Treating patients with decompensated GT 3?
Hepatitis C – growing disease burden

Recurrent Hepatitis C: Antiviral Strategies

- Prevent HCV recurrence
- Pretransplant Therapy
  - Prevent chronic hepatitis
  - Prevent cirrhosis and graft failure
  - Treatment of established disease
- Pre-emptive Therapy
- Transplant
- Graft loss
Treating decompensated cirrhosis
Reduced efficacy especially in CTP C

SOLAR 1/2 Studies of HARVONI + RBV for 12/24 weeks in 247 CTP B/C GT 1 Patients

- Analysis excluded 13 patients transplanted prior to posttreatment Week (FU) 12 with HCV RNA <LLOQ at last measurement prior to transplant, and 3 pretransplant patients who were CPT A at baseline. Error bars represent 95% confidence intervals (CIs).

Gane E, et al. APASL 2016
Treating decompensated cirrhosis
Reduced efficacy especially in GT 3

- UK EAP for 409 CTP B/C pts 12 wks
- LDV/SOF±RBV or DCV/SOF±RBV for 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>SOF/DCV</th>
<th>SOF/DCV/RBV</th>
<th>SOF/LDV</th>
<th>SOF/LDV/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 N=</td>
<td>50</td>
<td>88.2%</td>
<td>84.6%</td>
<td>91.3%</td>
</tr>
<tr>
<td>G3 N=</td>
<td>60</td>
<td>71.4%</td>
<td>40</td>
<td>64.9%</td>
</tr>
</tbody>
</table>

Foster G et al. J Hepatol 2016
Treating decompensated cirrhosis
Is it worth it?

SVR is associated with rescue from death/transplant

Foster G et al. J Hepatol 2016
Treating decompensated cirrhosis
Do we rescue patients?

♦ DAAs improve liver synthetic function

HARVONI + RBV for 12 weeks in 247 CTP B/C patients

- Improved (n=183)
- No Change (n=48)
- Worse (n=16)

♦ 76% of CPT C pts ⇒ CPT A or B
♦ 40% of CPT B pts ⇒ CPT A
♦ NO Patient progressed to CTP-C

Gane E, et al. AASLD 2015 Poster #1049
Treating decompensated cirrhosis
Is there a point of “no return”

- Baseline MELD but NOT Δ MELD predicts outcome

Adverse events at 15 months post-SVR

<table>
<thead>
<tr>
<th>% with AEs</th>
<th>MELD &lt;15</th>
<th>Baseline MELD &gt;15</th>
<th>MELD &gt;2pts at 6 months</th>
<th>MELD unchanged</th>
<th>MELD &gt;2pts at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>44</td>
<td>71</td>
<td>40</td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>

P < 0.001

P = NS

Foster G et al. J Hepatol 2016

Treating decompensated cirrhosis
Is there a point of “no return”

- 103 patients listed for decompensated HCV
- SOF/RBV, SOF/LDV, SOF/DCV
- 34 deactivated

### Baseline Predictors

<table>
<thead>
<tr>
<th>Variable</th>
<th>% Delisting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline MELD</td>
<td></td>
</tr>
<tr>
<td>&lt;16</td>
<td>25/51 (49%)</td>
</tr>
<tr>
<td>16–20</td>
<td>7/38 (18%)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>2/13 (15%)</td>
</tr>
</tbody>
</table>

### Cumulative incidence of inactivation

- **MELD <16**
- **MELD 16-20**
- **MELD >20**
What is the Point of No Return?

HARM outweighs BENEFIT, if high MELD

- Low efficacy: 60% in GT 3
- Relapse with NS5A RASs – retreatment?
- Low safety of RBV (+ SOF? If renal dysfn)
- Even if achieve SVR, risk of MELD purgatory
  - lose priority on list and die

WAIT AND TREAT AFTER TRANSPLANT
Wait and treat after transplant
SVR rates are excellent after transplant

Charlton M. Gastroenterology 2015;149:649-59
Houssel-Derby P, et al. EASL 2016, Barcelona. #PS018
ILTS CONSENSUS RECOMMENDATION 2:

- HCV-infected patients with advanced decompensated cirrhosis with MELD >25 should not undergo antiviral therapy

**Strength of recommendation:** Conditional  
**Quality of Data:** Very Low
Acute Hep C
Treat or wait?
### Acute Hepatitis C: Treat now or wait?

