What is Known: Published Data on HCV Treatment Failure

Presenter: Eleanor Wilson, University Of Maryland
Retreatment of Hepatitis C
Studies and Questions

Eleanor Wilson, MD MHS
April 20th, 2017
Background: Retreatment of HCV

• HCV retreatment has changed with HCV treatment regimens
  • IFN/RBV
  • IFN/RBV + PI
  • SOF/RBV
  • NSSA-inhibitors

• AASLD/EASL guidelines address these, with varying levels of evidence
  • Patients may choose to defer retreatment if they can
  • If needed, retreatment should combine
    • a DAA with a high genetic barrier to resistance (SOF)
    • RBV if possible/tolerated
    • 1-2 other DAAs, preferably at least one from a novel class
Background: HCV Treatment Failure

Why do patients fail HCV treatment with DAAs?

- Treatment experience
- Fibrosis stage
- Viral load
- Immunodeficiency
- Resistance
- Adherence
- Reinfection
Sofosbuvir and Ribavirin for Treatment-Naïve HCV GT 1
NIH SPARE Trial: Design

Drug Dosing
Sofosbuvir: 400 mg once daily
Low-dose Ribavirin (divided bid): 800 mg/day
Weight-based Ribavirin (divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Sofosbuvir and Ribavirin for Treatment-Naïve HCV GT 1
NIH SPARE Trial: Results

NIH SPARE : HCV <12 IU/ml by Study Timepoint

- **Pilot SOF/wb RBV**: 80% (8/10), 96% (24/25), 96% (24/25)
- **SOF/ld RBV**: 90% (9/10), 88% (22/25), 96% (24/25)
- **SOF/wb RBV**: 90% (9/10), 48% (12/25), 68% (17/25)

T cell response to HCV Treatment

Interferon-γ + Spots (fold increase)

SVR after SOF/RBV

Relapse after SOF/RBV

Baseline

End of treatment

Shrivastava J Viral Hepat 2017
Sofosbuvir and Ribavirin for Treatment-Naïve HCV GT 1
NIH SYNERGY (Retreatment arm) Trial: Design

Ledipasvir/Sofosbuvir 12 weeks

SYNERGY D
N =14

Week 0 12 24

SVR12

Drug Dosing
Ledipasvir/Sofosbuvir: 90mg/400 mg once daily

Sofosbuvir and Ribavirin for Treatment-Naïve HCV GT 1
NIH SPARE Trial: Results

NIH SPARE: HCV <12 IU/ml by Study Timepoint

SOF = Sofosbuvir; RBV = Ribavirin; LDV/ = Ledipasvir; ld = Low dose; wb = Weight-based

T cell response to HCV (re)Treatment

Shrivastava J Viral Hepat 2017
LDV/SOF Failure Study: LDV/SOF for retreatment of genotype 1 with prior failure to LDV/SOF

**Design**

Chronic HCV infection
Genotype 1
Failure to achieve SVR on LDV/SOF-containing regimen for 8 or 12 weeks
Compensated cirrhosis (liver biopsy or Fibrotest > 0.75 + APRI > 2) allowed
No HBV or HIV co-infection

Open-label

N = 41

LDV/SOF 90/400 qd

SVR$_{12}$

**Objective**

- Primary endpoint: SVR$_{12}$ (HCV RNA < 15 IU/ml) by intention to treat, with 2-sided 95% CI, no statistical hypothesis

*Lawitz E. EASL 2015, Abs. O005*

Slides adapted from HCV-Trials.com
SYNERGY D: LDV/SOF for retreatment of genotype 1 with prior failure to LDV/SOF/GS-9669 ± GS-9451

**Design**

- Chronic HCV infection
- Genotype 1
- Failure to achieve SVR on LDV/SOF-containing regimen for 4 or 6 weeks
- No HBV or HIV co-infection

- Open-label

- N = 34

- LDV/SOF 90/400 qd

- SVR_{12}

**Objective**

- Primary endpoint: SVR_{12} (HCV RNA < 12 IU/ml) by intention to treat, with 2-sided 95% CI, no statistical hypothesis

*Wilson E. EASL 2015, Abs. LP09*
*Wilson E. CID 2016;62(3):280-8*

Slides adapted from HCV-Trials.com
RAVS & Susceptibility of DAAs

HCV RNA

IFN-free, DAA-based treatment

Sensitive (wild-type) viral variant

Resistant viral variant with profoundly reduced susceptibility

Resistant viral variant with moderately reduced susceptibility

Start

End of treatment

SVR12

LLOD in blood

Pawlotsky JM Gastroenterology 2016; 1-17
Persistence of NS5A Mutants

Wyles D et al. EASL 2015
### Amino Acid Position and Substitutions

<table>
<thead>
<tr>
<th>NSSA Inhibitor</th>
<th>Genotype 1a</th>
<th>Genotype 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M28</td>
<td>Q30</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>V</td>
</tr>
<tr>
<td>Daclatasvir (DCV) (77, 78)</td>
<td>205</td>
<td>–</td>
</tr>
<tr>
<td>Elbasvir (EBR) (79)</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Ledipasvir (LDV) (77, 78)</td>
<td>61</td>
<td>–</td>
</tr>
<tr>
<td>Ombitasvir (OMV) (77, 80)</td>
<td>8,965</td>
<td>58</td>
</tr>
<tr>
<td>Velpatasvir (VEL) (87)</td>
<td>8</td>
<td>–</td>
</tr>
</tbody>
</table>

