Is DAA treatment failure still an issue?
Disclosures

- Board member for: MSD, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, AbbVie, GSK, Vertex, Idenix, Intercept

- Speaker for: MSD, Janssen, Gilead, BMS, Abbvie, Intercept
SVR is not anymore the challenge and failure is rare

Framework of DAAs failure in 2020

Number of patients who failed DAAs regimen with or without NS5A.I in France, between 2014 and 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)

Courtesy from Mark Sulkoswsi
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
The utility of HCV resistance testing prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown.

- If reliable resistance testing is performed, retreatment can be guided by probabilities of response according to the resistance team (B2).

Patients who failed on a regimen containing SOF + SMV should be retreated with a combination of SOF + NS5A inhibitor (B1).

Patients infected with HCV genotype 2,3, 5 and 6 who failed on a regimen containing an NS5A inhibitor should be retreated with SOF/VEL + RBV for 24 weeks.

Patients infected with HCV genotype 1 or 4 who failed on a regimen containing an NS5A inhibitor should be retreated with (B1):

- a combination of SOF + PrOD + RBV
- a combination of SOF + EBR/GZV + RBV
- a combination of SOF + SMV + DCV + RBV
- 12 weeks for genotype 1b or 4 patients with METAVIR score F0 to F2
- 24 weeks plus ribavirin for all patients with genotype 1a and for genotype 1b and 4 patients with METAVIR score F3 or with compensated cirrhosis)
AASLD/ IDSA recommendations 2018 for treatment failures

<table>
<thead>
<tr>
<th>GT</th>
<th>Failed treatment</th>
<th>GZR/E LB</th>
<th>SOF/LDV</th>
<th>SOF/VEL</th>
<th>GLE/PIB</th>
<th>SOF/VEL/VOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>NS3+PR</td>
<td>12w(F0-F3)</td>
<td>12w</td>
<td>12w</td>
<td>12w</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non NS5A</td>
<td>12w (1b)</td>
<td>12w</td>
<td>12w</td>
<td>12w</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS5A</td>
<td>16w (Iia,B)</td>
<td>12w</td>
<td>12w</td>
<td>12w</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>SOF+RBV</td>
<td>12w</td>
<td>12w</td>
<td>12w</td>
<td>12w (+RBV if F4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DAAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12w</td>
</tr>
<tr>
<td>G3</td>
<td>DAAs</td>
<td></td>
<td></td>
<td></td>
<td>12w</td>
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<tr>
<td>G4</td>
<td>DAAs</td>
<td></td>
<td></td>
<td></td>
<td>12w</td>
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</table>

EASL recommendations 2018 for treatment failures

<table>
<thead>
<tr>
<th>GT</th>
<th>Failed treatment</th>
<th>GZR/EL B</th>
<th>SOF/LDV</th>
<th>SOF/VEL</th>
<th>GLE/PIB</th>
<th>SOF/VEL/VOX</th>
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</thead>
<tbody>
<tr>
<td>G1</td>
<td>DAAs</td>
<td></td>
<td></td>
<td></td>
<td>12w +SOF</td>
<td>12w</td>
</tr>
<tr>
<td>G2</td>
<td>DAAs</td>
<td></td>
<td></td>
<td></td>
<td>12w+SOF</td>
<td>12W</td>
</tr>
<tr>
<td>G3</td>
<td>DAAs</td>
<td></td>
<td></td>
<td></td>
<td>12W+SOF</td>
<td>12w</td>
</tr>
<tr>
<td>G4</td>
<td>DAAs</td>
<td></td>
<td></td>
<td></td>
<td>12W+SOF</td>
<td>12w</td>
</tr>
</tbody>
</table>

Pts who failed twice DAAs with NS5A RASs: SOF/VEL/VOX +RBV or SOF+GLE/PIB+RBV 16-24w
Pts with decompensated cirrhosis: SOF/VEL+ RBV 24w
Glecaprevir/pibrentasvir (G/P) in DAAs failure (1)

Poordard F. et al. EASL 2017, Abs. PS-156

Randomisation 1:1

12 weeks
n = 44 (43 G1, 1 G4)

16 weeks
n = 47 (43 G1, 3 G4)

SVR 12, % patients

12 weeks
89
39
44

16 weeks
91
43
47

Breakthrough
Virological relapse
12 weeks
1 (2 %)
4 (9 %)

