DAAs in decompensated cirrhosis: pros and cons

C. Triantos
University Hospital of Patras
Conflicts of interest

Speaker and research/travel grants from MSD, Roche, Abbvie, Bristol-Myers Squibb, Bayer and Gilead Sciences.
• Benefits of achieving SVR in this setting

• Treatment with DAAs and efficacy

• Open questions

• Pros and cons of treating patients with end-stage liver disease

• Conclusions
Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Development of complications:
- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice

De-compensation shortens survival.

- All pts with cirrhosis: Median survival ~ 9 yrs
- Decompensated cirrhosis: Median survival ~ 1.6 yrs

Ginés P, Hepatology. 1987
Anticipated benefits of achieving SVR in waitlist patients

Two expected benefits:

- prevention of post-transplant recurrence of HCV
- stabilization or improvement of liver disease
Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis

van der Meer AJ, JAMA. 2012
HVPG Change in CP-A Cirrhotics treated with SOF + RBV for 48-Wks

- 37 patients had paired measurements pre-treatment and at end of treatment
- Mean change in HVPG was -1.2 mmHg
- 24% (9/37) had ≥20% reduction in HVPG
- 62% (23/37) had ≥10% reduction in HVPG
- Only significant factor associated with an HVPG decrease ≥20% was baseline MELD score <10

Afdhal N. EASL. 2015;LP13.
DAAs were able to reverse liver dysfunction and favour the inactivation and delisting of about one patient out of three and one patient out of five in 60 weeks, respectively.

Patients with lower MELD scores had higher chances to be delisted.

Belli L, J Hepatol 2016
Treatment with DAAS and efficacy in decompensated cirrhosis
Peginterferon alfa-2b and ribavirin in patients with hepatitis C virus and decompensated cirrhosis

- N=66, PEG/RBV, 24 w

- Therapy
  ✓ tolerated by 27 patients,
  ✓ dose reduced in 26 for toxicity,
  ✓ discontinued in 13 for intolerance.

- EOT and eradication rates were
  ➢ 82.6% and 43.5% for HCV 2/3
  ➢ 30.2% and 7.0% for HCV 1/4

Iacobellis A, J Hepatol 2007
Comparison of direct acting antiviral therapies for chronic hepatitis C with decompensated cirrhosis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Study (ref.)</th>
<th>Child-Pugh class</th>
<th>Genotypes</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/VDP ± RBV</td>
<td>12 weeks</td>
<td>ASTRAL-4</td>
<td>B</td>
<td>1</td>
<td>Genotype 1: 88–92% w/o RBV, 96% w/ RBV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4#</td>
<td></td>
<td>2</td>
<td>Genotype 2: 7 of 8 (88%) w/o RBV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(9)</td>
<td></td>
<td>3</td>
<td>Genotype 3: needs RBV (85%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>Genotype 4: 6 of 6 w/o RBV, 2 of 2 w/ RBV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>Genotype 6: 1 of 1 (only 1 included)</td>
</tr>
<tr>
<td>SOF/LDV + RBV</td>
<td>12 weeks</td>
<td>SOLAR-1</td>
<td>B</td>
<td>1 or 4</td>
<td>CPT B: 87%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3)</td>
<td></td>
<td>C</td>
<td>CPT C: 86%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOLAR-2</td>
<td>B</td>
<td></td>
<td>CPT B: 87%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4)</td>
<td></td>
<td>C</td>
<td>CPT C: 85%</td>
</tr>
<tr>
<td>SOF + DCV + RBV</td>
<td>12 weeks</td>
<td>ALLY-1</td>
<td>B</td>
<td>1, 2, 3, 4</td>
<td>CPT B: 94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* (5)</td>
<td></td>
<td>C</td>
<td>CPT C: 56%</td>
</tr>
</tbody>
</table>

#, genotype 1–6 included but failed to recruit any HCV genotype 5; *, genotypes 1–6 included but failed to recruit any HCV genotype 5 or 6; †, one HCV genotype 6 enrolled who also attained SVR with 24 weeks of SOF/VDP. SVR, sustained virologic response; SOF, sofosbuvir; VDP, velpatasvir; RBV, ribavirin; LDV, ledipasvir; DCV, daclatasvir; CPT, Child-Pugh-Turcotte.

Chua J, Ann Transl Med 2016
Comparison of direct acting antiviral therapies for chronic hepatitis C with decompensated cirrhosis

HCV Research, UK, significant risk of death or irreversible damage from HCV infection within 12 months

Fig. 2. Sustained virological response rates at 12 weeks post therapy for patients with decompensated cirrhosis. Error bars represent 95% confidence intervals. SOF, sofosbuvir; DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin.

