HCV treatment: state of the art and future challenges

Antonio Craxì
HCV cure rate has evolved substantially over the past 30 years.

**Interferon Based**
- 1984
  - SVR: 50%
  - Applicability: 30%
  - CURE: 15%

**Early DAAs**
- 2011
  - SVR: 60%
  - Applicability: 25%
  - CURE: 15%

**1st-Generation DAAs**
- 2014
  - SVR: 85%
  - Applicability: 80%
  - CURE: 68%

**Pan-genotypic**
- 2016
  - SVR: 99%
  - (including retx)
  - Applicability: 99%
  - CURE: 98%

### 8–12-Week Pan-genotypic Regimens Are Recommended for Most Patients*

<table>
<thead>
<tr>
<th>EASL Guidelines</th>
<th>Without Cirrhosis</th>
<th>With Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 1</td>
<td>Prior Treatment Experience</td>
<td>SOF/VEL</td>
</tr>
<tr>
<td>Treatment naive</td>
<td>12 wk</td>
<td>8 wk</td>
</tr>
<tr>
<td>Treatment experienced†</td>
<td>12 wk</td>
<td>8 wk</td>
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<tr>
<td>Genotype 2</td>
<td>Treatment naive</td>
<td>12 wk</td>
</tr>
<tr>
<td>Treatment experienced†</td>
<td>12 wk</td>
<td>8 wk</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>Treatment naive</td>
<td>12 wk</td>
</tr>
<tr>
<td>Treatment experienced†</td>
<td>12 wk</td>
<td>12 wk</td>
</tr>
<tr>
<td>Genotype 4, 5, 6</td>
<td>Treatment naive</td>
<td>12 wk</td>
</tr>
<tr>
<td>Treatment experienced†</td>
<td>12 wk</td>
<td>8 wk</td>
</tr>
</tbody>
</table>

**IFN-free, RBV-free, DAA-based regimens must be used (A1)**‡

wk, weeks.

* Treatment naive or treatment experienced; † Treatment experienced to pegIFN + RBV ± SOF or SOF + RBV;
‡ In HCV-infected patients ± compensated cirrhosis, including treatment-naïve and treatment-experienced (previously treated with pegIFN + RBV ± SOF or SOF + RBV) patients due to their virological efficacy, ease of use, safety and tolerability.

Patients treated with pegIFN/RBV ± protease inhibitor or IFN ± RBV. D/C, discontinuation; LTFU, lost to follow-up; RL, relapse.


ASTRAL-1, -2, -3: SOF/VEL for 12 Weeks in GT1–6 Treatment-Naive and -Experienced* Patients with and without Cirrhosis

* Patients treated with pegIFN/RBV ± protease inhibitor or IFN ± RBV. D/C, discontinuation; LTFU, lost to follow-up; RL, relapse.
**Integrated Efficacy Analysis:**

* G/P for 8 Weeks in GT1–6 Treatment-Naive and PRS-Experienced† Patients without Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>GT1</th>
<th>GT2</th>
<th>GT3†</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVR12 (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>943</td>
<td>943</td>
<td>470</td>
<td>202</td>
<td>198</td>
<td>59</td>
<td>92</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>965</td>
<td>952</td>
<td>474</td>
<td>206</td>
<td>208</td>
<td>62</td>
<td>13</td>
</tr>
<tr>
<td><strong>VF, n = 9</strong></td>
<td>98</td>
<td>99</td>
<td>99</td>
<td>98</td>
<td>95</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td><strong>(2 BT, 7 RL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VF, n = 1</strong></td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>97</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>(1 BT)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VF, n = 2</strong></td>
<td>98</td>
<td>99</td>
<td>99</td>
<td>95</td>
<td>95</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>(2 RL)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VF, n = 6</strong></td>
<td>95</td>
<td>97</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td><strong>(1 BT, 5 RL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VF, n = 0</strong></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

* Pooled SVR12 data from arms of nine phase 2 or 3 clinical trials (EXPEDITION-2; EXPEDITION-4; ENDURANCE 1, 2, 3 and 4; SURVEYOR-I Part 2; SURVEYOR-II Parts 1 and 2; and SURVEYOR-II Part 4 studies);
† Treatment experienced to pegIFN + RBV ± SOF; † All GT3 patients were treatment naive.
BT, breakthrough; RL, relapse; VF, virologic failure.

