Therapy in HCV Cirrhosis

• Definitions:
  – Compensated
  – Decompensated

• Anticipated effect of SVR
• Response to currently available therapies
• Does portal hypertension improve with SVR?
Compensated vs Decompensated Cirrhosis

- Patients with Decompensated Cirrhosis have portal htn and/or one or more of the following complications
  - Ascites (HRS, hepatic hydrothorax)
  - HE
  - Varices (esophageal, gastric)
  - Portal Hypertensive Gastropathy
  - HCC?
Compensated cirrhosis

survival probability

A

% 100

HBsAg +

anti-HCV +

months

0 12 24 36 48 60 72 84 96 108 120

patients at risk

HBsAg+ 161 153 136 126 116 102 90 71 51 33 19

anti-HCV+ 136 133 122 111 107 90 80 65 50 34 21

Fattovich G et al Am J Gastroenterol. 2002;97(11):2886-95
Survival probability of decompensated cirrhosis.

- HBsAg +
- anti-HCV +

Fattovich G et al. Am J Gastroenterol. 2002;97(11):2886-95
Baveno IV International Consensus Workshop Staging System for Cirrhosis: 1-Year Outcome Probabilities

Stage 1
- NO VARICES
  - NO ASCITES

Stage 2
- VARICES
  - NO ASCITES
  - 7%

Stage 3
- ASCITES ± VARICES
  - 6.6%

Stage 4
- BLEEDING ± ASCITES
  - 7.6%

Compensated
- 1%

Decompensated
- 3.4%

DEATH
- 20%

- 4%

- 4.4%

- 57%

Effect of SVR
SVR Reduced HCC and Liver-Related Complications in Patients With Bridging Fibrosis or Cirrhosis

307 HCV patients with bridging fibrosis (n=127) or cirrhosis (n=180) were evaluated by Cox regression analysis. Non-SVR in 67% of patients treated with pegylated interferon plus ribavirin. Median follow-up: 3.5 years.

SVR Reduced Risk of All-Cause Mortality

Retrospective analysis of veterans who received pegylated interferon plus ribavirin at any VA medical facility (2001-2008).
SVR=sustained virological response.
SVR Associated with Decreased All-Cause Mortality

530 patients with advanced fibrosis, treated with interferon-based therapy, and followed for 8.4 (IQR 6.4-11.4) years

van der Meer et al. JAMA 2012; 308:2584
COMPENSATED CIRRHOSIS
Effect of Tx Duration and RBV in Cirrhotic GT1 Pts (LDV/SOF)

- Pooled data (LONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, SIRIUS)
- No difference in SVR rate by HCV subtype

Effect of Tx Duration and RBV in Cirrhotic, PI-Experienced, GT1 Pts (LDV/SOF)

![Bar chart showing SVR12 (%) for 12 wks of LDV/SOF + RBV and 24 wks of LDV/SOF]

- 12 wks of LDV/SOF + RBV: 96 SVR12 (%)
- 24 wks of LDV/SOF: 97 SVR12 (%)

Pts with previous IFN, riba boceprevir, telaprevir, simeprevir, or faldaprevir

TURQUOISE II: Effect of Tx Duration in Cirrhotic GT1 Pts (OMV/PTV/RTV + DSV)

## Daclatasvir and Sofosbuvir ± RBV in Pts With GT 1 HCV

<table>
<thead>
<tr>
<th>Phase</th>
<th>Regimen</th>
<th>GT1 SVR, %</th>
<th>GT1 Baseline Cirrhosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>12 wks DCV + SOF + RBV (ALLY-1)(^{[1]})</td>
<td>82 (advanced cirrhosis)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95 (posttransplantation)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>8-12 wks DCV + SOF (ALLY-2)(^{[2]})</td>
<td>76 (8 wks; naive)</td>
<td>&lt; 18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96 (12 wks; naive)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>98 (12 wks; tx exp’d)</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>12-24 wks DCV + SOF ± RBV(^{[3]})</td>
<td>98 (12 wks; naive)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 (24 wks; naive)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>98 (24 wks; tx exp’d)</td>
<td></td>
</tr>
</tbody>
</table>