Foster G, J Hepatol 2016
DAAs in decompensated cirrhosis
Open questions
The reason **not well defined**

**Significant portal hypertension** may reduce hepatic exposure of DAAs by **significant porto-systemic shunting**.

Advanced cirrhosis may alter the **metabolism** of DAAs in the liver

*Pinzani M, 2016*
Limitations of the studies

- Lack of control groups

- Effects on the clinical aspects not well represented

- Patients with significant advanced liver disease were
  - either excluded or,
  - if included, their numbers were extremely low

✓ 2 Solar studies, CTP < 12
✓ Ally-1 study, only 4 pts meld score >20
✓ In a UK real-world study only (Foster G, J Hepatol 2016) only 15 patients had a MELD score >20
SVR12 rate lower for CP B/C vs CP A (78% vs 94%; \( P < .001 \))

- SAE incidence higher for CP B/C vs CP A (50% vs 11.7%; \( P < .001 \))
- Death rate higher for CP B/C vs CP A (6.4 % vs 0.9%; \( P < .001 \))

<table>
<thead>
<tr>
<th>Predictor</th>
<th>SAE</th>
<th>Death (On Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>Multiv. ( P ) Value</td>
</tr>
<tr>
<td>CP A vs B/C</td>
<td>2.16 (1.29-3.64)</td>
<td>.004</td>
</tr>
<tr>
<td>MELD</td>
<td>1.31 (1.2-1.43)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>MELD ( \geq 18 )</td>
<td>NR</td>
<td>.171</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.99 (0.98-0.99)</td>
<td>.008</td>
</tr>
<tr>
<td>Platelets ( &lt; 100,000 )</td>
<td>2.94 (1.8-4.8)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>
Treatment regimens comprising an NS3-4A protease inhibitor, such as simeprevir, ritonavir-boosted paritaprevir or grazoprevir, should not be used in patients with Child-Pugh B decompensated cirrhosis or with compensated cirrhosis but with previous episodes of decompensation and are contraindicated in patients with Child-Pugh C decompensated cirrhosis, because of the substantially higher protease inhibitor concentrations in these patients.
Lactic acidosis in patients with hepatitis C virus cirrhosis and combined ribavirin/sofosbuvir treatment

- SOF ± RBV
- 5/35 (14%) during therapy
- associated with hepatic decompensation including renal failure and infection
- severe (pH <7.3) in two patients.

Welker M, J Hepatol 2016

- mitochondrial toxicity unlikely

Hoofnagle J, Editorial, J Hepatol 2016
How soon may liver function improvement be expected?

- without decreased of mortality and rates of liver transplantation
- maybe due to the short f.u

  Mans M, Lancet Infect Dis, 2016

- HBV, CTP-B shorter time for a 2-point reduction in CTP score (5.9 vs. 14 months) vs CTP-C

  Bae S, JGH 2005

- severity of liver disease a more relevant determinant of early mortality than SVR

  Charlton M, Gastroenterology 2015

- adverse event free survival among treated patients with CTP-C or a MELD score >14 poor

  Cheung M. J Hepatol 2016
HCC Risk Persists After DAA Therapy in Pts With HCV-Related Cirrhosis

- Retrospective analysis of 344 HCV-infected pts with CP A or B cirrhosis treated with DAAs (SVR: 89%)
  - Pts followed for 12-24 wks after treatment completion
  - No HCC at baseline, but previous HCC permitted
- Overall HCC incidence after DAA therapy: 7.6%
  - In pts without previous HCC: 3.2%
  - In pts with previous HCC: 29.0%

- More advanced liver disease and previous HCC significant risk factors for HCC after DAAs

<table>
<thead>
<tr>
<th>Factor</th>
<th>No HCC (n = 318)</th>
<th>HCC (n = 26)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP class B, %</td>
<td>10.1</td>
<td>26.9</td>
<td>.02</td>
</tr>
<tr>
<td>Mean liver stiffness, kPa</td>
<td>23.2</td>
<td>28.1</td>
<td>.01</td>
</tr>
<tr>
<td>Liver stiffness, n</td>
<td></td>
<td></td>
<td>.005</td>
</tr>
</tbody>
</table>
  - kPa < 21.3            | 134              | 5            |         |
  - kPa > 21.3            | 101              | 16           |         |
| Mean platelets, x 1000/mm³ | 124.4       | 102.3        | .02     |
| Previous HCC, n         |                  |              | .0001   |
  - Yes                   | 42               | 17           |         |
  - No                    | 276              | 9            |         |

Multicenter study in Spain, 58 pts

Single center study in Italy, 59 pts

recurrences 28% and 29% vs

ANRS, 6-month recurrence rate was

n = 189, 10.6% - n=267 untreated, 18.7%
Changes in MELD scores following the HCV treatment in patients with decompensated cirrhosis

(A)