Integrated Efficacy Analysis:* G/P for 12 Weeks in GT1–6 Treatment-Naive Patients with Cirrhosis

ITT, SVR12 (%) in GT1–6

- Overall: 98%
- GT1: 97%
- GT2: 100%
- GT3: 99%
- GT4–6: 100%

* ITT SVR12 data from the pooled resistance analysis of G/P from phase 2 and 3 clinical studies (SURVEYOR-1 and -2; ENDURANCE-1–4; EXPEDITION-1 and -4).

POLARIS-2: SOF/VEL/VOX for 8 Weeks in DAA-Naive HCV-Infected Patients with and without Cirrhosis

- **ITT, SVR12 (%)**
  - Overall: 95, 93, 92, 97, 97, 99, 100
  - GT1: 98, 98, 99, 97, 100, 99, 97
  - GT1a: 800,000 IU/mL, BMI ≥ 30 kg/m², Q80K/L/R RAS, IL28B non-CC

In GT1a patients without cirrhosis, response was influenced by baseline HCV RNA ≥ 800,000 IU/mL, BMI ≥ 30 kg/m², Q80K/L/R RAS, IL28B non-CC

* “Other” includes patients with missing data and those that discontinued treatment prior to virologic suppression.

English Hepatitis C Registry: SVR12

- SVR12 for all patients: 95.59%
- SVR12 for GT3 patients: 95.04%

English Hepatitis C Registry: SVR12 in GT3 by Regimen and Severity of Liver Disease

*SVR significantly improved with SOF/VEL + RBV vs SOF/VEL or SOF + DCV + RBV in this subgroup.
†8 wks if no, mild, or moderate fibrosis; 12 wks if compensated cirrhosis. ‡12 wks if no, mild, or moderate fibrosis.

Difficult-to-treat patients: any left?
Genotype 3 with cirrhosis

GLE/PBR for 12 or 16 weeks in genotype 3 patients with compensated cirrhosis

Pooled analysis 7 phase 2/3 trials: Naïve patients

<table>
<thead>
<tr>
<th>Weeks cirrhosis</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 No</td>
<td>198/203</td>
</tr>
<tr>
<td>12 No</td>
<td>280/284</td>
</tr>
<tr>
<td>12 Yes</td>
<td>67/67</td>
</tr>
</tbody>
</table>

SURVEYOR-II, Part 3

<table>
<thead>
<tr>
<th>Weeks</th>
<th>SVR12 (%)</th>
<th>2 relapses</th>
<th>1 relapse</th>
<th>1 LTFU</th>
<th>1 breakthrough</th>
<th>1 relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE</td>
<td>91/96</td>
<td>20/22</td>
<td>21/22</td>
<td>39/40</td>
<td>45/47</td>
<td></td>
</tr>
<tr>
<td>TE*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic 12 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic 16 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhotic 12 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhotic 16 weeks</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Includes SOF-experienced patients
Genotype 3 with cirrhosis

POLARIS-2, and 3 (integrated efficacy analysis): SOF/VEL/VOX for 8 weeks in DAA-naïve patients

**Metavir F3**
- Genotype 3: 100%
- Genotype 5: 100%
- Genotype 6: 100%
- Total: 96%

**Metavir F4**
- Genotype 3: 98%
- Genotype 5: 100%
- Genotype 6: 100%
- Total: 95%

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Lawitz E, et al. EASL 2017, THU-273
Effectiveness of Therapy in 16,756 DAA Treated People in England: High Response Rates in GT3 HCV Infection Regardless of Degree of Fibrosis, But RBV Improves Response in Cirrhosis

Meta-analysis of the England Hepatitis C Treatment Registry to determine the effects of liver disease stage on patient outcomes when using different DAA regimens to treat HCV GT3 (N=16,756*)

Overall PP SVR12 rate was 96% in all GTs

In patients with HCV GT3 SVR12 rate was 95%

High SVR rates with 12 weeks of G/P were achieved in patients with GT3 and compensated cirrhosis

8 weeks of G/P and 12 weeks of SOF/VEL in patients with HCV GT3 and moderate fibrosis have similar efficacy. Addition of RBV to SOF/VEL significantly increases efficacy in patients with HCV GT3 and compensated cirrhosis

*Patients who received a valid treatment; †Graphical data has been estimated from the provided source presentation but no exact numbers are available; ‡G/P is contraindicated in patients with severe hepatic impairment (Child-Pugh C); §Treatment durations with G/P were 8 weeks in patients with no fibrosis, mild fibrosis or moderate fibrosis and 12 weeks in patients with compensated cirrhosis, past decompensated cirrhosis or decompensated cirrhosis; ‖Treatment durations were 12 weeks with SOF/VEL ± RBV for all stages of liver disease.