OPTIMIST-2 (Phase III): SVR12
SMV+SOF for 12 Weeks in Cirrhotics

SMV+SOF x 12 wks insufficient for GT1 cirrhatics

Lawitz E, et al. EASL 2015, Vienna. #LP04
DECOMPENSATED CIRRHOSIS
Study Design
GT 1 and 4, CPT Class B and C

- 108 patients randomized 1:1 to 12 or 24 weeks of treatment
- GT 1 or 4 treatment-naïve or -experienced patients with decompensated cirrhosis (CPT class B [score 7-9] or C [score 10–12]*)
- Broad inclusion criteria
  - No history of major organ transplant, including liver
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤10 mg/dL, hemoglobin ≥ 10 g/dL
  - CL_{cr} ≥40 mL/min, platelets >30,000 x 10^3/µL
- Stratified by CPT class B or C

Charlton et al Gastro 2015;149:649-659

*Patients with CPT scores 13-15 excluded.
## Results: Baseline Characteristics

**GT 1 and 4, CPT Class B and C**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CPT B 12 Weeks n=30</th>
<th>CPT B 24 Weeks n=29</th>
<th>CPT C 12 Weeks n=23</th>
<th>CPT C 24 Weeks n=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD score, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>6 (20)</td>
<td>8 (28)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10–15</td>
<td>21 (70)</td>
<td>16 (55)</td>
<td>16 (70)</td>
<td>13 (50)</td>
</tr>
<tr>
<td>16-20</td>
<td>3 (10)</td>
<td>5 (17)</td>
<td>7 (30)</td>
<td>12 (46)</td>
</tr>
<tr>
<td>21-25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Ascites, n (%)</td>
<td>17 (57)</td>
<td>17 (59)</td>
<td>22 (96)</td>
<td>25 (96)</td>
</tr>
<tr>
<td>Encephalopathy, n (%)</td>
<td>20 (67)</td>
<td>16 (55)</td>
<td>21 (91)</td>
<td>23 (88)</td>
</tr>
<tr>
<td>Median bilirubin, mg/dL (range)</td>
<td>2.0 (0.6-5.5)</td>
<td>1.4 (0.8-4.5)</td>
<td>2.9 (1.2-14.5)</td>
<td>3.8 (1.1-5.7)</td>
</tr>
<tr>
<td>Median albumin, g/dL (range)</td>
<td>2.9 (2.1-3.7)</td>
<td>3.0 (2.2-3.4)</td>
<td>2.6 (1.6-3.5)</td>
<td>2.6 (2.0-3.3)</td>
</tr>
<tr>
<td>Median INR (range)</td>
<td>1.3 (1.0-1.5)</td>
<td>1.3 (1.0-2.6)</td>
<td>1.4 (1.2-1.9)</td>
<td>1.4 (1.1-2.2)</td>
</tr>
<tr>
<td>Median platelets, x 10^3 μL (range)</td>
<td>88 (36-212)</td>
<td>73 (30-154)</td>
<td>81 (39-177)</td>
<td>71 (32-179)</td>
</tr>
<tr>
<td>Median hemoglobin, g/dL (range)</td>
<td>13.1 (9.7-16.3)</td>
<td>13 (9.9-15.4)</td>
<td>12.3 (10.6-14.9)</td>
<td>12.6 (7.5-15.8)</td>
</tr>
<tr>
<td>Median CL_Cr, mL/min (range)</td>
<td>98 (34-166)</td>
<td>81 (45-148)</td>
<td>77 (36-114)</td>
<td>78 (54-150)</td>
</tr>
</tbody>
</table>
Results: SVR12
GT 1 and 4, CPT Class B and C

LDV/SOF + RBV 12 Weeks
LDV/SOF + RBV 24 Weeks

SVR12 (%)

Overall
CPT B
CPT C

LDV/SOF + RBV 12 Weeks
LDV/SOF + RBV 24 Weeks

3 relapses
1 death
1 relapse
2 deaths
1 relapse
1 death
1 LTFU
1 relapse
1 death

45/52
42/47
26/30
24/27
19/22
18/20
Laboratory Results: MELD Score
Change From Baseline to Follow-Up Week 4