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFN ± RBV</td>
<td>All DAA therapy</td>
</tr>
<tr>
<td>- Poor tolerability</td>
<td>- Excellent tolerability</td>
</tr>
<tr>
<td>- Difficult to monitor</td>
<td>- No need to monitor</td>
</tr>
<tr>
<td>- 12-24 weeks duration</td>
<td>- Shorter duration?</td>
</tr>
<tr>
<td>- Poor adherence</td>
<td>- Adherence?</td>
</tr>
<tr>
<td>- High risk of reinfection</td>
<td>- Low risk of reinfection</td>
</tr>
<tr>
<td>- Wait until chronic</td>
<td>- Prevent transmission</td>
</tr>
<tr>
<td>- DAAs ⇒95% SVR</td>
<td>- Public Health benefit</td>
</tr>
<tr>
<td>- Stable harm reduction</td>
<td></td>
</tr>
</tbody>
</table>

**NO**

**YES**
Ultrashort duration DAA therapy for acute HepC
DARE-C II, HepNet, SLAM-C

- 3 studies in acute HepC
  - Only one was all genotypes (DARE-C)
  - Different definitions (acute vs. recent infection)

3. Deterding K, et al. EASL 2016, Barcelona. #LB08

Excellent tolerability
Need 2 DAAs but not RBV
4 weeks may be enough
What is reinfection rate?
What is the Risk of Reinfection?

Meta-analysis of 61 studies to determine reinfection

- 7969 Low-risk patients → 1% HCV recurrence at 5 years
- 771 High-risk IDU/prisoners → 11% HCV recurrence at 5 years
- 309 HIV coinfected patients → 15% HCV recurrence at 5 years

Active IDU, prisoners and HIV+ patients should be monitored for reinfection

Simmons B et al, Clin ID March 2016
The patient who has failed HARVONI, DAC/SOF or VIEKIRA PAK

Treat now or wait?
Phase II LDV/SOF ± RBV for 12-24 weeks in GT 1
Patients who have failed prior SOF therapy

Lawitz, APASL 2016, O-011
Phase II SOF/VEL+RBV for 24 weeks in GT 1–6
Patients who have failed prior DAA therapy

N=69
SOF 400mg/VEL 00mg + RBV

SVR12 (%)

<table>
<thead>
<tr>
<th></th>
<th>GT 1</th>
<th>GT 2</th>
<th>GT 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>59/65</td>
<td>33/34</td>
<td>13/14</td>
</tr>
</tbody>
</table>
| 1 relapse+ | 1 | 1 | 1
| 1 nonresponse | 1 | 2 relapses | 1 WC

Gane E et al. EASL 2016, Barcelona
Phase II SOF/VEL/VOX for 12 weeks in GT 1–6
Patients who have failed prior DAA therapy

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Treatment period</th>
<th>Week 12</th>
<th>Post-treatment (PT) period</th>
<th>PT Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=128</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOF 400mg/VEL 100mg/VOX 100mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SVR12 (%)

<table>
<thead>
<tr>
<th>Overall</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>99/127</td>
<td>100/63</td>
<td>100/21</td>
<td>97/34</td>
<td>100/9</td>
</tr>
</tbody>
</table>

### SVR12 (%) by Cirrhosis

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>67/67</td>
<td>60/61</td>
<td></td>
</tr>
</tbody>
</table>

### SVR12 (%) by Prior NS5A Experience

<table>
<thead>
<tr>
<th>Prior NS5A Experience</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>92/93</td>
<td>35/35</td>
<td></td>
</tr>
</tbody>
</table>

Lawitz E, et al. EASL 2016, Barcelona. #PS008

20
Phase II Data on GLE/PIB for 12 weeks in GT 1–6
Patients who have failed prior DAA therapy

Poordad F et al. EASL 2016, Barcelona. #GS11
The Patient with HBV coinfection

Treat HBV as well to prevent HBV Flare?
HARVONI for 12 weeks in GT 1 with HBV coinfection

LEPTON Phase II Pilot Study

N=10
LDV 90mg/SOF 400mg

- All HBsAg+, HBV DNA <3 log IU/mL

Gane E, et al. AVT (in press)
Mean and Individual HBV DNA Profiles
HBV/HCV Co-infection