16 weeks
4 (9 %)
0

Poordard F. et al.. EASL 2017, Abs. PS-156
Glecaprevir/pibrentasvir (G/P) in DAAs failure(2)

**Impact of cirrhosis**

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Régimen</th>
<th>SVR 12, % patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>G/P – 12 weeks</td>
<td>83</td>
</tr>
<tr>
<td>Yes</td>
<td>G/P – 12 weeks</td>
<td>93</td>
</tr>
<tr>
<td>No</td>
<td>G/P – 16 weeks</td>
<td>97</td>
</tr>
<tr>
<td>Yes</td>
<td>G/P – 16 weeks</td>
<td>75</td>
</tr>
</tbody>
</table>

**Impact of previous DAAs regimen**

<table>
<thead>
<tr>
<th>Previous DAAs</th>
<th>G/P – 12 weeks</th>
<th>G/P – 16 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI only</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>NS5A only</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>PI + NS5A</td>
<td>79</td>
<td>81</td>
</tr>
</tbody>
</table>

**Impact of RASs**

<table>
<thead>
<tr>
<th>RASs before treatment</th>
<th>G/P – 12 weeks</th>
<th>G/P – 16 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>NS3 only</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>NS5A only</td>
<td>83</td>
<td>96</td>
</tr>
<tr>
<td>NS3 + NS5A</td>
<td>80</td>
<td>25</td>
</tr>
</tbody>
</table>

Not an optimal option for NS5A failure especially in those who harbor NS5A + NS3 RASs

Poordard F. et al.. EASL 2017, Abs. PS-156
GLE/PIB in genotype 1 patients who failed DAAS regimen with NS5A I.

SVR 12 according to subtypes and treatment duration

- **G/P x 12 weeks**
  - All: 89% (88/99), GT-1b: 95% (20/21), GT-1a: 87% (68/78)
  - 4 relapse, 5 BT, 1 reinfection, 1 death

- **G/P x 16 weeks**
  - All: 95% (74/78), GT-1b: 100% (13/13), GT-1a: 94% (61/65)
  - 3 relapse, 1 BT

→ **G/P 12 or 16 weeks may be an option for patients with GT-1b but not in patients with GT-1a**

Sulkowski M et al., AASLD 2018, Abs. 226
SOF/VEL/VOX 12 weeks in DAA-experienced Patients

Overall NS5A Inhibitors (POLARIS-1) Other DAAs (POLARIS-4)

97  96  97

SVR12 (%)

6 relapses 1 on-treatment failure* 1 relapse
1 withdrew consent 1 LTFU 3 LTFU
1 LTFU 1 death

Bourliere M, ....,Zeuzem S et al. NEJM 2017; 376: 2134-2146
SOF/VEL/VOX 12 weeks (n=182)

SOF/VEL 12 weeks (n=151)

SVR12, %

GT 1a  
GT 1b  
GT 2  
GT 3  
GT 4

Zeuzem S, et al. AASLD 2016, Abs. 109 actualisé
Bourliere M,...,Zeuzem S et al. NEJM 2017; 376: 2134-2146
POLARIS-1: sofosbuvir/velpatasvir/voxilaprevir for 12 weeks in patients who failed DAAs regimen with NS5A.I

SVR 12

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

Bourliere M et al. NEJM 2017; 376: 2134-2146
No impact of RASs on high efficacy of SOF/VEL/VOX for 12 weeks in DAA experienced patients

Sarrazin C et al. J Hepatol 2018 ; 69:1221-1230
No impact of RASs on high efficacy of SOF/VEL/VOX for 12 weeks in DAA experienced patients

SVR according to genotype and baseline RAS

Sarrazin C et al. J Hepatol 2018; 69:1221-1230
No impact of RASs on high efficacy of SOF/VEL/VOX for 12 weeks in DAA experienced patients

SVR according to the number of baseline RAS

SVR according NS5A RAS position

Sarrazin C et al. J Hepatol 2018; 69:1221-1230
Is there any issue with emergent RASs in patients who failed SOF/VEL/VOX?