Genotype 3 with cirrhosis

ASTRAL-4: SOF/VEL in patients with decompensated cirrhosis

- **Overall**: 83/94, 86/94, 88/88, 86/90, 92/90, 96/96, 85/100, 86/86
- **GT I**: 75/90, 82/87, 77/90, 60/68, 65/68, 65/71, 7/14, 11/13, 6/12, GT2 4/4, GT4 4/4, GT4 2/2, GT6 3/4
- **GT 3**: 100, 100, 50, 50, GT2 4/4, GT4 2/2, GT6 1/1

SVR12 (%)
<table>
<thead>
<tr>
<th>Patients</th>
<th>Glecaprevir Pibrentasvir</th>
<th>Sofosbuvir Velpatasvir Voxilaprevir</th>
<th>Sofosbuvir Velpatasvir RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 3 Naïve Compensated cirrhosis</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>No</td>
</tr>
<tr>
<td>Genotype 3 Treatment-experienced Compensated cirrhosis</td>
<td>16 weeks</td>
<td>12 weeks</td>
<td>No</td>
</tr>
<tr>
<td>Genotype 3 Decompensated cirrhosis</td>
<td>No</td>
<td>No</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

www.hep-druginteractions.org
Smartphone App HEP iChart
Genotype 1a P/R experienced with cirrhosis

ASTRAL-1: SOF/VEL FOR 12 weeks. No impact of genotype

SVR12 (%)

- Total: 99% (618/624)
- Genotype 1a: 98% (206/210)
- Genotype 1b: 99% (117/118)
- Genotype 2: 100% (104/104)
- Genotype 4: 100% (116/116)
- Genotype 5: 97% (34/35)
- Genotype 6: 100% (41/41)

Genotype 1a P/R experienced with cirrhosis

ASTRAL-1: SOF/VEL FOR 12 weeks. No impact of cirrhosis and patient status

SVR12 (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Non-cirrhotic</th>
<th>Cirrhotic</th>
<th>Treatment-naïve</th>
<th>Treatment-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Patients</td>
<td>618/624</td>
<td>496/501</td>
<td>120/121</td>
<td>418/423</td>
<td>200/201</td>
</tr>
</tbody>
</table>

Genotype 1a P/R experienced with cirrhosis
Glecaprevir/Pibrentasvir for 8 or 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>GT1</th>
<th>GT2</th>
<th>GT3†</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVR12 (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>mITT, SVR12 (%)</strong></td>
<td>943</td>
<td>470</td>
<td>202</td>
<td>198</td>
<td>59</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td><strong>952</strong></td>
<td>471</td>
<td>204</td>
<td>204</td>
<td>59</td>
<td>2</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

**Integrated analysis: G/P for 8 Weeks in treatment-naive and -experienced* patients without cirrhosis**

- Overall: 99%
- GT1: 99%
- GT2: 99%
- GT3: 97%
- GT4: 100%
- GT5: 100%
- GT6: 100%

**EXPEDITION-I: G/P for 12 weeks in naïve or treatment-experienced patients with compensated cirrhosis**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>GT1</th>
<th>GT2</th>
<th>GT3†</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVR12 (%)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>145</strong></td>
<td>146</td>
<td>89</td>
<td>31</td>
<td>16</td>
<td>2</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

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* Includes patients with prior SOF use (8-week G/P, n = 7)
† All GT3 patients were treatment naïve

