Treating now vs. post transplant

Pros (for treating pre transplant)

- If SVR efficacy means
  - Better quality of life
  - Removal from waiting list
  - No post transplant recurrence
- Few drug drug interactions

Cons if treated pre transplant

- Progression despite SVR
- Decreased response rates in advanced fibrosis/cirrhosis
- Longer duration for some
- Toxicity?
- Risk of decompensation
- Sudden progression
- Health costs advanced disease?
- Post transplant recurrent disease easily treated
- Resistance with treatment failure
Scrutinising results in cirrhosis

- Comparative results in patients with advanced cirrhosis
- Safety
- Resistance
  - Retreatment options
- Pharmacokinetics
- Overall evidence decision
SVR12: Absence of Cirrhosis vs Cirrhosis
GT 1 Treatment-Experienced (ION-2)

Absence of Cirrhosis
Cirrhosis

Error bars represent 95% confidence intervals.

Afdhal et al. NEJM 2014
ALLY-1: DCV, SOF + RBV combination for HCV patients with advanced cirrhosis or post-transplant recurrence

- Post-transplant results similar to SOLAR trials
- CP C patients have reduced SVR secondary to relapse of unclear mechanism
- Effect on long-term outcomes critical to make decision of whether to treat CP C

Poordad F, et al. EASL 2015, Vienna. #LO8
LDV/SOF + RBV for the treatment of HCV in patients with decompensated cirrhosis: preliminary results of a prospective, multicenter study

- 108 patients randomized 1:1 to 12 or 24 weeks of treatment
- G1 or 4 tx-naïve or experienced patients with decompensated cirrhosis
- CPT class B (7–9) or C (score 10–12)

Flamm SL, et al. AASLD 2014, Boston. #239 Charlton Gastroenterology 2015

**Overall**
- LDV/SOF + RBV 12 wks: 45/52 SVR12
- LDV/SOF + RBV 24 wks: 42/47 SVR12

**CPT B**
- LDV/SOF + RBV 12 wks: 26/30 SVR12 (3 relapses, 1 death, 2 deaths)
- LDV/SOF + RBV 24 wks: 24/27 SVR12

**CPT C**
- LDV/SOF + RBV 12 wks: 19/22 SVR12 (1 relapse, 1 death, 1 LTFU)
- LDV/SOF + RBV 24 wks: 18/20 SVR12 (1 relapse, 1 death)
DCV + SOF in G1 mono-infected patients from French observational cohort ANRS CO22 HEPATHER

- Real-world French database
- 409 pts treated with DCV + SOF ± RBV
  - RBV n=92; no RBV n=317
  - 78% cirrhosis; 75% TE

- Factors associated with failure:
  - No RBV
  - 12-week duration
  - Cirrhosis

- 100% SVR for non-cirrhotics with all regimens
- Without RBV, 24 weeks better than 12 for cirrhotics
- RBV may eliminate need for extra 12 wks (as for LDV/SOF)
- Authors recommended 12 wks DCV + SOF + RBV for cirrhotics, though data limited (economic reasons cited)

Pol S, et al. EASL 2015, Vienna. #LO3
Final evaluation of 955 HCV patients treated with 12-week regimens containing SOF ± SMV in the TRIO network: Academic and community treatment of a real-world, heterogeneous population

Both regimens performed less well than in clinical trials in cirrhosis pts
- G1a performed less well than G1b
- PR/SOF performed well in treatment failure non-cirrhotic at 74% as predicted by FDA

Dieterich D, et al. EASL 2015, Vienna. #P0775
**BOSON: SOF + PEG-IFN/RBV for 12 weeks vs SOF + RBV for 16 or 24 weeks in G3 HCV-infected patients and treatment-experienced cirrhotic G2 patients**

- **SOF treatment-emergent variants L159F and V321A were observed in 9/78 (12%) pts:**
  - L159F was present at baseline and at the time of virologic failure in 1 patient, and only at the time of virologic failure in 6 patients.
  - V321A emerged at the time of virologic failure in 2 patients.