<table>
<thead>
<tr>
<th>Study</th>
<th>GT</th>
<th>Cirrhosis</th>
<th>NS3 RASs</th>
<th>NS5A RASs</th>
<th>NS5B NI RASs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>Relapse</td>
<td>Baseline</td>
</tr>
<tr>
<td>Polaris-1</td>
<td>1a</td>
<td>Yes</td>
<td>Q80K &gt;99%</td>
<td>Q80K &gt;99%</td>
<td>Q30T, L31M</td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>Yes</td>
<td>Q80K &gt;99%</td>
<td>Q80K &gt;99%</td>
<td>Y93N 98%</td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>Y93H 72%</td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>Y93H 31%</td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>A30K 99%</td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>4d</td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>L30R</td>
</tr>
<tr>
<td>Polaris-4</td>
<td>1a</td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Deferred Polaris-1</td>
<td>1a</td>
<td>No</td>
<td>Q80K</td>
<td>Q80K</td>
<td>M28T Q30H</td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>Yes</td>
<td>T54S V55I</td>
<td>T54S V55I</td>
<td>Q30Q/L Y93Y/H</td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>Y56H D168A/V</td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>No</td>
<td>Q80K</td>
<td>V36V/A Q80K</td>
<td>M28T Q30H H58N</td>
</tr>
</tbody>
</table>

Sarrazin C et al. J Hepatol 2018; 69:1221-1230
Bourliere, M et al. Lancet HG 2018: 3:559-65
SOF/VEL/VOX in DAAs failures « real-life data »

Real-life confirms clinical trials

<table>
<thead>
<tr>
<th>Country</th>
<th>SVR 12 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>98.5</td>
</tr>
<tr>
<td>Spain</td>
<td>91</td>
</tr>
<tr>
<td>USA</td>
<td>93</td>
</tr>
<tr>
<td>France</td>
<td>95</td>
</tr>
<tr>
<td>Germany</td>
<td>100</td>
</tr>
<tr>
<td>USA « TRIO »</td>
<td>99</td>
</tr>
<tr>
<td>USA VA</td>
<td>94.8</td>
</tr>
</tbody>
</table>

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

POLARIS 1-4

USA TRIO

Belperio PS, et al. AASLD 2018, Abs. 227

Ruane P et al; GHS 2018
Bourliere M et al NEJM 2017

Bacon B, et al AASLD 2018, Abs. 706
Vermehren J, et al AASLD 2018, Abs. 676
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>5 (36 %)</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>9 (64 %)</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>12 (86 %)</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*
**Sofosbuvir plus glecaprevir/pibrentasvir in G/P failure**

- **MAGELLAN-3**, Evaluate efficacy and safety of sofosbuvir + G/P + ribavirin for 12 or 16 weeks in patients who failed a previous treatment with G/P

### Study design and patient's characteristic

<table>
<thead>
<tr>
<th>RAS s at baseline</th>
<th>GT- non 3 without cirrhosis 12 weeks (n = 2)</th>
<th>GT-3+ GT-non 3 + cirrhosis 16 weeks (n = 21)</th>
<th>All (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3 only</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NS5A only</td>
<td>2 (100)</td>
<td>16 (76,2)</td>
<td>18 (78,3)</td>
</tr>
<tr>
<td>NS3 + NS5A</td>
<td>0</td>
<td>5 (23,8)</td>
<td>5 (21,7)</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Wyles D. et al., EASL 2018, Abs. PS-04
Sofosbuvir plus glecaprevir/pibrentasvir in G/P failure

SVR-12 according to genotype

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

→ 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-040
Sofosbuvir plus glecaprevir/pibrentasvir in DAAs failure

In the French ATU

Virological response

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

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de Lédinghen V. et al. EASL 2018, Abs. THU-29
We have options for any DAAs failure in 2019

**DAA1 non NS5A**: SOF+PEG±RBV, SOF±RBV, SOF+SMV±RBV,

**DAA1 NS5A**: LDV/SOF±RBV, SOF+DCV±RBV, DCV+PEG±RBV,

**DAA2 NS5A**: SOF/VEL/VOX, glecaprevir/pibrentasvir, SOF+ glecaprevir/pibrentasvir
Conclusions
Approach to persons with HCV failure

• Consider re-infection as a cause of recurrent viremia
• Assess adherence/persistence prior regimen
• Assess 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 recommended
• Cirrhosis or prior therapy with both NS5A and NS3 protease inhibitor
  – RAS testing recommended?
  – Consider triple regimens SOF/VEL/VOX or SOF+G/P
  – Consider Ribavirin and extended duration (16 or 24w)

(not really useful so far!!)