Genotype 1a P/R experienced with cirrhosis

ASTRAL-4: SOF/VEL in patients with decompensated cirrhosis

### EASL 2018 recommendations

<table>
<thead>
<tr>
<th>Patients</th>
<th>Glecaprevir Pibrentasvir</th>
<th>Sofosbuvir Velpatasvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a PR treatment-experienced</td>
<td>8 weeks (no cirrhosis)</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>12 weeks (cirrhosis)</td>
<td></td>
</tr>
<tr>
<td>Genotype 1a HCV RNA &gt;800,000 IU/mL</td>
<td>8 weeks (no cirrhosis)</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>12 weeks (cirrhosis)</td>
<td></td>
</tr>
<tr>
<td>Genotype 1 Decompensated cirrhosis</td>
<td>No</td>
<td>12 weeks + RBV*</td>
</tr>
</tbody>
</table>

*SOF/LDV + RBV 12 weeks if SOF/VEL not available
Difficult-to-treat patients: any left?

When next-generation NS5A inhibitors are available, the group of difficult-to-treat patients is limited:

- Genotype 3 patients with compensated cirrhosis are easy-to-treat with SOF/VEL/VOX for 12 weeks or G/P for 12 or 16 weeks
- Genotype 1a PR treatment-experienced patients, or genotype 1a patients with HCV RNA higher than 800,000 IU/mL are easy-to-treat with SOF/VEL for 12 weeks or G/P for 8 to 12 weeks
- Genotype 1 patients with Child-Pugh B cirrhosis are easy-to-treat with SOF/VEL + RBV for 12 weeks
- However, genotype 3 patients with Child-Pugh B decompensated cirrhosis and all patients with Child-Pugh C cirrhosis remain difficult-to-treat
Do RASs still have an impact on efficacy in the pan-genotypic era?
Framework of DAAs failure in 2020

124,000 patients will be DAA failure in USA
47,000 patients will be DAAs failure in 5 European country.
Since 2015, near all patients will be NS5A failure

Chhatwal J et al., EASL 2017 abstr. FRI-233
Reasons for DAAs failure

• **Treatment regimen**
  - Specific DAAs (intrinsic barrier for specific HCV strains)
  - Duration of treatment, adherence to treatment
  - Ribavirin

• **Cirrhosis**
  - Hepatic sanctuaries with low drug exposure due to distorted liver architecture and portal shunting of drug-rich blood

• **Host innate immunity**
  - IFN-lambda-4/IL-28B

• **Resistance associated substitutions**
  - Burden of liver infection (% hepatocytes infected estimated by HCV RNA level)
  - Specific RASs present and their impact on selected DAAs
  - Proportion of hepatocytes infected with HCV with RASs (estimated by % of the circulating population)
Resistance Considerations

Which classes are prone to resistance?

Barrier to PI and NS5A resistance

Protease, NS5A, and nonnucleotide NS5B inhibitors

Higher for GT1b vs GT1a

• Most patients with failure of current DAAs have emergent resistance-associated substitutions (RASs)
  - NS5A RASs persist much longer than PI RASs
• 15% of patients have baseline NS5A RASs with variable effects on GT1a response
• Second-generation drugs designed to cover RASs
Importance of resistance
Presence and long term kinetics of RASs

GT1/GT3 cohort (n=570 DAA failures, sequential samples of n=166 patients) documented sampling time after end of treatment (EOT), mean follow-up (FU): 8.8 months (0.2 – 56.0)

NS3 RASs

Follow up in months (FU)

Dietz et al., PS179, EASL 2019
Retreatment strategy depends on initial regimen

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
</table>
| After failure of PEG-IFNα + RBV, SOF + PEG-IFNα/RBV or SOF + RBV  
  • Retreat according to recommendations for TE patients, by HCV genotype | A | 1 |
| HCV resistance testing after failure of any DAA-based regimen (excluding regimens with SOF as the only DAA) is a useful guide to retreatment | B | 2 |
| After failure of DAA (PI and/or NS5A inhibitor)-containing regimen |
|   • First-line retreatment  
     – SOF/VEL/VOX for 12 weeks (without cirrhosis/with compensated cirrhosis)  
     – SOF/VEL + RBV* for 24 weeks (decompensated cirrhosis) | A | 1 | B | 2 |
|   • Patients with predictors of poor response, SOF + GLE/PIB for 12 weeks:  
     – Advanced liver disease  
     – Multiple courses of DAA-based treatment  
     – Complex NS5A RAS profile | B | 2 |
|   • Very difficult-to-cure patients:† SOF/VEL/VOX + RBV or SOF + GLE/PIB + RBV for 12 weeks or for 16 or 24 weeks | C | 2 |

