Successful treatment with telaprevir of post-transplant fibrosing cholestatic hepatitis C in an HIV co-infected patient

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Acta Gastroenterol Latinoam 2015;45:076-079

Summary

Hepatitis C recurrence is the main cause of graft loss in liver transplant patients co-infected with human immunodeficiency virus (HIV). These patients have higher risk of fibrosing cholestatic hepatitis, which is the most severe type of hepatitis C recurrence. Until direct antiviral agents were released, only a minority of patients could be satisfactorily treated. We describe the successful treatment with pegylated-interferon, ribavirin and telaprevir of an hepatitis C virus (HCV)/HIV co-infected patient who developed fibrosing cholestatic hepatitis after liver transplantation. A 40-year-old male (HCV genotype 1a; IL-28 CC) underwent liver transplantation for decompensated cirrhosis. On post-transplant day 60, he rapidly developed progressive jaundice, worsening of liver function tests and ascites. A transjugular liver biopsy confirmed the diagnosis of fibrosing cholestatic hepatitis. Treatment with pegylated-interferon, ribavirin and telaprevir was indicated for 48 weeks, achieving sustained virological response at 12 weeks of follow-up. The rapid negativization of the viral load observed during the first 4 weeks of treatment was associated with regression of ascites and jaundice. Red blood cell transfusions, erythropoietin and filgrastim were required for the management of anemia and neutropenia. Triple therapy with telaprevir might be indicated for the treatment of severe HCV recurrence in selected HCV/HIV co-infected patients, especially in countries with limited access to pegylated-interferon-free regimens.

Key words. Direct antiviral agents, graft loss, hepatitis C recurrence, protease inhibitors.

Hepatitis C fibrosante colestásica tratada con telaprevir luego del trasplante hepático en un paciente co-infectado con HIV

Resumen

La recurrencia de la hepatitis C post-trasplante hepático es la principal causa de pérdida del injerto en los pacientes coinfectados con el virus de la inmunodeficiencia humana (HIV). Estos pacientes presentan un riesgo elevado de recurrencia de la hepatitis C en su forma más grave, hepatitis colestásica fibrosante. En la era previa a los antivirales de acción directa, el tratamiento de la misma era ineficaz, pudiendo rescatar una menoría de los pacientes afectados. Presentamos el caso de un paciente coinfectado que desarrolló una recurrencia de hepatitis C colestásica fibrosante luego del trasplante, la cual fue tratada con éxito con interferón pegilado, ribavirina y telaprevir. Un paciente de 40 años de edad [virus de la hepatitis C (HCV) genotipo 1a; IL-28 CC] coinfecctado con HIV fue sometido a un trasplante hepático por cirrosis descompensada. En el día 60 post-trasplante desarrolló ictericia progresiva y ascitis severa. La biopsia hepática transjugular confirmó el diagnóstico de recurrencia de hepatitis C colestásica fibrosante. Se realizó tratamiento con interferón pegilado, ribavirina y telaprevir por 48 semanas, logrando respuestas virológicas sostenidas a 12 semanas de finalizado el mismo. La negativización de la viremia en las primeras 4 semanas de tratamiento se asoció con resolución de la ascitis y la ictericia. Durante el tratamiento requirió eritropoyetina, filgrastim y...
transfusion de glóbulos rojos para el manejo de la anemia y neutropenia. La triple terapia con telaprevir podría indicarse para el tratamiento de la recurrencia severa de la hepatitis C en pacientes coinfectados con HIV, especialmente en países en los que la accesibilidad a esquemas libres de interferón sea limitada.

**Palabras claves.** Antivirales de acción directa, pérdida del injerto, recurrencia de hepatitis C, inhibidores de proteasa.

**Abbreviations**
- HCV: Hepatitis C virus.
- HIV: Human immunodeficiency virus.
- SVR: Sustained virological response.
- PEG-INF: Peglated-interferon.
- RBV: Ribavirin.
- DAA: Direct antiviral agents.

Re-infection of the graft is the main cause of death and graft loss in patients with hepatitis C virus (HCV) infection undergoing liver transplantation. In some patients, HCV recurrence is characterized by an accelerated fibrosis process. Once cirrhosis of the graft develops, decompensation occurs in more than two thirds of the recipients, ultimately leading to re-transplantation or death.

A sub-group of patients who experience HCV recurrence develops an aggressive variant known as fibrosing cholestatic hepatitis, which is characterized by severe cholestasis, ballooning, perisinusoidal fibrosis and very high HCV viral load. Its prognosis is dismal, almost invariably characterized by rapid deterioration of liver function.