- **T** represents no data
- **<5 fold** indicates a 5-10 fold increase
- **5-100 fold** indicates a 5-100 fold increase
- **>100 fold** indicates a >100 fold increase
HCV Retreatment Studies GT-1

**Completed**

- LEPTON
- Rereatment
- GS-US-367-1168
- POLARIS-1
- POLARIS-4
- C-CREST 1 and 2 part C
- C-SURGE
- QUARTZ-1
- MAGELLAN-1, pt 1
- REVENGE
## HCV Retreatment Studies - Gilead

<table>
<thead>
<tr>
<th>Study</th>
<th>Prior Treatment</th>
<th>Retreatment regimen</th>
<th>Duration</th>
<th>N</th>
<th>SVR&lt;sub&gt;12&lt;/sub&gt;</th>
<th>Outcome predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEPTON</td>
<td>Combination DAA</td>
<td>SOF/VEL/VOX</td>
<td>6 weeks</td>
<td>30</td>
<td>67%</td>
<td>83% NS5A 87% NS3</td>
</tr>
<tr>
<td></td>
<td>Gane Gastroenterol 2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEPTON Retreatment</td>
<td>SOF/VEL or LEPTON</td>
<td>SOF/VEL + RBV</td>
<td>24 weeks</td>
<td>34</td>
<td>97%</td>
<td>96% - RAVs 100% + RAVs</td>
</tr>
<tr>
<td></td>
<td>Gane EASL 2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS-US-367-1168</td>
<td>NS5A or ≥2 classes DAAs</td>
<td>SOF/VEL/VOX</td>
<td>12 weeks</td>
<td>63</td>
<td>100%</td>
<td>No relapsers</td>
</tr>
<tr>
<td></td>
<td>Lawitz Gastroenterol 2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 1 DAA</td>
<td>SOF/VEL/VOX ± RBV</td>
<td>12 weeks</td>
<td>49</td>
<td>100%/96%</td>
<td>100% - RAVs 97% + RAVs</td>
</tr>
<tr>
<td>Lawitz Hepatology 2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POLARIS 1</td>
<td>NS5A</td>
<td>SOF/VEL/VOX</td>
<td>12 weeks</td>
<td>150</td>
<td>97%</td>
<td>98% - RAVs 96% + RAVs</td>
</tr>
<tr>
<td></td>
<td>Bourliere AASLD 2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POLARIS 4</td>
<td>Non-NS5A</td>
<td>SOF/VEL ± VOX</td>
<td>12 weeks</td>
<td>144</td>
<td>97%/91%</td>
<td>94% - RAVs 100% + RAVs</td>
</tr>
<tr>
<td></td>
<td>Zeuzem AASLD 2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suda et al</td>
<td>DCV/ASV</td>
<td>LDV/SOF + RBV</td>
<td>12 weeks</td>
<td>15</td>
<td>86.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>J Gastroenterol 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akuta et al</td>
<td>DCV/ASV</td>
<td>LDV/SOF</td>
<td>12 weeks</td>
<td>17</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>J Med Virol 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## HCV Retreatment Studies - Merck

<table>
<thead>
<tr>
<th>Study</th>
<th>Prior Treatment</th>
<th>Retreatment regimen</th>
<th>Duration</th>
<th>N</th>
<th>SVR&lt;sub&gt;12&lt;/sub&gt;</th>
<th>Outcome predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-CREST-1/2, pt C</td>
<td>Uprifosbuvir + EBR or RZR</td>
<td>Uprifosbuvir/GZR/RZR + RBV</td>
<td>16 weeks</td>
<td>2</td>
<td>100%</td>
<td>No relapsers</td>
</tr>
<tr>
<td>Serfaty AASLD 2016</td>
<td>Prior Treatment</td>
<td>Retreatment regimen</td>
<td>Duration</td>
<td>N</td>
<td>SVR&lt;sub&gt;8&lt;/sub&gt;</td>
<td>Outcome predictors</td>
</tr>
<tr>
<td>C-SURGE</td>
<td>LDV/SOF or EBR/GZR</td>
<td>Uprifosbuvir/GZR/RZR + RBV</td>
<td>16 weeks</td>
<td>45</td>
<td>98%</td>
<td>No relapsers*</td>
</tr>
<tr>
<td>Wyles AASLD 2016</td>
<td>Prior Treatment</td>
<td>Retreatment regimen</td>
<td>Duration</td>
<td>N</td>
<td>SVR&lt;sub&gt;8&lt;/sub&gt;</td>
<td>Outcome predictors</td>
</tr>
<tr>
<td>REVENGE</td>
<td>SOF+(SMV,DCV,LDV) ± RBV</td>
<td>SOF+EBR/GZR + RBV</td>
<td>16 weeks</td>
<td>12</td>
<td>100%</td>
<td>No relapsers</td>
</tr>
<tr>
<td>De Ledinghen AASLD 2016</td>
<td>Prior Treatment</td>
<td>Retreatment regimen</td>
<td>Duration</td>
<td>N</td>
<td>SVR&lt;sub&gt;8&lt;/sub&gt;</td>
<td>Outcome predictors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 weeks</td>
<td>13</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
## HCV Retreatment Studies - AbbVie