*Daily weight-based RBV (1,000 mg or 1,200 mg in patients <75 kg or ≥75 kg, respectively); start RBV at a dose of 600 mg daily and adjust dose depending on tolerance;
†Patients with NS5A RASs who failed twice to achieve SVR after a combination regimen including a PI and/or an NSSA inhibitor.
SOF/VEL/VOX 12 weeks in DAA-experienced Patients

Bourliere M, Zeuzem S et al. NEJM 2017; 376: 2134-2146
Sofosbuvir/velpatasvir/voxilaprevir versus sofosbuvir/velpatasvir in G1-6 patients who failed DAAs regimen without NS5A.I

SOF/VEL/VOX 12 weeks (n=182) 98 96 95 89 85 53 39 23 21 31 32 51 44 19
SOF/VEL 12 weeks (n=151) 100 97 95 94 94 85 51 44 24 22 33 34 54 52 19

Zeuzem S, et al. AASLD 2016, Abs. 109 actualis
Bourliere M,...,Zeuzem S et al. NEJM 2017; 376: 2134-214
sofosbuvir/velpatasvir/voxilaprevir for 12 weeks in patients who failed DAAs regimen with NS5A.I

- 6 patients relapse (1 G1a, 4 G3 and 1 G4) all F4

Bourliere M. et al. NEJM 2017; 376: 2134-2146
SOF/VEL/VOX in patients who failed GLE/PIB

- 14 patients who failed Glecaprevir/pibrentasvir regimen were retreated with SOF/VEL/VOX 12 weeks

### Patients characteristics

<table>
<thead>
<tr>
<th></th>
<th>n = 14</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cirrhosis</strong></td>
<td>7 (50%)</td>
</tr>
<tr>
<td><strong>Genotype 1a</strong></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2/5</td>
</tr>
<tr>
<td>Relapsers</td>
<td>5/5</td>
</tr>
<tr>
<td><strong>Genotype 3</strong></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>5/9</td>
</tr>
<tr>
<td>Relapsers</td>
<td>7/9</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>2/9</td>
</tr>
<tr>
<td><strong>RAS at baseline</strong></td>
<td></td>
</tr>
<tr>
<td>NS5A</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>NS3</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>NS5A +NS3</td>
<td>6 (43%)</td>
</tr>
<tr>
<td>None</td>
<td>2 (14%)</td>
</tr>
</tbody>
</table>

1 woman HCV GT3 without cirrhosis and initial RAS A30K relapse at 4 weeks

- SOF/VEL/VOX achieve high SVR in G/P failure

Pearlman B et al., AASLD 2018, Abs. 607
SOF/VEL/VOX in DAAs failures

« real-life data »

SVR 12

% 98,5 % 91 % 93 % 95 % 100 % 99 % 94,8 %

70 79 13 38 52 163 480
71 87 14 40 52 165 503

USA Spain USA France Germany USA « TRIO » USA VA

Real-life confirms clinical trials

Covert E et al. AASLD 2018, Abs. 583
Llaneras J et al. AASLD 2018, Abs. 683
earlman B et al. AASLD 2018, Abs. 607

Hézode C et al. AASLD 2018, Abs. 629
Vermehren J et al. AASLD 2018, Abs. 676
Bacon B et al. AASLD 2018, Abs. 706
Belperio PS et al., AASLD 2018, Abs. 227
SOF/VEL/VOX in patients who failed
SOF/VEL is there an issue?

USA - VA cohort
Belperio PS, et al. AASLD 2018, Abs. 227

POLARIS 1-4
Ruane P et al; GHS 2018
Bourliere M et al NEJM 2017

USA
Germany
TRIO
Bacon B, et al AASLD 2018, Abs. 706
Vermehren J, et al AASLD 2018, Abs. 676
TRIO Network: SOF/VEL/VOX Efficacy in US Practice

- Real-world data from providers and specialty pharmacies in the TRIO Health disease management program on SOF/VEL/VOX for 12 wks initiated between July 2017 and April 2018 (N = 196)
  - 88% treatment experienced, 78% GT1 HCV, 43% stage 1-3 CKD, 42% cirrhotic, 41% HTN