Outcomes after liver transplantation are poorer in HCV patients co-infected with the human immunodeficiency virus (HIV) than in HCV mono-infected patients. These patients are at higher risk of rapid fibrosis progression and fibrosing cholestatic hepatitis.

The management of HCV recurrence in co-infected patients is challenging. The global sustained virological response (SVR) rates are low in patients treated with pegylated-interferon (PEG-INF) plus ribavirin (RBV), especially in patients with fibrosing cholestatic hepatitis. Since the introduction of the direct antiviral agents (DAAs) boceprevir and telaprevir, higher SVR rates were reported for the treatment of HCV genotype 1 recurrence in mono-infected patients. However, this strategy is challenged by treatment-related toxicity and significant drug to drug interactions. Recently, sofosbuvir and simeprevir were recommended for the treatment of post-transplant HCV recurrence. However, access to these new DDAs is still limited in most countries. At the time this case-report was submitted, there was a single published case describing the use of telaprevir in combination with PEG-INF plus RBV in an HCV/HIV co-infected patient with severe HCV recurrence after liver transplantation.

We report the successful treatment with telaprevir in combination with PEG-INF and RBV in an HCV/HIV co-infected liver transplant recipient with severe fibrosing cholestatic HCV recurrence.

**Case report**

A 40-year-old Hispanic male patient co-infected with HCV (genotype 1a; IL-28 CC) and HIV underwent liver transplantation for decompensated cirrhosis. He had been a prior partial responder to PEG-INF plus RBV 4 years before liver transplantation. At the time of that treatment he had compensated cirrhosis and an anti-retroviral therapy consisting of ritonavir-boosted lopinavir, tenofovir and emtricitabine (HIV viral load was undetectable and the CD4+ cell count was 265/mm³). The MELD score at the time of transplantation was 32 and the Child-Pugh C-10. The HCV viral load was 13,900 IU/mL, HIV was undetectable and CD4 cell count was 279/mm³. Anti-retrovirals remained unchanged.

A 53 year old, heart-beating deceased female donor was used. The cause of death was an hemorrhagic cerebrovascular accident. The body mass index was 35. The cold ischemia time was 7 hours. The transplant was uneventful with a total duration of 6 hours. Induction was performed with basiliximab and steroids. The immediate postoperative course was complicated by arterial hypertension and a urinary tract infection, both successfully controlled with appropriate treatment. Tacrolimus was initiated on postoperative day 1, achieving blood trough levels between 7-12 ng/ml together with mycophenolate mofetil. Anti-retrovirals were re-initiated on post transplant day 40 with the same pre-transplant regimen. On post-transplant day 60, the patient rapidly developed progressive jaundice, worsening of liver function tests and tense ascites. Blood tests revealed significant liver dysfunction: total bilirubin 17.8 mg/dL, prothrombin concentration 62% and alanine aminotransferase 175 IU/L (Table 1). Liver ultrasoundography was normal. A transjugular liver biopsy was performed, which showed features of fibrosing cholestatic HCV recurrence: severe cholestasis, ballooning and perisinusoidal fibrosis.

After written consent was obtained, the patient was admitted for 2 weeks to start treatment with PEG-INF alfa-2a (180 ug/week), RBV (1,000 mg/day) and telaprevir (750 mg three times daily). Anti-retrovirals were switched to raltegravir, tenofovir and emtricitabine. Tacrolimus dose was carefully adjusted to obtain blood...
through levels of 8 to 12 ng/ml. Mycophenolate mofetil was discontinued. Pre-treatment HCV viral load was higher than 69,000,000 IU/mL. (Cobas TaqMan; lower limit of quantification 43 IU/mL, lower limit of detection 26 IU/mL, higher limit of quantification 69,000,000 IU/mL). Most significant treatment related adverse events were flu-like symptoms, anemia and neutropenia. Red blood cell transfusions (three units in two separate days), erythropoietin and filgrastim were required for the management of cytopenias. A progressive decline in CD4 cell count was observed during the treatment, requiring prophylaxis with azithromycin and trimethoprim-sulfamethoxazole. HIV viral load was persistently undetectable. Two therapeutic paracentesis were performed during the first 4 weeks of treatment. Ascites and jaundice resolved during the first 4 weeks of treatments and did not recur. Thereafter, treatment tolerability was optimal.

