Approved regimens for cirrhotic patients

Amsterdam, 4-5 december 2015
In the next 10 yrs, the number of decompensated cirrhosis will increase by 4.

Deuffic-Burban et al, Gastroenterology 2012
Increasing Prevalence of Cirrhosis among US Adults with Chronic HCV Infection

- APRI > 2.0:
  - Era 2 (1999-2006): 7.6%
  - Era 3 (2007-2012): 17%

- FIB-4 > 3.25:
  - Era 1 (1988-1994): 8.6%
  - Era 2 (1999-2006): 10.2%
  - Era 3 (2007-2012): 16%

Associated with aging and metabolic syndrome.

Prowpanga U, AASLD 2015, Abstract 88
Case 1. Fibrosis 4

63 yrs old man. HCV genotype 1b. Naïve.
Asymptomatic
Blood transfusion 35 yrs before
Liver biopsy 20 yrs before: chronic active hepatitis
Fibroscan: 15 kpas
Elevated transaminases (ALT 87 IU, AST 68 IU)
Upper endoscopy: normal
Lack of comorbidities

3 cm HCC detected on screening US------RF------Complete RX response
Case 1. Fibrosis 4

63 yrs old man  **HCV genotype 1a**  Treatment experienced*

  - Asymptomatic
  - Blood transfusion 35 yrs before
  - Liver biopsy 20 yrs before: chronic active hepatitis
  - Fibroscan: 15 kpas
  - Elevated transaminases (ALT 87 IU, AST 68 IU)
  - Upper endoscopy: normal
  - Lack of comorbidities

*- 2005: pegIFN + RBV at optimal doses----Partial Response
- 2012: Triple therapy with telaprevir, pegIFN, RBV---- Response with relapse
Case 2. Compensated cirrhosis with portal HPT

63 yrs old man. HCV genotype 1a. IL28B CT. Asymptomatic

Two prior failed therapies:
- 2005: pegIFN + RBV at optimal doses----Partial Response
- 2012: Triple therapy with telaprevir, pegIFN, RBV---- Response with relapse

Fibroscan: 19 kpas

Upper endoscopy: small EV

Laboratory tests: ALT 87 IU, AST 68 IU, GGT 69 IU, Hgb 12.5 g/dl, platelet count 78,000/u

Child A, MELD score 8

Comorbidities: IDDM, depression (citalopram)
Case 3. Decompensated cirrhosis

HCV genotype 1a. IL28B CT.
Two prior failed therapies:
- 2007: pegIFN + RBV at optimal doses----Null Response
- 2011: Triple therapy with telaprevir, pegIFN, RBV----premature D/C. Relapse

Upper endoscopy: large EV (prophylaxis - B-blocker)
Ascites (spironolactone 200 mg + furosemide 40 mg/day)
Laboratory tests: ALT 87 IU, AST 68 IU, GGT 69 IU, Hgb 11.5 g/dl, platelet count 30,000/u; Bilirubin 3.2 mg/dl, Albumin 2.7 mg/dl, INR 1.7, creatinine 1.5 mg/dl
MELD score 20, Child C
## Natural history of HCV cirrhosis

<table>
<thead>
<tr>
<th>Histology</th>
<th>F1–F3</th>
<th>F4 (Cirrhosis)</th>
<th>Major Descompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>No cirrhosis</td>
<td>Compensated</td>
<td>Decompensated</td>
</tr>
<tr>
<td>Symptoms</td>
<td>None</td>
<td>None (no varices)</td>
<td>No (varices present)</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVPG</td>
<td>&gt;6</td>
<td>≥10</td>
<td>≥12</td>
</tr>
<tr>
<td>HCS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biology</td>
<td>Fibrogenesis and neovascularization</td>
<td>Scar &amp; cross linking</td>
<td>Thick scars &amp; nodules</td>
</tr>
</tbody>
</table>

**Increasing fibrogenesis**

**Increasing vasodilatation**

**Worsening liver function**

---

HCS: hyperdynamic circulatory status; HE: hepatic encephalopathy; HRS: hepatorenal syndrome; HVPG: hepatic venous gradient; RA: refractory ascites; SBP: spontaneous bacterial peritonitis;

Modified from Friedman SL. Gastroenterology 2008;134:1655–69
Agenda

- Aims / Benefits of antiviral therapy in the cirrhotic population
- Treatment of the cirrhotic patient with DAAs
Agenda

- **Aims / Benefits of antiviral therapy in the cirrhotic population**

- **Treatment of the cirrhotic patient with DAAs**
Goals of antiviral therapy in the cirrhotic population

- Compensated cirrhosis:
  - Reduce rates of decompensation
  - Reduce rates of HCC development/HCC recurrence?
  - Reversal of cirrhosis