<table>
<thead>
<tr>
<th>Study</th>
<th>Prior Treatment</th>
<th>Retreatment regimen</th>
<th>Duration</th>
<th>N</th>
<th>SVR&lt;sub&gt;12&lt;/sub&gt;</th>
<th>Outcome predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QUARTZ-1</strong></td>
<td>Combination DAA</td>
<td>PrOD + SOF ± RBV</td>
<td>12 weeks</td>
<td>14</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Poordad AASLD 2016</td>
<td></td>
<td></td>
<td>24 weeks</td>
<td>6</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 weeks</td>
<td>2</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td><strong>MAGELLAN-I</strong></td>
<td>Combination DAA</td>
<td>GLE/PIB ± RBV</td>
<td>12 weeks</td>
<td>50</td>
<td>96%</td>
<td>Gt1a, RAVs</td>
</tr>
<tr>
<td>Poordad Hepatology 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HCV Retreatment Studies at ILC 2017

Saturday April 22nd Parallel Session HCV: DAA resistance and retreatment

• PS – 156 – F. Poordad, “MAGELLAN-1 Part 2: glecaprevir and pibrentasvir for 12 or 16 weeks in patients with chronic hepatitis C virus genotype 1 or 4 and prior direct-acting antiviral treatment failure”

• PS – 157 – S. Chevaliez, “Effect of resistance-associated substitutions on retreatment of direct acting antiviral-exposed patients in the real-world setting (ANRS C022 HEPATHER)”

• PS – 158 – M.C. Cheung, “Re-treatment of patients with decompensated chronic hepatitis C virus cirrhosis using 24 weeks of SOF and an NS5A inhibitor, ± RBV, after failing 12 week course”

• PS – 159 – H. Wedemeyer, “Safety and efficacy of the fixed dose combination regimen of MK-3682/grazoprevir/ruzasvir in cirrhotic or non-cirrhotic patients with chronic HCV GT1 infection who previously failed a direct-acting antiviral regimen (C-SURGE)”
Posters of interest at ILC 2017

• FRI-254 JL Callejo Panero et al, “Effectiveness of RBV with DAAs in treating non-cirrhotic patients with Gt1a or 4 HCV infection in real-world practice.”

• SAT-255 P Halfon et al, “Retreatment with Direct Active Antivirals of genotype 1, 3 and 4 chronic hepatitis C patients who previously failed an anti-NS5A- containing regimen in real world”

• SAT-287 U.V. Comandini et al, “Virological and clinical significance of detectable HCV-RNA below limit of quantification at End-of-Treatment in patients treated with direct antiviral agents”

• SAT-280 S.K. Roberts et al, “SOF/VEL/VOX results in high SVR12 rates when administered for 12 weeks in DAA-experienced patients or for 8 Weeks in DAA-naïve patients: an integrated analysis of the POLARIS-1, POLARIS-2, POLARIS-3 and POLARIS-4 studies”

• SAT-288 V. Cento et al, “The challenge of HCV-retreatment after DAA-failure: real-life experience advocates for caution”
HCV Retreatment Studies

Ongoing

- RESOLVE (NCT02745535) – combination DAA-experienced patients, 12 weeks SOF/VEL/VOX

Upcoming

- C-RESCUE (NCT03105349) – NS5A-experienced patients, 16 weeks EBR/GZR + SOF + RBV
- University of Florida HCV TARGET retreatment study in collaboration with AbbVie (NCT03092375) – SOF/NS5A-experienced (without PI) patients, GLE/PIB for 12 or 16 weeks ± RBV
SHARED - Surveillance of Hepatitis C Antiviral Resistance, Epidemiology and Methodologies Study

• International epidemiological study
  • 12 sites in 10 countries
• Number of patients (projected): 1000+
• Characteristics
  • Viral genotype/subtype
  • Disease stage
  • Geographic region
  • Resistance data
    • Baseline: Yes, in a subset
    • At failure: Yes, in a subset
• Treatment regimens
  • First treatment (regimen)
  • Second (re-)treatment regimen
  • Re-treatment outcome

Project Coordinator: Anita Howe, PHD
British Columbia Center for Excellence for Excellence for HIV/AIDS
Going Forward: HCV Retreatment

Guidelines have addressed retreatment strategies based on factors including:
- resistance
- treatment duration
- the addition of ribavirin

Moving forward, it’s clear that other factors can also influence response to therapy, including:
- immune-mediated factors
- poor adherence
- reinfection