<table>
<thead>
<tr>
<th>Regimens</th>
<th>n*</th>
<th>SVR</th>
<th>Improved</th>
<th>Unchanged</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF-LDV + RBV [16]</td>
<td>94</td>
<td>87%</td>
<td>63 (67%)</td>
<td>15 (16%)</td>
<td>16 (17%)</td>
</tr>
<tr>
<td>SOF-LDV + RBV[17]</td>
<td>136</td>
<td>83%</td>
<td>96 (71%)</td>
<td>18 (13%)</td>
<td>22 (16%)</td>
</tr>
<tr>
<td>SOF + DCV + RBV[18]</td>
<td>56</td>
<td>83%</td>
<td>25 (45%)</td>
<td>12 (21%)</td>
<td>19 (34%)</td>
</tr>
<tr>
<td>SOF + NS5A ± RBV [36]</td>
<td>220</td>
<td>75%</td>
<td>134 (61%)</td>
<td>33 (15%)</td>
<td>53 (24%)</td>
</tr>
<tr>
<td>GRZ-EBV[26]</td>
<td>27</td>
<td>90%</td>
<td>11 (41%)</td>
<td>10 (37%)</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>SOF-VLP ± RBV[28]</td>
<td>250</td>
<td>88%</td>
<td>136 (54%)</td>
<td>52 (21%)</td>
<td>62 (25%)</td>
</tr>
<tr>
<td>SOF + DCV + SMV[40]</td>
<td>18</td>
<td>100%</td>
<td>15 (83%)</td>
<td>0</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Total</td>
<td>801</td>
<td></td>
<td>480 (60%)</td>
<td>140 (17%)</td>
<td>181 (23%)</td>
</tr>
</tbody>
</table>

(B)

<table>
<thead>
<tr>
<th>Changes in MELD (points)</th>
<th>n (%)*</th>
<th>Changes in MELD (points)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved MELD (n = 480):</td>
<td></td>
<td>Worsened MELD (n = 181):</td>
<td></td>
</tr>
<tr>
<td>median -2 points (range 1–17)</td>
<td></td>
<td>median + 1 point (range 1–13)</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>148 (31%)</td>
<td>+ 1</td>
<td>98 (54%)</td>
</tr>
<tr>
<td>-2</td>
<td>125 (26%)</td>
<td>+ 2</td>
<td>50 (28%)</td>
</tr>
<tr>
<td>-3</td>
<td>95 (20%)</td>
<td>+ 3</td>
<td>14 (8%)</td>
</tr>
<tr>
<td>-4</td>
<td>44 (9%)</td>
<td>+ 4</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>-5</td>
<td>32 (6.5%)</td>
<td>+ 5</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>≥6</td>
<td>36 (7.5%)</td>
<td>+ ≥6</td>
<td>9 (5%)</td>
</tr>
</tbody>
</table>
Reversion of disease manifestations after HCV eradication

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients evaluated</td>
<td>93</td>
<td>81</td>
<td>39</td>
<td>250</td>
</tr>
<tr>
<td>Time at evaluation</td>
<td>SVR-4</td>
<td>SVR-24</td>
<td>SVR-12</td>
<td>SVR-12</td>
</tr>
<tr>
<td>MELD changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>67%</td>
<td>73%</td>
<td>40%</td>
<td>54%</td>
</tr>
<tr>
<td>In CTP-B cirrhosis</td>
<td>64%</td>
<td>65%</td>
<td>43%</td>
<td>54%</td>
</tr>
<tr>
<td>In CTP-C cirrhosis</td>
<td>70%</td>
<td>83%</td>
<td>67%</td>
<td>-</td>
</tr>
<tr>
<td>Worsening</td>
<td>17%</td>
<td>16%</td>
<td>40%</td>
<td>25%</td>
</tr>
<tr>
<td>In CTP-B cirrhosis</td>
<td>17%</td>
<td>20%</td>
<td>43%</td>
<td>25%</td>
</tr>
<tr>
<td>In CTP-C cirrhosis</td>
<td>18%</td>
<td>11%</td>
<td>0%</td>
<td>-</td>
</tr>
</tbody>
</table>

CTP, Child-Turcotte-Pugh score; DAA, direct-acting antiviral; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; SVR, sustained virological response (at 4; 12 or 24 weeks after DAA therapy).

van der Meer A, J Hepatol 2016
Hepatic decompensation during the course of direct-acting antiviral therapy of hepatitis C

- various times
  - early
  - late
  - shortly after stopping

- typically marked by worsening jaundice and signs of hepatic failure with minimal changes in serum aminotransferase or alkaline phosphatase levels.