CPT B
12 wk (n=30)*
24 wk (n=29)*

CPT C
12 wk (n=23)*
24 wk (n=26)*

*Missing FU-4: n=2 CPT B 12 wk; n=4 CPT B 24 wk; n=2 CPT C 12 wk; n=7 CPT C 24 wk.
Laboratory Results: Median (IQR) Total Bilirubin Change From Baseline to Follow-Up Week 4

12 Weeks

1. **CPT B**
   - Baseline: [Graph with median (IQR) values]
   - PT Wk 4: [Graph with median (IQR) values]
   - p <0.008

2. **CPT C**
   - Baseline: [Graph with median (IQR) values]
   - PT Wk 4: [Graph with median (IQR) values]
   - p <0.002

24 Weeks

3. **CPT B**
   - Baseline: [Graph with median (IQR) values]
   - PT Wk 4: [Graph with median (IQR) values]
   - p <0.005

4. **CPT C**
   - Baseline: [Graph with median (IQR) values]
   - PT Wk 4: [Graph with median (IQR) values]
   - p <0.001
# Results: Overall Safety Summary

**GT 1 and 4, CPT Class B and C**

## Overall Safety

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>CPT B</th>
<th></th>
<th>CPT C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AE</strong></td>
<td>12 Weeks (n=30)</td>
<td>24 Weeks (n=29)</td>
<td>12 Weeks (n=23)</td>
<td>24 Weeks (n=26)</td>
</tr>
<tr>
<td>AE</td>
<td>29 (97)</td>
<td>27 (93)</td>
<td>23 (100)</td>
<td>26 (100)</td>
</tr>
<tr>
<td>Grade 3–4 AE</td>
<td>2 (7)</td>
<td>8 (28)</td>
<td>6 (26)</td>
<td>11 (42)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>3 (10)</td>
<td>10 (34)</td>
<td>6 (26)</td>
<td>11 (42)</td>
</tr>
<tr>
<td>Treatment-related SAEs</td>
<td>2 (7)</td>
<td>0</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Treatment DC due to AE</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (3)</td>
<td>2 (7)</td>
<td>2 (9)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

- **Related SAEs:** Anemia (2), hepatic encephalopathy, peritoneal hemorrhage
- **Early discontinuations:** Sepsis, hepatic encephalopathy, peritoneal hemorrhage
- **Deaths:** septic shock (2), multi-organ failure and septic shock (2), oliguric renal failure, cardiac arrest
LDV/SOF+RBV for 12 or 24 Weeks in 329 Decompensated and Post-Liver Transplant HCV GT 1 and GT 4 Patients

Manns, EASL, 2015, GO2

- Broad inclusion criteria:
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤ 10 mg/dL, Hemoglobin ≥ 10 g/dL
  - CrCl ≥ 40 mL/min, Platelets > 30,000/mL
- RBV dosing
  - F0–F3 and CTP A cirrhosis: weight-based (< 75 kg = 1000 mg; 75 kg = 1200 mg)
  - CTP B and C cirrhosis: dose escalation, 600–1200 mg/d
### Demographics

