Treating HCV Prior to Liver Transplantation

What Are the Treatment Options?

Xavier Forns
Liver Unit
Hospital Clinic, CIBEREHD, IDIBAPS
Barcelona
Disclosures

Unrestricted Grant Support: Janssen and Abbvie

Advisor: Gilead, Jansen and Abbvie
Which drug regimens are safe and efficacious?

1. Compensated cirrhosis (HCC)

2. Decompensated cirrhosis
Which drug regimens are safe and efficacious?

1. Compensated cirrhosis (HCC)

2. Decompensated cirrhosis
Safety and efficacy of DAA in decompensated cirrhosis

Protease Inhibitors
- Simeprevir
- Paritaprevir
- Grazoprevir

NS5A inhibitors
- Daclatasvir
- Ledipasvir
- Ombitasvir
- Elbasvir
- Velpatasvir

NS5B polymerase inhibitors
- Sofosbuvir (NI)
- Dasabuvir (NNI)

From Bartenschlager et al. Nature Reviews 2013
Safety and efficacy of DAA in G1 (4) compensated cirrhosis

* The combination of SOF+DAC+RBV can also be used in G1 (G4) patients with cirrhosis

Safety and efficacy of DAA in G1 (4) compensated cirrhosis

- Real world data
- Large cohort of cirrhotics (n=491)
- Nearly half (45%) history of previous decompensation
- Most patients treated without RBV
- Similar results in OPTIMIST-2 (SOF+SMV no RBV in cirrhosis)

- Real world data (Spanish Cohort)
- Large cohort of cirrhotics (n=946), most G1b
- SVR12: 91%

Safety and efficacy of DAA in G1 (4) compensated cirrhosis

SIRIUS French Study
- Cirrhotics who failed PI-based regimen (n=155)
- Randomized to 12 weeks with RBV vs 24 weeks without RBV

Afdhal N NEJM 2014, Bourlière M Lancet Infect Dis 2015
Safety and efficacy of DAA in G1 (4) compensated cirrhosis

- 60 cirrhotics
- G1b
- Naive or Experienced
- P/r+O+D

SVR12

94%

Poordad FJ NEJM 2014, Feld J Hepatol 2016
Safety and efficacy of DAA in G1 (4) compensated cirrhosis

- Lower response rates in G1a with baseline NS5A RAVs:
  - Add RBV and extend to 16 weeks

**SVR12**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
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<tbody>
<tr>
<td>GZV+EBV</td>
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<td>96%</td>
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Safety and efficacy of DAA in G1 (4) compensated cirrhosis

- 120 of 121 cirrhotics achieved SVR12
- 72/73 G1 infected cirrhotics achieved SVR12
- The remaining patients were G2, 4, 5 or 6
Safety and efficacy of DAA in G3 compensated cirrhosis

SOF+RBV 24w 79%
PR+SOF 12w 88%
SOF+DAC+RBV (12-16w) 86%
SOF+VEL 91%

* SOF+DAC for 24 w. (no RBV) obtains similar SVR12 rates (French CUP)

58 patients with treated HCC (BCLC 0 and A) on complete response, who underwent DAA therapy.

Median time between HCC treatment and DAA initiation: 11 m (P25-75 3-23)

Median time between last radiologic confirmation of complete response and DAA initiation: 1.7 m (P25-75 0.85-3.4)

Tumor recurrence: 16 (27.6%) patients. Median follow-up after DAA therapy 3.5 m (1-8)

Recurrence rate is significantly higher than the expected based on previous studies
Which drug regimens are safe and efficacious in this group?

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Membraneous Web

Bartenschlager R  Nature Reviews 2013
Safety and efficacy of DAA in decompensated cirrhosis

Overall safety is good. Cases of severe bradycardia (if combined with amiodarone), a few cases of lactic acidosis and pulmonary hypertension have been reported postmarketing. Few safety data if CP > 12
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Patients with decompensated cirrhosis (CP ≥ 7)
NHS England Expanded Access Program

Treatment duration 12 w; most patients with RBV

SVR rates similar than in ALLY-1 study in Child B/C (82%)

Safety and efficacy of DAA in decompensated cirrhosis

SOF and Velpatasvir (+/- RBV) in G1-G6 Child B decompensated cirrhosis

Curry MP NEJM 2015
### Safety and efficacy of DAA in decompensated cirrhosis

**SOF and Velpatasvir (+/- RBV) in G1-G6 Child B decompensated cirrhosis**

<table>
<thead>
<tr>
<th></th>
<th>SOF/VEL (12w)</th>
<th>SOF/VEL+RBV (12 w)</th>
<th>SOF/VEL (24 w)</th>
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<tbody>
<tr>
<td>Discontinuation</td>
<td>1 (1)</td>
<td>4 (5)</td>
<td>4 (4)</td>
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<tr>
<td>Deaths*</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>3 (3)</td>
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<tr>
<td>SAEs</td>
<td>17 (19)</td>
<td>14 (16)</td>
<td>16 (18)</td>
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<td>Hb &lt; 10 g/dL</td>
<td>7 (8)</td>
<td>20 (23)</td>
<td>8 (9)</td>
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<tr>
<td>Hepatic Encephalopathy</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>1 (1)</td>
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<tr>
<td>Sepsis</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td>1 (1)</td>
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<tr>
<td>GI hemorrhage</td>
<td>3 (3)</td>
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Sepsis and liver failure were the most common causes of death

Curry MP *NEJM* 2015
### DDI in HCV-infected liver transplant recipients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cefotaxime</th>
<th>Seguril</th>
<th>B-blockers</th>
<th>Ca-antagonist</th>
<th>Amiodarone</th>
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<tbody>
<tr>
<td>Sof/LDV</td>
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<td>Simeprevir</td>
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<thead>
<tr>
<th>Drug</th>
<th>Atorvastatin</th>
<th>Acenocumarol</th>
<th>Metformin</th>
<th>Fluconazol</th>
<th>Omeprazol</th>
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- **Green**: No interaction
- **Orange**: Potential interaction
- **Red**: Drugs should not be coadministered

Treatment regimens in patients awaiting LT

**G1 and G4***

- SOF/LDV + RBV 12 w vs SOF/LDV 24 w.
- SOF/DAC+ RBV (12-24 weeks)
- SOF/VEL (12 weeks), consider RBV in decompensated patients

**G3**

- Sofosbuvir/Daclatasvir+ RBV (12-24 weeks)
- Sofosbuvir/Velpatasvir + RBV (12 weeks)

* 3D or GZV/EBV (G1b) and 3D+RBV or GZV/EBV+RBV (G1a) in compensated cirrhosis awaiting LT for HCC