Management of HCV in Decompensated Liver Disease

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Hannover Medical School

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Conflict of interest

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Management of HCV in Decompensated Liver Disease

Three Questions

How ?

Why ?

Who not ?
Management of HCV in Decompensated liver disease
Three Questions

How?
What treatment options are available?

Why?

Who not?
Approved DAAs 2017

**...previr**
- Simeprevir
- Paritaprevir/r
- Grazoprevir
- Glecaprevir
- Voxilaprevir

**...asvir**
- Daclatasvir
- Ledipasvir
- Ombitasvir
- Velpatasvir
- Elbasvir
- Pibrentasvir

**...buvir**
- Sofosbuvir (NI)
- Dasabuvir (NNI)

Adapted from Manns & Cornberg, Lancet Infectious Diseases 2013 May;13(5):378-9
Available IFN-free DAA Regimens

- Sofosbuvir 400 mg 1/d
  - Daclatasvir 60 mg 1/d
    - ± Ribavirin

- Sofosbuvir 400 mg 1/d
  - Ledipasvir 90 mg 1/d
    - ± Ribavirin

- Sofosbuvir 400 mg 1/d
  - Velpatasvir 90 mg 1/d
    - ± Ribavirin

- Sofosbuvir 400 mg 1/d
  - Velpatasvir 90 mg 1/d
    - Voxilaprevir 150 mg 1/d

- Glecaprevir 300 mg 1/d
  - Pibrentasvir 120 mg 1/d

- Paritaprevir/r 150/100 mg 1/d
  - Ombitasvir 25 mg 1/d
    - ®
  - Dasabuvir 250 mg 2/d
    - ± Ribavirin

- Grazoprevir 100 mg 1/d
  - Elbasvir 50 mg 1/d
    - ± Ribavirin
Not all DAAs are suitable in decompensated cirrhosis – PIs are not recommended in CHILD B/C patients

Retrospective analysis of all phase 2/3 trials
- 1066 patients with cirrhosis
- 13 patients experienced a hepatic decompensation (1.2%)

Real-World data base (paritaprevir/ritonavir)
- 26 patients died
- 10 patients required a liver transplant
- 16 patients experienced an impairment of liver function

2.4 Hepatic Impairment

No dosage adjustment of ZEPATIER is recommended in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) [see Contraindications (4), Use in Specific Populations (8.9), and Clinical Pharmacology (12.3)].

2.3 Hepatic Impairment

MAVYRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C) [see Contraindications (4), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].
Available IFN-free and PI-free DAA Regimens

- Sofosbuvir 400 mg 1/d
  - Daclatasvir 60 mg 1/d
  ± Ribavirin

- Sofosbuvir 400 mg 1/d
  - Ledipasvir 90 mg 1/d
  ± Ribavirin

- Sofosbuvir 400 mg 1/d
  - Velpatasvir 90 mg 1/d
  ± Ribavirin

- Paritaprevir 150/100 mg 1/d
  - Ombitasvir 25 mg 1/d
  - Dasabuvir 250 mg 2/d
  ± Ribavirin

- Grazoprevir 100 mg 1/d
  Elbasvir 50 mg 1/d
  ± Ribavirin

- Pibrentasvir 120 mg 1/d
  - Glecaprevir 300 mg 1/d
  - Paritaprevir/r 150/100 mg 1/d
  - Ombitasvir 25 mg 1/d
  - Dasabuvir 250 mg 2/d
  ± Ribavirin

- Velpatasvir 90 mg 1/d
  - Voxilaprevir 150 mg 1/d
  ± Ribavirin
Available DAA Regimens
Limited in decompensated cirrhosis...

...but still very effective...
SOLAR-1 and 2: LDV/SOF + RBV in HCV GT1/4 Pre-Transplant Patients with Decompensated Cirrhosis

- No difference in SVR rates for GT1-infected patients treated for 12 and 24 weeks
- Too few GT4-infected patients for meaningful comparisons
- Virologic response was associated with improved MELD and CPT scores in patients with cirrhosis, largely due to improvements in synthetic function

*Analysis excluded three pre-transplant patients that were CPT-A at baseline.
Safety?
Ledipasvir, Sofosbuvir, Ribavirin (SOLAR – 2 Study)

- No deaths were considered treatment related

<table>
<thead>
<tr>
<th>Overall Safety</th>
<th>Post-Transplant</th>
<th>Pre/Post-Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F0-F3 + CPT A</td>
<td>CPT B + CPT C</td>
</tr>
<tr>
<td>Patients, n (%)</td>
<td>12 Weeks n=86</td>
<td>24 Weeks n=82</td>
</tr>
<tr>
<td>AE</td>
<td>79 (92)</td>
<td>78 (95)</td>
</tr>
<tr>
<td>Grade 3–4 AE</td>
<td>16 (19)</td>
<td>20 (24)</td>
</tr>
<tr>
<td>SAE</td>
<td>12 (14)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Treatment-related SAEs</td>
<td>0</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Treatment DC due to AE</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Manns et al., Lancet Infect Dis. 2016
ASTRAL-4: SOF/VEL ± RBV in HCV Patients with Decompensated Liver Disease: SVR12 – pangenotypic!