- Main side effect was anemia (4–12%).

- **Peg-IFN RBV with SOF still a treatment option for G3**
- **16 week SOF + RBV for G3 did not meet expectation**
- **Newer DAAs with activity against G3 still a necessity**

**SVR12 in G3 by treatment history and cirrhosis status**

- **SOF + RBV 16 weeks**
  - No cirrhosis: 58/70 (82.9%)
  - Cirrhosis: 12/21 (57.1%)

- **SOF + RBV 24 weeks**
  - No cirrhosis: 65/72 (90.3%)
  - Cirrhosis: 18/22 (81.8%)

- **SOF + PEG/RBV 12 weeks**
  - No cirrhosis: 41/54 (75.9%)
  - Cirrhosis: 44/49 (91.3%)

- **SVR12 in G3**
  - Treatment-naive: 94/112 (83.9%)
  - Treatment-experienced: 10/11 (90.9%)

- **SVR12 in G3 by cirrhosis status**
  - No cirrhosis: 58/70 (82.9%)
  - Cirrhosis: 21/23 (91.3%)

- **SVR12 in G3 by treatment history**
  - Treatment-naive: 82/94 (87.2%)
  - Treatment-experienced: 12/21 (57.1%)

Foster GR, et al. EASL 2015, Vienna. #LO5
Daclatasvir (DCV) + sofosbuvir (SOF) ± ribavirin (RBV) in G3 patients: Interim analysis of a French multicenter compassionate use program

- 601 G3 pts received:
  - DCV + SOF for 12 wks (4%)
  - DCV + SOF + RBV for 12 wks (17%)
  - DCV + SOF for 24 wks (15%)
  - DCV + SOF + RBV for 24 wks (64%)

- Patients:
  - ≥F3 / extrahepatic manifestations / post-LT HCV recurrence / indication for liver or kidney transplant
  - Mostly male (75%), mono-infected (83%), cirrhotic (77%), treatment-experienced (73%)
  - Median BL platelets 118.5 x 10^9/L
  - Median BL albumin 39.0 g/L

- SVR4

<table>
<thead>
<tr>
<th></th>
<th>12 wks</th>
<th>24 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cirrhotic pts</td>
<td>11/12</td>
<td>5/6</td>
</tr>
<tr>
<td>Cirrhotic pts</td>
<td>22/29</td>
<td>52/59</td>
</tr>
</tbody>
</table>

- 12-week regimen effective for non-cirrhotic G3 pts
- Cirrhotics appear to benefit from 24 weeks
- Effect of RBV not included in analysis

Hezode C, et al. EASL 2015, Vienna. #LP05
Treatment of decompensated HCV cirrhosis in patients with diverse genotypes: 12 weeks SOF + NS5A inhibitors ± RBV is effective in HCV G1 and G3

- Restricted regimen: 12 weeks SOF only
- Encouraging results in G1 somewhat concerning G3
- G3 SVR favored by SOF + DCV vs SOF + LDV, compared with EC_{50}s
- Estimates of risk benefit may assist decision-making
Safety and effectiveness of SOF-based regimens for the treatment of HCV G3 and 4 infections: Interim analysis of a prospective, observational study

- G4 is more effectively treated with 2 oral DAAs
- G3 treatment with SOF/RBV was less effective in real-world
  - TE cirrhosis – only 44% SVR
- Markers of advanced liver disease (MELD, albumin, platelet count) predictive of SVR

Alqahtani S, et al. EASL 2015, Vienna. #P0840
Integrated safety analysis of SOLAR 1 and 2: LDV/SOF + RBV in >600 decompensated and post-LT patients with HCV infection

Pre-transplant
CP B + C
n=215

Completed treatment
195
20 (9%) d/c treatment
9 adverse events
4 deaths
7 liver transplants

Post-transplant
F0–F3 and CP A
n=320

Completed treatment
319
11 (3%) d/c treatment
5 adverse events
1 death
1 investigator discretion
2 non-compliance
1 lost to follow-up
1 withdrew consent