- Decompensated cirrhosis:
  - Improve survival while in the WL for LT
  - Prevent HCV recurrence post-LT
  - Improve clinical condition and reduce the need for LT
HCV & Therapy: effects on outcome


Changes in Fibrosis

- Pretreatment
- Posttreatment


N=530

Liver-related mortality or liver transplantation

N=530

P <0.01


Effect of SVR on the risk of LT, HCC, death

Meta-analysis of 129 studies in 34,563 patients with HCV (mean FU ≈ 5 yrs)

- LT
  - General: 2.2
  - Cirrótico: 0.2
  - Coinfectad.: 0.6
  - SVR: 7.3
  - NR: 2.7

- Death
  - General: 4.5
  - Cirrótico: 3.6
  - Coinfectad.: 1.3
  - SVR: 10.5
  - NR: 11.3
  - General: 10

- HCC
  - General: 2.9
  - Cirrótico: 5.3
  - Coinfectad.: 0.9
  - SVR: 9.3
  - NR: 13.9

Hill et al, AASLD 2014 (abst 44)
Fibrosis Regression Among Patients Achieving SVR with DAA Therapy*

N=100, followed prospectively with Fibroscan® every 6 mos

Change in Stage (estimated by TE)

60%

Time to Regression

F3-4 at Baseline

Median: 2.5 yrs

Cirrhosis at Baseline

Median: 3.0 yrs

*82% DAA; 45% SOF-based therapy

Crislien AM, AASLD Abstract 108
SVR Associated with Fewer Cirrhosis-Related Complications

- Multicenter study of patients with compensated/decompensated cirrhosis treated with SMV/SOF ±RBV for 12-24 wks; 84% achieved SVR
- Compared to 269 untreated/non-SVR matched controls
- Median MELD=9 and CP score 6

Bivariate Cox Regression Analysis of Factors Associated with Liver Transplantation / Death

<table>
<thead>
<tr>
<th>Covariate</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-SVR/untreated (vs. SVR)</td>
<td>6.9 (1.02 - 51.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>CP-B/C (vs. CP-A)</td>
<td>1.8 (1.03 - 3.7)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Saxena et al. AASLD 2015, Abstract #1825
Aims / Benefits of antiviral therapy in the cirrhotic population

Treatment of the cirrhotic patient with DAAs
Treatment of the compensated cirrhotic patient with DAAs

- HCV genotype
- PK profile of treatment
- Prior treatment response
- Patient comorbidities (i.e.: renal impairment,..)
- Drug-Drug interactions
- Severity of liver impairment

Compensated cirrhosis
## Factors Associated with Lower SVR Rates with LDV-SOF in Genotype 1 Patients

<table>
<thead>
<tr>
<th>Population (Abstract)</th>
<th>N</th>
<th>Key Characteristics</th>
<th>Predictors of Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA (Backus, Abstract 93)</td>
<td>3763</td>
<td>Treatment-naïve</td>
<td>• African-American race</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29% cirrhosis</td>
<td>• Advanced fibrosis (FIB-4&gt;3.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37% AA</td>
<td>• 8 Wks treatment</td>
</tr>
<tr>
<td>TRIO (Curry, Abstract 1108;Afdhal, Abstract LB17)</td>
<td>895</td>
<td>Treatment-naïve Non-cirrhotics 18% AA</td>
<td>• Academic center</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• African-American race</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Low platelet count</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Type of DAA therapy</td>
</tr>
<tr>
<td>HCV-Target (Terrault, Abstract 94)</td>
<td>969</td>
<td>53% Treatment naïve 38% cirrhosis 20% AA</td>
<td>• PPI use at start of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Low albumin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Elevated bilirubin</td>
</tr>
</tbody>
</table>
TRIO: SVR12 Influenced by Type of Treatment, Presence of Cirrhosis (platelet count <100K) and Treatment Setting

Afdhal N, AASLD 2015, LB17
Possible Mechanisms for Decreased Response in Cirrhosis

• Drug toxicity
  Increased adverse events with early discontinuation

• Drug delivery
  Intrahepatic shunting with decreased exposure in hepatocytes

• Drug uptake/metabolism
  Altered cytochrome p450 function

• Altered Immune function
  Reduced Kupffer cell mass
  Altered cytokine milieu
- Of 513 patients, 20 failed to achieve SVR12
  - 18 relapsed
  - 1 LTFU, 1 death (presumed infection)
### SOF/LDV ± RBV 12-24 weeks

