Treatment of Hepatitis C Recurrence after Liver Transplantation

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Agenda

1. Introduction

2. Treatment options for hepatitis C recurrence after transplantation
   - Clinical trials
   - Real life cohorts

3. Unsolved issues
Hepatitis C and Liver Transplantation

Prieto et al, Hepatology 1999

Years after transplantation

Patient survival

Proportion developing cirrhosis

Months after transplantation

Prieto et al, Hepatology 1999
Hepatitis C and Liver Transplantation


Berenguer M et al, Am J Transpl 2008

Survival RVS (n = 33) vs. NR (n = 56)
P = 0.032

Follow-up (days)

Patient survival

No SVR (n = 26)
SVR (n = 11)

HVPG (mmHg)

p = 0.003
p = 0.004
p = 0.047
p = 0.003

6.7
12.0
5.0
3.5


Berenguer M et al, Am J Transpl 2008
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Sofosbuvir + RBV

- 40 LT recipients (>6mo)
- 33 were G1
- 16 cirrhotics
- DC due to AE =2
- Relapse 9 patients

Charlton et al, Gastroenterology 2015
Mild-Moderate fibrosis (F0-F2) \( \rightarrow \) n=34
- G1a \( \rightarrow \) 85%

CNI adjustment (Tac 0.5mg/w and CyA 1/5 of previous dose)

<table>
<thead>
<tr>
<th></th>
<th>w4</th>
<th>EOT</th>
<th>SVR4</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV-RNA undetectable (%)</td>
<td>100</td>
<td>100</td>
<td>96</td>
<td>96</td>
</tr>
</tbody>
</table>

Anemia 17%
- Rejection 0
- Renal Impairement 0
- Early Discontinuation 3%
- SAEs 6%
- Deaths 0

Kwo P, NEJM 2014
Randomized trial (1:1), Genotype 1 or 4, naïve or treatment experienced
F0-F3, Child A, B, C

SOF/LDV + RBV

SVR12
Ledipasvir/Sofosbuvir + RBV

- F0-F3: 53/55, 96, 25/26, 24/25, 22/26, 15/18, 3/5, 2/3
- Child A: 55/56, 98, 25/26, 96, 85, 83, 60
- Child B: 96, 96, 96, 24/25, 67
- Child C: 67

Reddy et al, AASLD2014
Sofosbuvir + Simeprevir ± RBV

- 123 LT recipients
- 105 with SVR12 data
- 30% F3-F4
- 82% treatment-experienced
- 12% PI failure

Pungpapong et al, Hepatology 2015
Sofosbuvir + Simeprevir ± RBV

143 LT recipients, >60% with cirrhosis, >20% with MELD>10, including PI failures

Brown et al, AASLD 2014
Sofosbuvir + Daclatasvir ± RBV

- CULPIT cohort, 23 patients with FCH

Leroy et al, AASLD 2014
Simeprevir + Daclatasvir ± RBV

RNA undetectable (%)

<table>
<thead>
<tr>
<th></th>
<th>W2</th>
<th>W4</th>
<th>W12</th>
<th>EOT</th>
<th>PTW12</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>4</td>
<td>13</td>
<td>24</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>SMV+SOF</td>
<td>7</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>SMV+DCV</td>
<td>10</td>
<td>12</td>
<td>12</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

W2, W4, W12, EOT, PTW12

Londoño, AASLD 2014
Agenda

1. Introduction

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3. Unsolved issues
• Which is the right time to start antiviral therapy? Is pre-emptive therapy a good option?

• Is there a point where we might be able to eradicate HCV but not to revert liver cirrhosis (liver function, portal hypertension)?

• Which one is the best regimen?
Which is the right time to start antiviral therapy?

- Severe acute hepatitis/early recurrence (<12 months from liver transplant with typical biochemical and histological findings) n=52
- Post transplant compensated and decompensated cirrhosis (liver biopsy (F4) or clinical decompensation) n=52

- Early term due to AE n=7
- Liver transplant n=12
- Death n=13

SOF Compassionate Use Program SOF + RBV ± PEG n=104

Treatment After Liver Transplant: Unsolved Issues

- Which is the right time to start antiviral therapy?

![Bar Chart]

- Patients HCV RNA < LLOQ (%)
  - EOT: 82, 76/93
  - SVR: 59, 54/92

- SVR (%)
  - Early: 73
  - Late: 43
Which is the right time to start antiviral therapy?
### Treatment After Liver Transplant: Unsolved Issues

**Is pre-emptive therapy a good option?**

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Pre-emptive     | 1. It may prevent the infection of the graft  
2. It may prevent the development of liver fibrosis | 1. Difficult administration (renal function, potential for DDI, ability to take oral medications)  
2. No data on safety and efficacy with DAAs. |

Mariño, Londoño & Forns. Current Opinion in Organ Transplant, *accepted*
Treatment After Liver Transplant: Unsolved Issues

• Is there a no-return point?

**CTP A Patients (n=48)**
- 12 Wk (n=23)
- 24 Wk (n=25)

**CTP B Patients (n=41)**
- 12 Wk (n=21)
- 24 Wk (n=20)

Reddy, AASLD, 2014,
Treatment After Liver Transplant: Unsolved Issues

• Which one is the best regimen?
  - The degree of liver dysfunction
  - Renal function
  - Drug-drug interactions
Treatment After Liver Transplant: Unsolved Issues

- Which one is the best regimen?

<table>
<thead>
<tr>
<th>DRUG</th>
<th>METABOLISM/ELIMINATION</th>
<th>CIRRHOSIS</th>
<th>RENAL FAILURE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CTP-A</td>
<td>CTP-B</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Kidney</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Liver</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Paritaprevir/r</td>
<td>Liver</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>Liver</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>Liver</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Liver</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Dasabuvir</td>
<td>Liver</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>
Treatment After Liver Transplant: Unsolved Issues

- Which one is the best regimen? Drug-drug interactions?

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy volunteers</td>
<td>Dose adjustment</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>No change</td>
<td>Not necessary</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>↑ SMV 19%</td>
<td>Under investigation</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>No change</td>
<td>Not necessary</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>No change</td>
<td>Not necessary</td>
</tr>
<tr>
<td>Paritaprevir/r</td>
<td>↑ 5.8 fold</td>
<td>↓ 5 fold</td>
</tr>
</tbody>
</table>

Gambato et al, J Hepatol 2014
Conclusions

- After liver transplantation, antiviral therapy administered in patients with mild fibrosis stages achieves higher response rates as compared to patients with cirrhosis and decompensation.

- The election of antiviral regimen should be based on patients' characteristics (liver function, immunosuppression, renal function).

- The use of pre-emptive therapy needs further investigation.

- It is currently unknown if there is a no-return point in which antiviral therapy should not be administered.