Completed treatment
103
11 (10%) d/c treatment
5 adverse events
3 deaths
2 investigator discretions
1 protocol violation

Randomized
N=660

Treatment-emergent deaths

<table>
<thead>
<tr>
<th>Did not complete treatment</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>Pre CP B</td>
</tr>
<tr>
<td>Cardiac arrest in setting of sepsis</td>
<td>Pre CP B</td>
</tr>
<tr>
<td>Oliguric renal failure</td>
<td>Pre CP C</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Pre CP C</td>
</tr>
<tr>
<td>GI bleeding and liver failure</td>
<td>Pre CP C</td>
</tr>
<tr>
<td>Multi-organ failure and septic shock</td>
<td>Pre CP C</td>
</tr>
<tr>
<td>Cardiac arrest due to ischemic heart disease</td>
<td>Pre CP C</td>
</tr>
<tr>
<td>Staphylococcus aureus sepsis</td>
<td>Pre CP C</td>
</tr>
<tr>
<td>GI bleeding &amp; liver failure</td>
<td>Post CP A</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalitis</td>
<td>Post CP A</td>
</tr>
<tr>
<td>Thoracic aorta aneurysm dissection</td>
<td>Post CP B</td>
</tr>
<tr>
<td>Internal bleeding</td>
<td>Post CP B</td>
</tr>
<tr>
<td>Multi-organ failure with sepsis</td>
<td>Post CP B</td>
</tr>
<tr>
<td>Multi-organ failure due to decompensated cirrhosis</td>
<td>Post CP B</td>
</tr>
<tr>
<td>Infiltrative multifocal hepatocarcinoma</td>
<td>Post CP C</td>
</tr>
<tr>
<td>Intestinal ischemia</td>
<td>Post CP C</td>
</tr>
</tbody>
</table>

Died ≤30 days after completing treatment

<table>
<thead>
<tr>
<th>Died ≤30 days after completing treatment</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis and multi-organ failure</td>
<td>Pre CP B</td>
</tr>
<tr>
<td>Liver failure due to chronic liver rejection</td>
<td>Post F0–F3</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Post CP A</td>
</tr>
<tr>
<td>Multi-organ failure due to liver failure</td>
<td>Post CP C</td>
</tr>
</tbody>
</table>

*17 post-transplantation CP C patients were enrolled
†One patient who was randomized was not dosed

Samuel D, et al. EASL 2015, Vienna. #P0774
HCV-TARGET: Safety and efficacy of SOF-containing regimens in HCV-infected patients with reduced renal function

### Safety outcomes by baseline eGFR

<table>
<thead>
<tr>
<th>Dichotomous = n (%)</th>
<th>eGFR ≤30 n=17</th>
<th>eGFR 31–45 n=56</th>
<th>eGFR 46–60 n=157</th>
<th>eGFR &gt;60 n=1559</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common AEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (18)</td>
<td>19 (34)</td>
<td>56 (36)</td>
<td>543 (35)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (6)</td>
<td>9 (16)</td>
<td>19 (12)</td>
<td>274 (18)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (18)</td>
<td>8 (14)</td>
<td>33 (21)</td>
<td>247 (16)</td>
</tr>
<tr>
<td>Anemia AE</td>
<td>6 (35)</td>
<td>16 (29)</td>
<td>37 (24)</td>
<td>246 (16)</td>
</tr>
<tr>
<td>Required transfusion(s)</td>
<td>2 (12)</td>
<td>5 (9)</td>
<td>3 (2)</td>
<td>31 (2)</td>
</tr>
<tr>
<td>Erythropoietin start on treatment</td>
<td>1 (6)</td>
<td>8 (14)</td>
<td>14 (9)</td>
<td>50 (3)</td>
</tr>
<tr>
<td><strong>RBV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in RBV due to anemia</td>
<td>3 (38)</td>
<td>8 (30)</td>
<td>33 (42)</td>
<td>185 (19)</td>
</tr>
<tr>
<td>RBV discontinuation</td>
<td>0 (0)</td>
<td>4 (15)</td>
<td>1 (1)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>5 (29)</td>
<td>6 (11)</td>
<td>4 (3)</td>
<td>14 (1)</td>
</tr>
<tr>
<td>Renal or urinary system AEs</td>
<td>5 (29)</td>
<td>6 (11)</td>
<td>13 (8)</td>
<td>84 (5)</td>
</tr>
<tr>
<td>Any serious AEs</td>
<td>3 (18)</td>
<td>13 (23)</td>
<td>8 (5)</td>
<td>100 (6)</td>
</tr>
<tr>
<td>Cardiac serious AEs</td>
<td>1 (6)</td>
<td>2 (4)</td>
<td>8 (5)</td>
<td>53 (3)</td>
</tr>
<tr>
<td>Early treatment discontinuation</td>
<td>1 (6)</td>
<td>4 (6)</td>
<td>3 (4)</td>
<td>38 (4)</td>
</tr>
<tr>
<td>Early treatment discontinuation AE</td>
<td>1 (6)</td>
<td>2 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- More anemia and more monitoring with SOF-containing regimen
- Does not validate safety of DAA utilization