<table>
<thead>
<tr>
<th>Duration/ ± RBV</th>
<th>Total</th>
<th>Treatment Naïve</th>
<th>Treatment Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall SVR12</td>
<td>96%</td>
<td>98%</td>
<td>95%</td>
</tr>
<tr>
<td>12 wk</td>
<td>95%</td>
<td>97%</td>
<td>94%</td>
</tr>
<tr>
<td>24 wk</td>
<td>98%</td>
<td>99%</td>
<td>98%</td>
</tr>
<tr>
<td>LDV/SOF</td>
<td>95%</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>97%</td>
<td>99%</td>
<td>96%</td>
</tr>
<tr>
<td>LDV/SOF 12 wk</td>
<td>92%</td>
<td>96%</td>
<td>90%</td>
</tr>
<tr>
<td>LDV/SOF + RBV 12 wk</td>
<td>96%</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>LDV/SOF 24 wk</td>
<td>98%</td>
<td>97%</td>
<td>98%</td>
</tr>
<tr>
<td>LDV/SOF + RBV 24 wk</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

SVR12, %
### SVR in HCV GT1 treatment-naive and experienced cirrhotic patients

<table>
<thead>
<tr>
<th>Response</th>
<th>12-week arm</th>
<th>24-week arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>92.2%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Prior Relapse</td>
<td>93.3%</td>
<td>100%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Prior Null Response</td>
<td>80.0%</td>
<td>92.9%</td>
</tr>
</tbody>
</table>

#### SVR12, % Patients

- 59/64 (Naïve)
- 14/15 (Prior Relapse Response)
- 11/11 (Prior Partial Response)
- 40/50 (Prior Null Response)

#### 3D + RBV

- 3D: ABT-450/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid
- RBV: 1000-1200 mg/d

---

The largest impact of RAVs on treatment outcome was observed in patients with cirrhosis treated for 24 weeks of LDV/SOF (and no ribavirin).
Sofosbuvir + RBV for G3
24 weeks therapy
Valence

ALLY-3: DCV+SOF 12 weeks
SVR12

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>All Patients</th>
<th>Naïve</th>
<th>Pretreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>105/109</td>
<td>73/75</td>
<td>32/34</td>
</tr>
<tr>
<td>Present</td>
<td>20/32</td>
<td>11/19</td>
<td>9/13</td>
</tr>
</tbody>
</table>

SVR12 (%)a

- **aHCV-RNA<LIC (25 UI/mL), detectable or undetectable**
- **bAmong 32 patients with cirrhosis, 11 (34%) had baseline platelet count ≤100 × 10⁹ cells/mL.**
- **cCirrhosis stage determined by biopsy (METAVIR 4), FibroScan (>14.6 kPa), or FibroTest ≥0.75 & APRI >2 in 141 patients; 11 patients had non conclusive results (FibroTest between >0.48 & <0.75 or APRI >1 - ≤2).**

ALLY-3+: SOF+DCV+RBV 12 vs 16 wks

SVR12: Patients with Cirrhosis

**ITT ANALYSIS**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>12 Weeks</th>
<th>16 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>VBT</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**OBSERVED ANALYSIS**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>12 Weeks</th>
<th>16 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>VBT</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

---

a **VBT** (virologic breakthrough): confirmed HCV RNA \( \geq 1 \log_{10} \text{IU/mL} \) above nadir, or \( \geq \text{LLOQ} \) if previously \( < \text{LLOQ}_{\text{TND}} \) or TND;

b **Relapse**: confirmed HCV RNA \( \geq \text{LLOQ} \) at any posttreatment visit following \( < \text{LLOQ}_{\text{TND}} \) at end of treatment;

c Dilated cardiomyopathy on Day 72, not related to treatment; cirrhosis status diagnosed by liver biopsy (F4) \( n = 9 \); FibroScan \( \geq 14.6 \), \( n = 27 \).
DCV+SOF±RBV in GT-3
SVR4 in advanced fibrosis/cirrhosis

(N=106)

SVR-4, %

DCV + SOF ± RBV
12 weeks

Cirrhosis
22/29
76%

No cirrhosis
11/12
92%

DCV + SOF ± RBV
24 weeks

Cirrhosis
52/59
88%

No cirrhosis
5/6
83%
# Genotype 1 Treatment

<table>
<thead>
<tr>
<th>Population</th>
<th>LDV/SOF</th>
<th>OMV/PTV/RTV + DSV</th>
<th>SMV + SOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1a, no cirrhosis</td>
<td>12 wks</td>
<td>12 wks + RBV</td>
<td>12 wks ± RBV</td>
</tr>
<tr>
<td>GT 1a, cirrhosis</td>
<td>12 wks</td>
<td>24 wks + RBV</td>
<td>24 wks ± RBV</td>
</tr>
<tr>
<td>GT 1b, no cirrhosis</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
</tr>
<tr>
<td>GT 1b, cirrhosis</td>
<td>12 wks</td>
<td>12 wks + RBV</td>
<td>24 wks</td>
</tr>
<tr>
<td>GT 1 P/R failure, no cirrhosis</td>
<td>12 wks</td>
<td>12 wks + RBV (1a)</td>
<td>12 wks ± RBV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 wks (1b)</td>
<td></td>
</tr>
<tr>
<td>GT 1 P/R failure, cirrhosis</td>
<td>24 wks or 12 wks + RBV</td>
<td>24 wks + RBV (1a)</td>
<td>24 wks ± RBV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 wks + RBV (1b)</td>
<td></td>
</tr>
<tr>
<td>GT 1 SOF failure, cirrhosis</td>
<td>24 wks ± RBV</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>GT 1 PI failure, no cirrhosis</td>
<td>12 wks</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>GT 1 PI failure, cirrhosis</td>
<td>24 wks or 12 wks + RBV</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C.
### GT3 recommendations (EASL 2015)

