>6.8</td>
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<td>173</td>
<td>199</td>
<td>813</td>
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<td>135</td>
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<td>2.6</td>
<td>146</td>
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<tr>
<td>May 15</td>
<td>358</td>
<td>330</td>
<td>327</td>
<td>4.6</td>
<td>8,571,687</td>
<td>&lt;20</td>
<td>102</td>
<td>11.8</td>
<td>3</td>
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<td>24</td>
<td>122</td>
<td>1</td>
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<tr>
<td>July 15</td>
<td>17</td>
<td>25</td>
<td>128</td>
<td>0.9</td>
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<tr>
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<tr>
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<td>5.9</td>
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treatment targets, HIV and HCV, both of which should be managed sufficiently and aggressively. Hepatitis C virus control is the key factor, as HIV has been controlled adequately with HAART, and it can be implemented either in pre-transplantation or in post-transplantation period. The main goal of the HCV treatment is the achievement of undetectable HCV-RNA levels for a long period after the treatment completion, which has been called sustained virologic response (SVR). Pearlman et al have defined sustained virologic response (SVR) as “aviremia” 24 weeks after completion of antiviral therapy for chronic hepatitis C virus (HCV) infection [7]. In the past, Pegylated interferon (PegIFN) and ribavirin (RBV) were the only available HCV treatment choices. However, both have shown very poor outcomes, with limited efficacy and poor tolerance [4]. Fortunately, during the last couple of years that dismal picture has changed dramatically mainly because discovery of DAAs. DAAs target specific proteins-enzymes of HCV life cycle and can be categorized into four main categories: NS5A inhibitors, NS3/4A protease inhibitors, NS5B polymerase inhibitors (nucleoside and non- nucleoside) and NS5A inhibitors [8]. A number of recent studies have reported exceptional outcomes in HCV mono-infected patients, with SVR 12 in 94% and SVR 24 in 99% of treated population [9,10]. However, HCV treatment in HIV/HCV co-infected liver transplant candidates and furthermore in HIV/HCV co-infected liver transplant recipients is intricate and demanding. Balancing immunosuppression with minimizing HCV recurrence and HIV infection is challenging and often counter-intuitive. As observed in our case, the immunosuppression after liver transplantation in HIV-HCV co-infected patients can suppress the recipient's defenses to such a degree as to facilitate early HCV recurrence and can lead to liver transplant rejection. Possible underlying mechanisms are the inadequate immunosuppression due to drug interactions between ART medications and immunosuppressant, and cross-reactivity between memory T cells, with subsequent hepatocellular injury [5,11,12]. Treatment of rejection with steroids creates a vicious cycle, by suppressing the immune system and accelerating HCV recurrence. A key to breaking the vicious cycle of rejection is the new direct-acting antiviral drugs for HCV as demonstrated in this case with the combination therapy of Ribavirin, Ledipasvir and Sofosbuvir. This demonstrates that DAAs can be used safely to achieve long term and durable SVR after treatment of HCV recurrence in HIV-HCV co-infected liver transplanted patients, without serious drug interactions or adverse effects.

One of the major concerns in treating the HIV-HCV co-infected liver transplant recipients is the drug interactions between antiretroviral therapy, anti-HCV therapy and immunosuppressive therapy. The first approved HCV protease inhibitors (PIs), boceprevir and telaprevir, are potent inhibitors of cytochrome P450 3A (CYP3A), demonstrating serious DDIs with HIV protease inhibitors and several non-nucleoside reverse transcriptase inhibitors (NNRTIs) [13]. It would be safer to avoid combination of those DAAs with efavirenz. Furthermore, by inhibiting the CYP3A4 there is a need for reduction of the dosages in calcineurin inhibitors (CNIs), such as tacrolimus/ cyclosporine and mammalian target of rapamycin inhibitors like sirolimus (MTORi) [13]. However, the combination of Sofosbuvir/Ledipasvir for HCV treatment has shown
a safer drug interaction profile and the co-administration with Raltegravir, Abacavir, Lamivudine and Tacrolimus seems to be safe and without need for medication dose adjustment.

A limited number of studies have addressed the HCV treatment with DAAs, in HCV/HIV co-infected liver transplant recipients. Grant et al. has described eight HCV/HIV co-infected liver transplant recipients, six with genotype 1a, one with genotype 1b and one with genotype 2b, who were treated with either Sofosbuvir/Ribavirin or Sofosbuvir-Simeprevir-Ribavirin [14]. Seven out of the total eight patients completed a 12 weeks therapy and all achieved SVR 12 without significant adverse drug interactions. Campos-Varela et al. has described two cases of HCV/HIV co-infected liver transplant recipients, both genotype 1a, who were treated with DAAs and both achieved SVR 12 [15]. Alkhouri et al. have described a case of successful HCV treatment of a HIV liver transplant recipient with the combination of Telaprevir/Ribavirin/Pegylated Interferon [16]. Future studies with larger populations are needed to evaluate the possibility of treating HCV/HIV liver transplant recipients with DAAs and their interactions with immunosuppressive and antiretroviral medications. The advent of DAA drugs has given the opportunity in HCV-HIV population to counter the deleterious effect of HCV on liver allografts after transplantation. In our opinion HIV-HCV co-infection is no longer a contraindication for liver transplantation.

References