The patient was treated for 48 weeks, receiving telaprevir, PEG-INF plus RBV during the first 12 weeks, and PEG-INF plus RBV thereafter. The HCV viral load was detectable but unquantifiable at treatment week 4, and undetectable at treatment weeks 12, 24 and 48. Adherence to treatment was optimal and no dose reductions were required in any of the medications. The patient achieved SVR at 12 weeks after the end of therapy (SVR-12) and is currently asymptomatic, with normal liver function tests. A transient elastography (Fibroscan®) was performed at end of treatment showing a 6.7 Kpa, corresponding to a fibrosis stage grade of 0-1.

**Discussion**

The presentation of this case illustrates the successful treatment of fibrosing cholestatic HCV recurrence with telaprevir, PEG-INF and RBV in an HIV co-infected patient. Fibrosing cholestatic hepatitis after liver transplantation is an unfortunate situation. In patients who do not respond to treatment, re-transplantation is the only remaining choice once liver failure develops. However, re-transplantation of HCV/HIV co-infected patients is associated with poor outcomes and is controversial.19

Prior studies have shown that co-infected patients have higher HCV viral loads after transplantation, higher rate of fibrosing cholestatic hepatitis and a more rapid progression of fibrosis.20 Our patient had several risks factors for developing severe HCV recurrence. The donor was 53 years old and had a BMI of 35. Moreover, the MELD at transplantation was 32. These characteristics have been previously described to be associated with worse outcomes.20

There is not general agreement on the optimal immunosuppression for co-infected patients after liver transplantation. Our patient received induction with basiliximab and steroids. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil and steroids. We chose this immunosuppression regimen for two reasons. First, because rejection was described to be more frequent in co-infected than in mono-infected patients.20 Second, because it has been described that treatment of rejection (steroid boluses) is associated with more severe HCV disease.20

**Table 1. Laboratory characteristics before, during and after treatment.**

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>On treatment</th>
<th>Post-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 4</td>
<td>Week 12</td>
<td>Week 24</td>
<td>Week 4</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>15</td>
<td>12</td>
<td>9.2</td>
<td>11.7</td>
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<tr>
<td>WBC count (per mm³)</td>
<td>5,440</td>
<td>4,850</td>
<td>1,600</td>
<td>1,800</td>
</tr>
<tr>
<td>ANC (per mm³)</td>
<td>4,134</td>
<td>3,443</td>
<td>1,088</td>
<td>1,026</td>
</tr>
<tr>
<td>CD4+ (per mm³)</td>
<td>150</td>
<td>74</td>
<td>120</td>
<td>56</td>
</tr>
<tr>
<td>Platelets (per mm³)</td>
<td>146,900</td>
<td>312,000</td>
<td>135,000</td>
<td>103,200</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>17.8</td>
<td>2</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>176</td>
<td>42</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>207</td>
<td>241</td>
<td>209</td>
<td>176</td>
</tr>
<tr>
<td>PC (%)</td>
<td>62</td>
<td>99</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.2</td>
<td>3</td>
<td>3.7</td>
<td>4</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.7</td>
<td>0.6</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>HCV RNA (IU/mL)</td>
<td>&gt; 69,000,000</td>
<td>Det/Unq</td>
<td>Undetected</td>
<td>Undetected</td>
</tr>
</tbody>
</table>


Three red blood cell units were transfused during the first four weeks of treatment. Erythropoietin (4,000 units three times weekly) was started on treatment week 3. Filgrastim (300 mcg weekly) was started on treatment week 12.
We decided to initiate triple therapy with PEG-INF, RBV and telaprevir. Anti-retrovirals were switched to minimize drug interactions and tacrolimus dose was property adjusted. Mycophenolate was discontinued in order to lower the risk of treatment-induced cytopenias. The rapid reduction in HCV viral load induced by the triple therapy was associated with resolution of the ascites and normalization of liver function tests. Moreover, SVR-12 was achieved after 48 weeks of therapy.

Daclatasvir and sofosbuvir successful treatment of fibrosing cholestatic HCV recurrence in an HCV mono-infected patient has already been reported.31 Sofosbuvir and simeprevir were recently recommended for the treatment of HCV in different settings.17 The combination of these DAAs with or without RBV would have been the ideal treatment for the patient we report. However, these drugs might not be widely available in the near future. Meanwhile, we believe that different strategies should be implemented to prevent and treat the aggressive HCV recurrence in co-infected patients: from adequate donor-recipient matching to antiviral treatment, even in cases in whom marginal treatment tolerability is anticipated.

References