<table>
<thead>
<tr>
<th>Treatment Experienced†</th>
<th>LDV/SOF ± RBV</th>
<th>SOF/VEL ± RBV</th>
<th>EBR/GZR ± RBV</th>
<th>PrOD</th>
<th>Other SOF regimens§</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>163/165</td>
<td>88/92</td>
<td>17/17</td>
<td>10/10</td>
<td>16/16</td>
</tr>
<tr>
<td>Treatment Naive</td>
<td>19/21</td>
<td>19/20</td>
<td>17/19</td>
<td>10/11</td>
<td>16/17</td>
</tr>
<tr>
<td>Any regimen</td>
<td>193/196</td>
<td>94/96</td>
<td>94/95</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

SVR12 (%)

- *Primary endpoint.
- †One patient with prior GLE/PIB achieved SVR.
- ‡Regimens prior to SOF/VEL/VOX.
- §Includes DCV + SOF (n = 10), SOF + RBV (n = 6), PegIFN + SOF + RBV (n = 1).

Sofosbuvir plus glecaprevir/pibrentasvir in G/P failure

SVR-12 according to genotype

- **GT-1a**
- Compensated cirrhosis
- Failure to SOF/LDV then to G/P

1 relapse patient

**SVR-12 96%**

SOF +G/P +RBV for 16 weeks is an option for GT-3 who have failed previous treatment with G/P

Wyles D et al, EASL 2018, Abs. PS-04
Sofosbuvir plus glecaprevir/pibrentasvir in DAAs failure (French ATU)

Virological response

End of treatment    SVR-12 (%)  SVR-4   SVR-12

All  86,5  93,3  84,8  95  100  100
SOF  45  42  28  19  15  6
G/P  81,2  90  81,5  26  27  22

SOF + G/P treatment for 12 weeks is a therapeutic option in DAAs failures

de Lédinghen V. et al. EASL 2018, Abs. THU-29
Approach to persons with HCV failure

• Consider re-infection as a cause of recurrent viremia
• Assess adherence/persistence prior regimen
• Reassess genotype
• Assess liver disease stage: No cirrhosis, cirrhosis CTP A or B/C
• No cirrhosis and single DAA failure
  - Retreat with least two DAAs predicted to be active based on prior DAA use or directly use triple regimen for 12w (SOF/VEL/VOX or SOF+G/P)
  - RAS testing not compulsory
• Cirrhosis or prior therapy with both NS5A and NS3 inhibitor
  - RAS testing recommended
  - Use only triple regimens SOF/VEL/VOX or SOF+G/P
  - (if liver functions allows use of a PI….)
  - Consider Ribavirin and extended duration (16 or 24w)
Approach to persons with 2\textsuperscript{nd} line DAA failure

- 2\textsuperscript{nd}-line DAA failures are rare
- Patients with multiple negative treatment predictors
- No approved / validated re-treatment options
- Strategies for DAA-retreatment
  - select DAAs according to viral resistance testing
  - multiple targeting regimens only (PI + NS5A + SOF)
  - extend treatment duration to 16 – 24 weeks
  - add Ribavirin
The HCV Care Cascade Involves Several Steps

Due to the length of the process, many patients are lost during the path to treatment.

1. Screen (anti-HCV)
2. Confirmed viral load
3. Link to care
4. HCV treater (see a specialist)
5. Pre-treatment assessment
6. Start of treatment
7. Week 4
8. Week 8
9. Week 12 if cirrhotic
10. SVR12 CURE

The HCV Care Cascade:
- Screen for anti-HCV
- Confirm viral load
- Link to care
- See a specialist for HCV treatment
- Pre-treatment assessment
- Start of treatment
- Follow-up visits at weeks 4, 8, and 12
- SVR12 CURE

Due to the length of the process, many patients are lost during the path to treatment.
APRI Test Is a Reliable, Non-invasive Method

Phase 3, open-label, single-arm, randomized, multicenter study to evaluate the safety and efficacy of 8 weeks of G/P in 230 treatment-naive adults with chronic HCV GT1–6 infection and APRI ≤ 1

Screening | BL | 8 weeks | Post-treatment Week 12

Open-label treatment

G/P 300/120 mg

SVR12

Patients with SVR12, %

100

mITT

ITT

0 VF
3 D/C
5 missing SVR12

APRI, aspartate aminotransferase to platelet ratio index; BL, baseline; D/C, discontinuation; VF, virologic failure.