SOF/VEL + RBV resulted in highest SVR12 in patients with decompensated liver disease

*Patient with nondetectable drug levels at time of virologic failure.


NO CHILD C PATIENTS!
Highly Effective DAA Treatment for Patients with Decompensated Cirrhosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>12 Week</th>
<th>24 Week</th>
<th>12 Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF + RBV</td>
<td>131/155</td>
<td>140/158</td>
<td>82/87</td>
</tr>
<tr>
<td>SOF/VEL + RBV</td>
<td></td>
<td></td>
<td>94</td>
</tr>
</tbody>
</table>

- SOLAR-1 and SOLAR-2: CPT B and CPT C, Pre- and Post-Transplant
- ASTRAL-4: CPT B, Pre-TX

Advanced liver cirrhosis was defined by at least one of the following criteria:

- Fibroscan (transiente elastography) > 20 kPa
- Platelets < 90,000 Tsd./µl
- Albumin < 35 g/l
- Clinical signs of liver decompensation (e.g. ascites, variceal bleeding)

Safety and Efficacy confirmed in Real-World
Virological response in patients with advanced cirrhosis - results from the German Hepatitis C-Registry (DHC-R)
Safety and Efficacy confirmed in Real-World
Virological response in patients with advanced cirrhosis - results from the German Hepatitis C-Registry (DHC-R)

HCV genotypes

HCV genotype 1; n= 862 (78%)
HCV genotype 2; n =26 (2.4%)
HCV genotype 3; n=175 (15.8%)
HCV genotype 4; n=41 (3.7%)
HCV genotype 5; n=1 (1%)
HCV genotype 6; n=1 (1%)

Virological response (SVR-12)

89.6%
73.1%
75.4%
85.4%

patients with SVR-12 data; n= 1106

Deterding, Berg et al., parallel session EASL 2017
How to treat HCV patients with decompensated cirrhosis

Open Issues

- What to do with genotype 3?
- What shall we do with treatment failures?
- What to do in patients with severe renal impairment?
Management of HCV in Decompensated liver disease

Three Questions

How?

Why?

Who not?
Management of HCV in Decompensated liver disease
Three Questions

How?

Why? What can we achieve?

Who not?
Successful treatment improves **Quality of Life** in HCV patients with decompensated cirrhosis

- Patient reported outcomes in the ASTRAL-4 study
- RBV therapy was associated with temporary impairment of PROs during treatment
Ledipasvir, Sofosbuvir, Ribavirin (SOLAR - 2 Study)
Median Total Bilirubin and Albumin/Change From Baseline to FU 4

CPT B + CPT C

Median Total Bilirubin (mg/dL)
Baseline
FU Week 4
(11.2) (19.1)

Median Total Albumin (g/dL)
Baseline
FU Week 4
Normal range (3.3-4.9)
Normal range (0.2-1.2)
p <0.001

Manns et al., EASL 2015; Lancet Infect Dis. 2016
Long-term liver function improvement – bilirubin and albumin results from the German Hepatitis C-Registry (DHC-R)

Baseline bilirubin $1.1 \pm 0.8$ mg/dl

Baseline albumin $35.9 \pm 8.5$ g/l
Arm 2: HVPG Change Through Posttreatment Week 48 in Patients with Baseline HVPG ≥12 mm Hg Who Achieved SVR12 (n=9)

<table>
<thead>
<tr>
<th>Week</th>
<th>Screen</th>
<th>Baseline</th>
<th>EOT</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>24</td>
<td>72</td>
<td>120</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Observation Period</th>
<th>Treatment Period</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>mm Hg</td>
<td>n</td>
</tr>
<tr>
<td>-----</td>
<td>-------</td>
<td>----</td>
</tr>
<tr>
<td>9</td>
<td>+1.3 (2.8)</td>
<td>9</td>
</tr>
<tr>
<td>Median Δ (range)</td>
<td>1.5 (-2.5–7.0)</td>
<td>9</td>
</tr>
</tbody>
</table>