<table>
<thead>
<tr>
<th></th>
<th>Post-Transplant</th>
<th>Pre/Post-Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 Weeks (n=86)</td>
<td>24 Weeks (n=82)</td>
</tr>
<tr>
<td></td>
<td>12 Weeks (n=78)</td>
<td>24 Weeks (n=82)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>58 (32–73)</td>
<td>60 (44–74)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>69 (80)</td>
<td>65 (79)</td>
</tr>
<tr>
<td>Median HCV RNA, log(_{10}) IU/mL (range)</td>
<td>6.5 (3.8–7.5)</td>
<td>6.5 (4.7–7.4)</td>
</tr>
<tr>
<td>GT, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>41 (48)</td>
<td>42 (51)</td>
</tr>
<tr>
<td>1b</td>
<td>34 (40)</td>
<td>30 (37)</td>
</tr>
<tr>
<td>4</td>
<td>11 (13)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>IL28B non-CC, n (%)</td>
<td>74 (86)</td>
<td>65 (79)</td>
</tr>
<tr>
<td>Prior HCV treatment, n (%)</td>
<td>72 (84)</td>
<td>65 (79)</td>
</tr>
<tr>
<td>MELD &gt; 15, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median total bilirubin, mg/dL (range)</td>
<td>0.8 (0.2-13.7)</td>
<td>0.8 (0.2-2.2)</td>
</tr>
<tr>
<td>Median albumin, g/dL (range)</td>
<td>4.0 (2.8-4.8)</td>
<td>3.9 (3.1-4.6)</td>
</tr>
<tr>
<td>Median INR (range)</td>
<td>1.0 (0.9-3.7)</td>
<td>1.0 (0.9-2.1)</td>
</tr>
<tr>
<td>Median platelets, x 10(^3)/µL (range)</td>
<td>142 (35-434)</td>
<td>134 (48-331)</td>
</tr>
<tr>
<td>Ascites, n (%)</td>
<td>3 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Encephalopathy, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Manns, EASL, 2015, GO2*
Results: SVR12

27 subjects in the 24 week arm have not reached SVR12.
7 subjects who were transplanted and 3 subjects did not meet inclusion criteria are excluded.

Error bars represent 2-sided exact 90% confidence intervals.

LDV/SOF + RBV

12 Weeks

24 Weeks

F0-F3 & CPT A
Post-Transplant

82/86

64/65

SVR12 (%)

CPT B & C
Pre and Post

61/72

60/68

85

88

95

98
SVR12

3 subjects (1 CPT B/24 Wk, 1 CPT C/12 Wk and 1 CPT C/24 Wk) excluded (transplant on study); 5 Pre-CPT C/24 Wk, 4 Post-CPT B/24 Wk and 1 post-CPT C/24 Wk subjects have not reached SVR12. Error bars represent 2-sided exact 90% confidence intervals.
MELD Score Change From Baseline to Follow-up Week 4

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

Median Total Bilirubin and Albumin
Change From Baseline to Follow-Up Week 4

F0-F3 + CPT A

Normal range (0.2-1.2)

p < 0.001

Baseline

FU Week 4

CPT B + CPT C

Normal range (3.3-4.9)

p < 0.001

Baseline

FU Week 4
## Change in CPT Class From Baseline to Follow-up Week 4

### All Cirrhotic Subjects (CPT A, B, or C)

<table>
<thead>
<tr>
<th>Follow-up Week 4 CPT</th>
<th>Baseline CPT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (5–6) n=73</td>
</tr>
<tr>
<td>A (5–6)</td>
<td>67 (96)</td>
</tr>
<tr>
<td>B (7–9)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>C (10–12)</td>
<td>0</td>
</tr>
<tr>
<td>No assessment</td>
<td>3</td>
</tr>
</tbody>
</table>
### Overall Safety Summary

<table>
<thead>
<tr>
<th>Overall Safety</th>
<th>Post-Transplant</th>
<th>Pre/Post-Transplant</th>
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<tbody>
<tr>
<td></td>
<td>F0-F3 + CPT A</td>
<td>CPT B + CPT C</td>
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<tr>
<td>Patients, n (%)</td>
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<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>

*Fall, anemia (5), vomiting, diarrhea, hyperbilirubinemia; †Edema, dehydration, HCC (2), type 2 diabetes mellitus, hyperbilirubinemia.

- No deaths were considered treatment related
Can we improve portal hypertension?

- Safety and efficacy of SOF+RBV in HCV-infected patients with portal hypertension ± decompensated liver disease

- Inclusion criteria
  - Compensated (CPT 5–6; A) or decompensated (CPT 7–9; B) cirrhosis with esophageal or gastric varices
  - Hepatic venous pressure gradient (HPVG) >6 mm Hg

<table>
<thead>
<tr>
<th>Week</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>HVPG at Day 0 and Week 48</td>
<td>Observation</td>
</tr>
<tr>
<td>24</td>
<td>SOF 400 mg + RBV 1000–1200 mg</td>
<td>SOF 400 mg + RBV 1000–1200 mg</td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72</td>
<td></td>
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<tr>
<td>96</td>
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</tbody>
</table>