**SMART-C: Monitoring During GLE/PIB in Treatment-Naive Patients With GT1-6 HCV Infection**

- Multicenter, randomized, open-label phase IIIb study

  Treatment-naive patients with GT1-6 HCV infection, HCV RNA > 10,000 IU/mL, and no cirrhosis* (N = 380)

  - **Simplified monitoring**: Medication dispensed at BL; no on-treatment clinic visits
  - **Standard monitoring**: Medication dispensed at BL and Wk 4; clinic visits with physician, study nurse, and pathology at Wks 4 and 8

  *Exclusion criteria: anticipated poor adherence, IDU within past 6 mos, positive urine drug screen.

  GLE/PIB With Simplified Monitoring (n = 253)
  GLE/PIB With Standard Monitoring (n = 127)

  AEs and adherence assessed by study nurse via phone contact at Wks 4 and 8 in all patients. GLE/PIB dosed orally at 300/120 mg QD.

  **Primary endpoint**: SVR12 in ITT population (6% noninferiority margin)

  **Secondary endpoints**: SVR12 in mITT and PP populations, adherence by Wk 20 pill count, treatment discontinuation and completion, safety

SMART-C: Efficacy and Safety

- VF: 2 (1.6%) standard vs 6 (2.4%) simplified
- Adherence > 95%: 98% standard vs 96% simplified

<table>
<thead>
<tr>
<th>Treatment-Emergent AEs, n (%)</th>
<th>Standard (n = 127)</th>
<th>Simplified (n = 253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>70 (55)</td>
<td>133 (53)</td>
</tr>
<tr>
<td>Grade 1/2</td>
<td>69 (54)</td>
<td>131 (52)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (0.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Common AEs (> 5%)
  - Fatigue: 30 (14) standard vs 52 (15) simplified
  - Headache: 26 (12) standard vs 43 (13) simplified
  - Nausea: 25 (12) standard vs 17 (5) simplified

- Serious AEs: 0 standard vs 3 (1.2) simplified

- Unscheduled visits
  - On treatment: 3 (2) standard vs 11 (4) simplified
  - Total: 8 (6) standard vs 20 (8) simplified

*Excludes death (n = 1), LTFU (n = 14), or missing HCV RNA (n = 1).
†Excludes discontinuation (n = 2) in addition to mITT exclusions.

Shortened Duration Pan-genotypic Therapy with G/P for 6 Weeks among People with Acute and Recent HCV Infection

Open-label study to assess the efficacy of G/P for 6 weeks in patients with acute and recent HCV infection* in Australia, New Zealand, and England (N = 30)

<table>
<thead>
<tr>
<th>Baseline Characteristics, n (%)</th>
<th>ITT population (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>30 (100)</td>
</tr>
<tr>
<td>MSM</td>
<td>26 (87)</td>
</tr>
<tr>
<td>HIV/HCV co-infection</td>
<td>23 (77)</td>
</tr>
<tr>
<td>History of IDU</td>
<td>14 (47)</td>
</tr>
<tr>
<td>HCV re-infection</td>
<td>4 (13)</td>
</tr>
<tr>
<td>HCV GT</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24 (80)</td>
</tr>
<tr>
<td>2</td>
<td>1 (3)</td>
</tr>
<tr>
<td>3</td>
<td>2 (7)</td>
</tr>
<tr>
<td>4</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

- 1 patient with acute GT1a HCV had virologic failure, confirmed as relapse on sequencing
- Patient had baseline HCV RNA level of $\sim 8 \log_{10} \text{IU/mL}$

* Recent infection defined as HCV infection of $< 12$ months' duration with a first positive anti-HCV antibody and/or HCV RNA within 6 months of enrollment and either acute clinical hepatitis within the past 12 months (jaundice or ALT > 10 × upper limit of normal) or documented anti-HCV antibody seroconversion within 18 months; † Neutropenia on day 1, resolved on treatment without intervention.

LTFU, lost to follow-up; MSM, men who have sex with men; PP, per protocol; VF, virologic failure.

Simply does not necessarily mean EASY