≥20% ↓ | ≥15% ↓ | Screen | Baseline | EOT | Follow-up Wk 48 post-SVR12
---|---|---|---|---|---
---|---|---|---|---|---
---|---|---|---|---|---
---|---|---|---|---|---
---|---|---|---|---|---
---|---|---|---|---|---

Afdhal et al, EASL, 2016
Ledipasvir, Sofosbuvir, Ribavirin (SOLAR-2 Study)

**MELD Score Change From Baseline to FU 4**


**Pre/Post-Transplant (CPT B and C, n=136*)**

<table>
<thead>
<tr>
<th>Change in MELD Score</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>-17</td>
<td>(-17)</td>
</tr>
<tr>
<td>-11</td>
<td>(-11)</td>
</tr>
<tr>
<td>-8</td>
<td></td>
</tr>
<tr>
<td>-6</td>
<td></td>
</tr>
<tr>
<td>-4</td>
<td></td>
</tr>
<tr>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

*Missing FU-4: n=24

**Manns et al., EASL 2015**
Survival Benefit of Direct-Acting Antiviral Therapy in Patients with Decompensated Cirrhosis

- Observed incidence of deaths in patients with hepatic decompensation in the SOLAR studies was compared with mortality predicted by survival models derived from HCV patients with hepatic decompensation in the pre-DAA era.

- DAA therapy is associated with significant decrease in mortality risk in patients with decompensated HCV cirrhosis, by as much as 60% within the first year of therapy.

Kim et al HEPATOLOGY. 2017 66(1). LB27
Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study

Luca Saverio Belli¹,*, Marina Berenguer², Paolo Angelo Cortesi³, Mario Strazzabosco⁴, Susanne-Rasoul Rockenschaub⁵, Silvia Martini⁶, Cristina Morelli⁷, Francesca Donato⁸, Riccardo Volpes⁹, Georges-Philippe Pageaux¹⁰, Audrey Coilly¹¹, Stefano Fagioli¹², Giuliana Amaddeo¹³, Giovanni Perricone¹, Carmen Vinaixa², Gabriela Berlakovitch⁵, Rita Facchetti³, Wojciech Polak¹⁴, Paolo Muiesan¹⁵, Christophe Duvoux¹³, for the European Liver and Intestine Association (ELITA)

- n=103 patients with decompensated cirrhosis
- 11 European centres
- All patients listed for liver transplant
- All patients received DAA therapy
- 33% (n=34/103) could be delisted
- Delisted patients showed significant improvement of liver function
Decrease of decompensated HCV liver disease on liver transplant wait-listing in the era of DAA antiviral therapy

Ledipasvir, Sofosbuvir, Ribavirin (SOLAR-2 Study)
MELD Score Change From Baseline to FU 4

Pre/Post-Transplant (CPT B and C, n=136*)

MELD Score Change

Change in MELD Score

(-17) (-11) (8)

*Missing FU-4: n=24*
Management of HCV in Decompensated liver disease
Three Questions

How?

Why?

Who not?
Management of HCV in Decompensated liver disease
Three Questions

How?

Why?

Who not? What is the point of no return?
Sofosbuvir and Velpatasvir (ASTRAL – 4 Study)
Improvement of MELD-Score in patients with decompensated cirrhosis
Post-treatment week 12

Curry et al., N Engl J Med. 2015
No overall improvement of MELD Scores in the Spanish HEPA-C Registry

843 patients with cirrhosis → 175 Child-Pugh B/C

MELD improvement: 36%
MELD worsening: 33%

MELD > 18 associated with death
Management of HCV in Decompensated liver disease
Delisting unlikely in patients with advanced cirrhosis?

- Patients with MELD >16-20 also experienced improvement of liver function
- Delisting in only 15-18% vs. 49% in patients with MELD-scores <16
Management of HCV in Decompensated liver disease
Risk factors for worsening?

Change in MELD Score
6 months

- treated
- untreated

Age < 65, Albumin > 35, Sodium > 135

≈ 75%

≈ 50%
Who gets better? Predictors of clinically meaningful improvements in liver function among patients with decompensated cirrhosis receiving DAA therapy

Omar Elsherif¹,², Elliot B Tapper²,³, KC Huang⁴, Anu Osinusi⁴, Michael Charlton⁵, Michael Manns⁶, Nezam Afdhal², Diana M. Brainard⁴, Norah Terrault⁷, Michael Curry²

¹St James’s Hospital, Dublin, ²Beth Israel Deaconess Medical Centre, Boston, ³University of Michigan, Ann Arbor, ⁴Gilead Sciences Inc, Foster City, ⁵Intermountain Medical Centre, Salt Lake City, ⁶Hannover Medical School, Hannover, ⁷USCF, San Francisco