Saxena V, et al. EASL 2015, Vienna. #LP08
Effect of long-term viral suppression with SOF + RBV on hepatic venous pressure gradient in HCV-infected patients with cirrhosis and portal hypertension

Afdhal N, et al. EASL 2015, Vienna. #LP13

Median total albumin and bilirubin at baseline and follow-up Week 4 (all pts, N=96)

Normal range total albumin: 3.3–4.9 g/dL

Normal range total bilirubin: 0.2–1.2 mg/dL

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

Afdhal N, et al. EASL 2015, Vienna. #LP13
Effect of long-term viral suppression with SOF + RBV on hepatic venous pressure gradient in HCV-infected patients with cirrhosis and portal hypertension

- SOF + RBV for 48 weeks: SVR rate of 72%
- Clinical improvement occurs after viral suppression more rapidly than remodeling of fibrosis and reduction in HVPG
- 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*
PK and safety of co-administered ABT-450/r, ABT-267 and ABT-333 as a single dose in subjects with normal hepatic function and in subjects with mild, moderate, and severe hepatic impairment

- **Mild impairment:** ABT-450, -333 and -267 exposures not clinically significantly different (AUCs up to ±30% different)
- **Moderate impairment:** ABT-333 and -267 exposures not clinically significantly different (AUCs ≤30% lower), ABT-450 exposures moderately higher (AUC 62% higher)
- **Severe impairment:** ABT-450 and -333 exposures significantly higher
The prevalence and effect of HCV NS5A resistance-associated variants in subjects with compensated cirrhosis treated with LDV/SOF ± RBV

**SVR12 rates by resistance level of baseline NS5A RAVs**

- **Treatment-naive**
  - G1a: 11/12 (92%) for >100-fold resistance, 3/3 (100%) for <100-fold resistance, 70/70 (100%) for none
  - G1b: 94% for >100-fold resistance, 100% for <100-fold resistance, 100% for none

- **Treatment-experienced**
  - G1a: 67 for >100-fold resistance, 100% for <100-fold resistance, 97% for none
  - G1b: 95% for >100-fold resistance, 100% for <100-fold resistance, 96% for none

- **NS5A RAVs important in G1 treatment-failure cirrhotics**
- RBV, not ↑ duration, overcomes effective NS5A RAVs on relapse

Sarrazin C, et al. EASL 2015, Vienna. #P
Urgent lessons to be learned from DAA IFN free therapy in decompensated cirrhosis

- What degrees of cirrhosis impair response?
- What is the optimal duration of therapy for different stages of cirrhosis?
- Is mortality less than expected in this population?
- Is the long term outcome better in Child Pugh C when treated pre transplant?
- What are the consequences of relapse?
- Are pre-existent resistant variants more critical in this group?
- Are there higher rates of adverse events in patients with decompensated cirrhosis?
- To what degree is disease reversible? Is the natural history of the disease altered? Is mortality lessened in this group?