Role of resistance and resistance testing for managing HCV

3rd International HIV/Viral Hepatitis Co-Infection Meeting, AIDS 2016, Sunday 17th July 2016, Durban, South Africa

Jürgen Kurt Rockstroh
Department of Medicine I,
University Hospital Bonn,
Bonn, Germany
Conflict of Interest

Jürgen Rockstroh has received:

- Honoraria for lectures and/or consultancies from Abbott, AbbVie, Bionor, BMS, Cipla, Gilead, Janssen, Merck and ViiV.
- Research grants from Dt. Leberstiftung, DZIF, NEAT ID.
General aspects of DAA resistance
General aspects

• The advent of direct-acting agents (DAAs) has improved treatment of HCV but may be limited by primary drug resistance and also development of RAS (resistance-associated substitutions) in the setting of virological failure
Not All Direct-Acting Antivirals are Created Equal

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protease Inhibitor*</th>
<th>Protease Inhibitor**</th>
<th>NS5A Inhibitor</th>
<th>Nuc Polymerase Inhibitor</th>
<th>Non-Nuc Polymerase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance profile</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Pangenotypic efficacy</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Antiviral potency</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Adverse events</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

- ● Good profile
- ● Average profile
- ● Least favorable profile

*First generation. **Second generation.
Prevalence of Baseline GT1a NS5A RAVs: Impact of RAV Definition and Sensitivity of Detection

NS5A Inhibitor Class RAVs detected in this study at amino acid positions:
M28(all), Q30(all), L31(all), P32L, H58D/R, and Y93(all)

Ombitasvir-specific RAVs detected in this study:
M28T/V, Q30E/R, H58D, Y93C/F/H/L/N

1% Detection Threshold
- NS5A class RAVs present: 28%
- No RAV: 72%

15% Detection Threshold
- NS5A class RAVs present: 15%
- No RAV: 85%

1% Detection Threshold
- 1 RAV: 19%
- ≥ 2 RAVs: 4%
- No RAV: 77%

15% Detection Threshold
- 1 RAV: 1%
- No RAV: 88%

Stopping Rules—The Facts: Multiple Mutations May Be More Troublesome

- Loss of detectable resistance in patients with resistant variant(s) at failure of TVR + pegIFN/RBV (analysis includes only patients with follow-up data)

<table>
<thead>
<tr>
<th></th>
<th>V36M Alone*</th>
<th>R155K Alone†</th>
<th>V36M + R155K</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of 1a failures</td>
<td>10</td>
<td>20</td>
<td>46</td>
</tr>
<tr>
<td>(WT: 16%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median mos to loss</td>
<td>6 (4-9)</td>
<td>10 (9-13)</td>
<td>13 (10-13)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Comparison of V36M vs V36M + R155K: \( P < .0001 \). †Comparison of R155K vs V36M + R155K: \( P = .48 \).

Long-Term Persistence of HCV NS5A Variants After Treatment With LDV

- NS5A RAVs in patients who failed HCV treatment with ledipasvir (LDV) in the absence SOF
  - Positions 24, 28, 30, 31, 32, 58, 93 that confer >2.5-fold reduced susceptibility to LDV in vitro were included

Almost all patients developed NS5A RAVs at treatment failure

Wyles D, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O059.
Persistence of RAVs in Patients who Relapsed after 3D

67/2510 patients with genotype 1a and virologic failure after 3D

<table>
<thead>
<tr>
<th>RAVs Location</th>
<th>24 wks post-treatment</th>
<th>48 wks post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3 RAVs (paritaprevir)</td>
<td>46% (N=67)</td>
<td>9% (N=57)</td>
</tr>
<tr>
<td>NS5A RAVs (ombitasvir)</td>
<td>97% (N=70)</td>
<td>96% (N=51)</td>
</tr>
<tr>
<td>NS5B RAVs (dasabuvir)</td>
<td>75% (N=44)</td>
<td>57% (N=35)</td>
</tr>
</tbody>
</table>

(Krishnan et al., EASL 2015)
What do the guidelines say?
EASL Recommendations on Treatment of Hepatitis C 2015

European Association for the Study of the Liver *

- The HCV genotype and genotype 1 subtype (1a/1b) must be assessed prior to treatment initiation and will determine the choice of therapy (A1)

- \textit{IL28B} genotyping has no role in the indication for treating hepatitis C with the new DAAs (A1)

- HCV resistance testing should not be performed prior to therapy, because the SVR rates are very high both in patients without and with detectable amounts of resistance-associated variants by means of population sequencing at baseline (with the exception of patients infected with subtype 1a who receive the combination of PegIFN-\(\alpha\), ribavirin and simeprevir) (A1)

- The utility of HCV resistance testing (i.e. the determination of the sequence of the DAA target region) prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown (B2)
What does the label say?
What does the label say?