Mean HBV DNA
Individual HBV DNA

HBV DNA (log_{10}/mL)

Week
Posttreatment Week
Mean and Individual ALT Profiles
HBV/HCV Co-infection
Treating patients with renal failure

Ed Gane
New Zealand Liver Transplant Unit
## Treatment of HCV in Renal Impairment

### What drugs are safe?

<table>
<thead>
<tr>
<th>DAA Class</th>
<th>Name</th>
<th>AUC&lt;sub&gt;24&lt;/sub&gt; if eGFR &lt;30 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NS3 Protease inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Grazoprevir&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>ABT-493</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>NS5A inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ledipasvir&lt;sup&gt;6&lt;/sup&gt;</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ombitasvir&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Elbasvir</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>ABT-530</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Non-NUC NS5B</strong></td>
<td>Dasabuvir&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>NUC NS5B Inhibitor</strong></td>
<td>Sofosbuvir&lt;sup&gt;1&lt;/sup&gt;</td>
<td>6x</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>&gt;10x</td>
<td></td>
</tr>
</tbody>
</table>
VIEKIRA PAK Phase II Trials in Renal Failure

RUBY-1 Study

- 20 GT1 patients with eGFR <30ml/min, include HD, no cirrhosis

<table>
<thead>
<tr>
<th>GT 1a (n=13)</th>
<th>GT 1b (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D regimen + RBV200mg/day</td>
<td>3D regimen</td>
</tr>
</tbody>
</table>

Week 0 | Week 12 | Week 12 | Week 24 | To Week 48

(i) Efficacy

- 90% SVR12
- 1 relapse, 1 death

(ii) Safety

<table>
<thead>
<tr>
<th></th>
<th>Viekira Pak + RBV (G 1a)</th>
<th>Viekira Pak (Gt 1b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>62%</td>
<td>29%</td>
</tr>
<tr>
<td>SAE</td>
<td>22%</td>
<td>14%</td>
</tr>
<tr>
<td>RBV reduced</td>
<td>69%</td>
<td>0%</td>
</tr>
<tr>
<td>Hb &lt;100</td>
<td>54%</td>
<td>29%</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- Only safety issue is RBV
- RUBY-II removes RBV in all patients and includes cirrhotics

Pockros PJ, et al. AASLD 2015, San Francisco. #1039
Grazoprevir/Elbasvir (ZEPATIER) in HCV GT 1

C-SURFER: Efficacy in ESRD

- 235 GT1 patients with eGFR <30ml/min, include HD, cirrhosis

(i) Efficacy

94%

- 94% SVR12
- 1 relapse
- 1 death
- 2 LTFU
- 2 WD

(ii) Safety

<table>
<thead>
<tr>
<th></th>
<th>GZR/EBR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx-related AE</td>
<td>34%</td>
<td>35%</td>
</tr>
<tr>
<td>SAE</td>
<td>14%</td>
<td>17%</td>
</tr>
<tr>
<td>DC from AE</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Hb &lt;100</td>
<td>24%</td>
<td>27%</td>
</tr>
<tr>
<td>ALT&gt;5xULN</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Sofosbuvir in Renal Impairment
HCV TARGET Real World Study

Treatment regimen by baseline eGFR

SVR12 by baseline eGFR and by treatment regimen*

*Among patients with known outcome

Saxena V, et al. EASL 2015, Vienna. #LP08
Sofosbuvir in Renal Impairment

Open-label study in HCV pts with GFR <30

Week 0 24 0 24 0 12

Part 1
n=20

Part 2
n=15

SVR12

QD: once-daily; RBV: ribavirin; SOF: sofosbuvir

Martin P et al. AASLD 2015, San Francisco. #1128
Gane E, et al. AASLD 2014, Boston. #966
Sofosbuvir in Renal Impairment
Open-label study in HCV pts with GFR <30

- **On treatment suppression**

  - GFR <30 ml/min (n=10)
  - GFR >60 ml/min (n=114)*

- **SVR12**

  - AEs all due to RBV toxicity. NO evidence of SOF toxicity
  - eGFR improved during treatment (26\(\rightarrow\)36 mL/min)
  - Next group is LDV/SOF for 12 weeks without RBV (GT 1)

*PHOTON-1 study

Martin P et al. AASLD 2015, San Francisco. #1128
Gane E, et al. AASLD 2014, Boston. #966