Afdhal N, et al. EASL 2015, Vienna. #LP13
Effect of SOF + RBV on HVPG in HCV-infected patients with cirrhosis and portal hypertension

Completed treatment n=20
Paired HVPG measurements n=19*

SOF + RBV 48-wk n=21
Completed treatment n=19
Paired HVPG measurements for treatment period n=18*

Arm 1
SOF + RBV 48-wk n=25
Completed treatment n=20

Arm 2
Observation 24-wk n=25
Completed treatment n=19

D/C treatment (5)
• AE (2)
• Efficacy failure (2)
• Withdrew consent (1)

Not randomized (13)

Screened N=63
Randomized n=50

Completed treatment n=20

SOF + RBV 48-wk n=21
Completed treatment n=19

Patients who did not achieve SVR12
CP A: 1 relapsed, 1 early d/c due to AE, 1 lost to follow-up, and 1 withdrew consent
CP B: 6 relapsed, 1 breakthrough, 1 non-responder, and 1 early d/c due to AE

Overall 33/46
CP A 14/18
CP B 19/28

Afdhal N, et al. EASL 2015, Vienna. #LP13
Effect of SOF + RBV on HVPG in HCV-infected patients with cirrhosis and portal hypertension

Median total albumin and bilirubin at baseline and follow-up Week 4

- **Baseline**
  - Median total albumin: 3.3–4.9 g/dL
  - p<0.0001
  - Normal range total albumin: 3.3–4.9 g/dL

- **f/u 4**
  - Median total albumin:
  - Normal range total albumin: 0.2–1.2 mg/dL
  - p<0.0001

Arms 1 and 2: HVPG change over observation and 48-week treatment periods

- **Observation**
  - Arm 1 Wk/Arm 2 Wk
  - Observation
  - Start treatment
  - End treatment

- **Start treatment**
  - 0/24

- **End treatment**
  - 48/72

Afdhal N, et al. EASL 2015, Vienna. #LP13
HVPG % change after treatment in subset of patients with baseline HVPG ≥12 mm Hg

- Effect of SVR12 and long-term viral suppression/cure on HVPG may manifest later, and is being explored in these patients 1 year post-treatment

Afdhal N, et al. EASL 2015, Vienna. #LP13
Sofosbuvir
183 patients

12 weeks
N=50

Ribavirin
N=25
SMV N=1
LDV N=4
DCV N=7
SOF+RBV N=13

No ribavirin
N=25
SMV N=8
LDV N=4
DCV N=13

24 weeks
N=133

Ribavirin
N=74
SMV N=2
LDV N=6
DCV N=38
SOF+RBV N=28

No ribavirin
N=59
SMV N=0
LDV N=4
DCV N=55

*DCV: daclatasvir; LDV: ledipasvir; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Coilly et al AASLD 2015
Virological responses

Overall population: 84%
Cirrhosis: 88%
HCC: 80%

SVR12

A: 83% (66/80)
B: 85% (39/46)
C: 84% (31/37)

p=ns

CHILD PUGH
Clinical and biological responses (CBR)

**HCC. N=70**
- Complete response*: 30%
- Partial response**: 13%
- No response: 57%

** Decompensated Cirrhosis. N=53**
- 72% Child A
- 21% Child B
- 25% Child C

---

* Total bilirubin < 35µmol/L + PT>50% + albumin>35g L + no ascites + no hepatic encephalopathy
** Child Class Change
Performance to predict complete CBR in cirrhotic patients

Childs A/B or MELD < 10-15

AUC for Child-Pugh score: 0.814

<table>
<thead>
<tr>
<th>7.5 value of Child-Pugh Score</th>
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<tbody>
<tr>
<td>Se</td>
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<tr>
<td>79%</td>
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</tbody>
</table>
Summary

• Natural history is very different when comparing compensated vs decompensated cirrhotics
• SVR is excellent and improves outcomes in patients with cirrhosis
• Improvement in portal HTN after SVR remains elusive
  – Might only be achieved in pts with low MELD score
  – Might need more time to see effect of SVR