#### Non-cirrhotic patients* (mono & coinfected)

<table>
<thead>
<tr>
<th>GT-3</th>
<th>24 sem</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>SOF + SMV</th>
<th>DCV + SOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + RBV</td>
<td>SOF + LDV</td>
<td>OBV/PTV/r + DSV</td>
<td>OBV/PTV/r</td>
<td>SOF + SMV</td>
<td>DCV + SOF</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

#### Compensated cirrhosis* (mono & coinfected)

<table>
<thead>
<tr>
<th>GT-3</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>SOF + SMV</th>
<th>DCV + SOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + RBV</td>
<td>SOF + LDV</td>
<td>OBV/PTV/r + DSV</td>
<td>OBV/PTV/r</td>
<td>SOF + SMV</td>
<td>DCV + SOF</td>
<td>24 weeks + RBV</td>
</tr>
</tbody>
</table>

*naïve & non-responders to PegIFN+RBV

### Toxicity associated with RBV

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>LDV/SOF 12 and 24 Wk n=251</th>
<th>LDV/SOF + RBV 12 and 24 Wk n=262</th>
<th>Total N=513</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>190 (76)</td>
<td>225 (86)</td>
<td>415 (81)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>118 (47)</td>
<td>196 (75)</td>
<td>314 (61)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>19 (8)</td>
<td>20 (8)</td>
<td>39 (8)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>15 (6)</td>
<td>9 (3)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Treatment-related serious AE</td>
<td>1 (&lt;1)</td>
<td>4 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>AE leading to study drug modification/interruption</td>
<td>3 (1)</td>
<td>38 (15)</td>
<td>41 (8)</td>
</tr>
<tr>
<td>Treatment D/C due to AE</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Grade 3–4 lab abnormality</td>
<td>39 (16)</td>
<td>35 (13)</td>
<td>74 (14)</td>
</tr>
<tr>
<td>Hemoglobin &lt;10 g/dL</td>
<td>1 (&lt;1)</td>
<td>26 (10)</td>
<td>27 (5)</td>
</tr>
<tr>
<td>Hemoglobin &lt;8.5 g/dL</td>
<td>0</td>
<td>3 (1)</td>
<td>3 (&lt;1)</td>
</tr>
</tbody>
</table>
HCV-TARGET: SVR12 with LDV/SOF Therapy by Subgroups

Completed treatment as of 7/1/2015 and have available virological outcomes. Patients who discontinued due to AE or were lost to follow-up are excluded.

SVR12: SVR at 12 (±1) weeks post treatment
# Natural history of HCV cirrhosis: SVR rates with IFN-free regimes

Modified from Friedman SL. Gastroenterology 2008;134:1655–69

<table>
<thead>
<tr>
<th>Histology</th>
<th>Clinical</th>
<th>Symptoms</th>
<th>Hemodynamic</th>
<th>HVPG</th>
<th>HCS</th>
<th>Functional</th>
<th>Biology</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1–F3</td>
<td>No cirrhosis</td>
<td>None</td>
<td>None (no varices)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>F4 (Cirrosis)</td>
<td>Compensated</td>
<td>No (varices present)</td>
<td>No (varices present)</td>
<td>No (varices present)</td>
<td>No (varices present)</td>
<td>No (varices present)</td>
<td>No (varices present)</td>
</tr>
<tr>
<td>Major Descompensation</td>
<td>Decompenesation</td>
<td>Recurrent variceal bleeding, HRS, SBP</td>
<td>Any antiviral combination (GT, local availability)</td>
<td>PK (renal &amp; liver impairment), DDI</td>
<td>Increasing fibrogenesis</td>
<td>Thicken &amp; nodules, Insoluble scar</td>
<td>Worsening liver function</td>
</tr>
</tbody>
</table>

HCS: hyperdynamic circulatory status; HE: hepatic encephalopathy; HRS: hepatorenal syndrome; HVPG: hepatic venous gradient; RA: refractory ascites; SBP: spontaneous bacterial peritonitis;