Charlton M, Gastroenterology 2015
Saxena V, Hepatology 2015
Kalafeteli M, J Gastrointestin Liver Dis 2015
Stine JG, Dig Dis Sci 2014
Dyson JK, J Hepatol 2016
Hepatic decompensation during the course of direct-acting antivi-ral therapy of hepatitis C

- all-oral regimens - not caused by direct toxicity
- unrelated to therapy and coincidental ?
  - part of the natural history
- rapid clearance of HCV infection with
  - downregulation of the chronically activated innate and adaptive immune systems

BUT no control group

Hoofnagle J, J Hepatol 2016
Potential paradoxical consequence of DAA therapy

‘MELD purgatory’

• not progress to a stage where LT is indicated.

• might lose eligibility or priority for LT

• Even if their life-expectancy improves in the short-term,
  ➢ not recover to any meaningful extent
  ➢ may be left without access to transplantation but with a poor QOL
  life

‘MELD purgatory’

van der Meer A, J Hepatol 2016
• a point where antiviral therapy was less effective in improving liver function.

• Ally-1, CPT-C lower SVR (56%) vs CPT-A (92%) and B (94%)
  Poordad F, Hepatology 2016

• Solar 2, most common reason for non-SVR in the CPT-C patients was death from progressive liver failure
  Manns M, J Hepatol 2015

• “point of no return” has also been illustrated in HBV
• MELD >20 were considered too sick and were not inactivated or delisted
  
  Belli L, J Hepatol 2016

• Many centers don’t currently list liver candidates until MELD >20
  - the listed candidates will not be inactivated or delisted after SVR

• 1/3 deaths in waiting list deaths occur in the low- MELD group

• In long-term follow-up will the inactivated and delisted patients still die of liver decompensation or HCC or get re-listed for transplantation? inactivation and delisting might actually be harmful!
  
  Everson G, J Hepatol 2016
Optimal Timing of Hepatitis C Treatment for Patients on the Liver Transplant Waiting List

Figure 2. Comparison of life expectancy by MELD score under pre-LT versus post-LT treatment of hepatitis C in decompensated cirrhosis patients on the waiting list.

Figure 3. Difference in life years if HCV is treated pre-LT versus post-LT in patients with decompensated cirrhosis on the transplant waiting list. The error bars represent 95% confidence interval generated by probabilistic sensitivity analysis. Patients having MELD ≤ 27 will benefit from pre-LT HCV treatment (shown by the shaded region).

Chhatwal J, Hepatology 2016
• Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score $\geq 18-20$ should be transplanted first and treated after transplantation.

• If the waiting time is more than 6 months, these patients can be treated before transplantation

• Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities
ΚΑΤΕΥΘΥΝΤΗΡΙΕΣ ΟΔΗΓΙΕΣ ΧΡΗΣΗΣ ΝΕΟΤΕΡΩΝ ΑΝΤΙΙΚΩΝ ΦΑΡΜΑΚΩΝ ΣΕ ΛΟΙΜΩΞΗ ΜΕ ΤΟΝ ΙΟ ΤΗΣ ΗΠΑΤΙΤΙΔΑΣ C

• Η κύρια αντιμετώπιση παραμένει η μεταμόσχευση ήπατος

• Αντιική θεραπεία, MELD ≤20,
• μπορεί και MELD >20, εφόσον υπάρχει μικρή πιθανότητα μεταμόσχευσης ήπατος εντός 6 μηνών

• SOF/LDV (γονότυπος 1, 4, 5, 6)
• SOF και DCV ή SOF/VEL (γονότυπος 1, 2, 3, 4, 5, 6).
• 12 εβδομάδες
• προτείνεται RBV

• Όχι αναστολείς πρωτεάσης

ΕΕΜΗ, 01/17
Pros of treating patients with end-stage liver disease

- SVR!
- Liver function often improves
- Improve QOL on wait list
- May reverse symptoms of decompensation
Pros of treating patients with end-stage liver disease

- May prevent death on the waiting-list
- May obviate the need for LT
- Save an organ thus benefiting the organ pool
- Prevent post-LT HCV recurrence
- Drug-drug interactions post-LT

✓ May be the only option in situations where LT is unavailable or contraindicated
Cons of treating patients with end-stage liver disease

- SVR rates are lower
- Tolerability of RBV limited
- Renal dysfunction makes treatment more difficult
- Patients with SVR may end up in MELD purgatory
Cons of treating patients with end-stage liver disease

• Removes option of anti-HCV positive donor (longer wait times)

• Excellent therapies available to treat post-LT, high SVR rates

• Still at risk of progressive liver disease

• Still at risk of hepatocellular carcinoma

• In those who failed therapy, exposure to NS5A inhibitors may compromise the SVR rates when retreating after LT
Conclusions

- Safe but fewer treatment options available (Protease inhibitors contraindicated)

- Improved with longer therapy and/or adding RBV

- SVR may prevent further decompensation but uncertain whether the severe fibrosis could be reversed
  - Might need more time to see effect of SVR

- Pros and cons!

- MELD purgatory

- Careful consideration of severity of decompensation, waiting time, donor options