ILTS, Prague, 2017
Results- CPT Stage at post-treatment week 24 for patients achieving SVR 12

Baseline CPT B (7-9); n=412

- 37% of patients stayed in CPT B
- 61% of patients were down-staged to CPT A
- 2% of patients were up-staged to CPT C

Baseline CPT C (10-12); n=81

- 15% of patients stayed in CPT C
- 63% of patients were down-staged to CPT A
- 22% of patients were down-staged to CPT B

165 patients down-staged to CPT A at post treatment W24
328 patients had decompensated cirrhosis at post treatment W24

Elsheirf et al , ILTS, Prague, 2017
“MELD purgatory” was defined as persistent CPT class B or C decompensation with a MELD score < 15 at the end of follow-up: 7.7 %
## Results - Predictors of down-staging to CPT A

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race: Non white vs white</td>
<td>0.23</td>
<td>0.13-0.55</td>
<td>0.0003</td>
</tr>
<tr>
<td>BMI: &lt; 30 vs ≥ 30</td>
<td>1.88</td>
<td>1.17-3.02</td>
<td>0.0089</td>
</tr>
<tr>
<td>Ascites: None vs mild or severe</td>
<td>3.36</td>
<td>2.08-5.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Encephalopathy: None vs grade 1 or above</td>
<td>3.46</td>
<td>2.22-5.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin: per unit g/dL</td>
<td>0.30</td>
<td>0.18-0.48</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Elsherif et al., ILTS, Prague, 2017
BEAAA Score*

<table>
<thead>
<tr>
<th>Category</th>
<th>Findings</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>&lt; 25</td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Ascites</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>ALT</td>
<td>&gt; 1.5 x ULN</td>
<td>1</td>
</tr>
<tr>
<td>ALB</td>
<td>&gt; 3.5 g/dL</td>
<td>1</td>
</tr>
</tbody>
</table>

*BMI, Encephalopathy, Ascites, ALT and Albumin (BEAAA)

BEAAA score of 4 – 5 was associated with a HR of 52.3 of treatment benefit
IMPACT: SVR 2 yrs after SMV/DCV/SOF in PH or decompensated cirrhosis

Change in CP scores at 2-year FU*

<table>
<thead>
<tr>
<th>Baseline (N=19)</th>
<th>2-year FU (n=15**)</th>
<th>Baseline (N=21)</th>
<th>2-year FU (n=17**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (CP A)</td>
<td>19 (100%)</td>
<td>14 (93%)</td>
<td>21 (100%)</td>
</tr>
<tr>
<td>Discontinued:</td>
<td>3/19 (16%)</td>
<td></td>
<td>Discontinued:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3/21 (14%)</td>
</tr>
<tr>
<td>Moderate (CP B)</td>
<td>1 (7%)</td>
<td>10 (59%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (29%)</td>
<td></td>
</tr>
<tr>
<td>Severe (CP C)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For patients who attended their 2-year FU visit; **1 ongoing patient in each group did not attend their 2-year FU visit, each patient had maintained their baseline CP status at their 2.5 year FU visit

Lawitz et al, Hep Dart, 05 December 2017, Abstract No 10
Decompensated HCV Liver Disease

Urgent unmet need:

Defining the “Point of no return”
Management of HCV in Decompensated liver disease
Better to treat after transplantation?
Glecaprevir/Pibrentasvir in patients after transplantation

Conducted in Australia, Canada, Italy, New Zealand, Puerto Rico, Spain, Taiwan, the United Kingdom and the United States

Open-label Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>12-week G/P N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n/%</td>
<td>75</td>
</tr>
<tr>
<td>White race†, n/%</td>
<td>78</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>60 (39 – 78)</td>
</tr>
<tr>
<td>BMI, median (range), kg/m²</td>
<td>26.0 (17.4 – 42.5)</td>
</tr>
<tr>
<td>Genotype‡, n/%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>HCV RNA, median (range), log₁₀ IU/mL‡</td>
<td>6.5 (4.0 – 7.6)</td>
</tr>
<tr>
<td>Fibrosis, n/%†</td>
<td></td>
</tr>
<tr>
<td>F0-F1</td>
<td>80</td>
</tr>
<tr>
<td>F2</td>
<td>6</td>
</tr>
<tr>
<td>F3</td>
<td>14</td>
</tr>
</tbody>
</table>

G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; BMI, body mass index.
† Race was self-reported. ‡Genotype determined by the Versant HCV Genotype Inno-LiPA Assay Version 2.0. § HCV RNA quantified by Roche COBAS AmpliPrep/TaqMan v2.0. Data missing for 2 patients.

Reau N et al., EASL  2017
Management of HCV in Decompensated liver disease
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Who not?