• When considering OLYSIO (Simeprevir) combination treatment with peginterferon alfa and ribavirin in HCV genotype 1a patients, patients should be tested for the presence of virus with the NS3 Q80K polymorphism before starting treatment.

• Zepatier label USA: Genotype 1a: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended.

• Daklinza® (daclatasvir) and Sunvepra® (asunaprevir) licensed in Japan.
QUEST: No Benefit of Simeprevir if Q80K Positive

Q80K present in 34% of GT1a patients
No benefit of simeprevir if Q80K positive

OPTIMIST 2: SMV + SOF in HCV Mono-Infx with GT1 and Cirrhosis

- SVR12 Rates (95% CI) by:

### Prior Treatment History
- **Treatment-naïve**
  - 88 (94.0; 100)
  - 44/50

- **Treatment-experienced**
  - 79 (87.0; 100)
  - 42/53

### IL28B Genotype
- **CC**
  - 86 (98.8; 100)
  - 25/29

- **CT**
  - 85 (92.1; 100)
  - 40/54

- **TT**
  - 79 (80.1; 100)
  - 15/19

### HCV Geno/Subtype, and Baseline Q80k
- **GT1a**
  - 83 (92.8; 100)
  - 60/72

- **GT1a with Q80k**
  - 74 (60.1; 86.9)
  - 25/34

- **GT1a without Q80k**
  - 92 (74.0; 93.2)
  - 35/34

- **GT1b**
  - 84 (82.7; 100)
  - 26/31

### Platelets, Albumin, and FibroScan Score (Intent-to-treat Population)
- **Platelets <90,000/mm³**
  - 68 (90.7; 100)
  - 13/19

- **Platelets ≥90,000/mm³**
  - 87 (89.1; 100)
  - 73/54

- **Albumin <4 g/dL**
  - 74 (93.1; 100)
  - 32/53

- **Albumin ≥4 g/dL**
  - 94 (89.1; 100)
  - 47/50

- **FibroScan Score >20 kPa**
  - 80 (68.2; 85.1)
  - 12/15

- **FibroScan Score >12.5-20 kPa**
  - 100 (93.1; 100)
  - 11/11

---

#AIDS2016 | @AIDS_conference

Lawitz E, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TULBPE11
C-EDGE TN + C-EDGE CO-INFECTION: NS3/4A Resistance Associated Variants

<table>
<thead>
<tr>
<th></th>
<th>RAV Status in Patients with Baseline Sequence</th>
<th>SVR12</th>
<th>SVR12 NS3 RAVs ≤5-fold potency loss</th>
<th>SVR12 NS3 RAVs &gt;5-fold potency loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n/m)</td>
<td>% (N/n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 1a RAVS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline NS3 RAVS</td>
<td>53.4 (155/290)</td>
<td>96.1</td>
<td>(149/155)</td>
<td>96.1 (149/155)</td>
</tr>
<tr>
<td>No baseline NS3 RAVs</td>
<td>46.6 (135/290)</td>
<td>93.3</td>
<td>(126/135)</td>
<td></td>
</tr>
<tr>
<td>Genotype 1b RAVS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline NS3 RAVS</td>
<td>17.4 (30/172)</td>
<td>96.7</td>
<td>(29/30)</td>
<td>96.1 (25/26)</td>
</tr>
<tr>
<td>No baseline NS3 RAVs</td>
<td>82 (142/172)</td>
<td>99.3</td>
<td>(141/142)</td>
<td></td>
</tr>
</tbody>
</table>

†The resistance analysis population includes all patients from the full analysis set who have sequencing data available and who either achieved SVR12 or met criteria for virologic failure

N = number of patients who achieved SVR12
m = number of patients with evaluable baseline sequence
n = number of patients with or without a baseline RAV


The following NS3 RAV(s) are considered to have >5-fold resistance to GZR based on GT1a replicons: Y56H, R155G/T/W, A156G/T/V/L, D168A/G/T/V/L/I/F/Y/E/H/K/R.
# C-EDGE TN + C-EDGE CO-INFECTION: NS5A Resistance Associated Variants

## Resistance analysis population (294 GT1a; 173 GT1b)†

<table>
<thead>
<tr>
<th></th>
<th>RAV Status in Patients with Baseline Sequence % (n/m)</th>
<th>SVR12 All Patients % (N/n)</th>
<th>SVR12 NS5A RAVs ≤5-fold potency loss</th>
<th>SVR12 NS5A RAVs &gt;5-fold potency loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a RAVS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline NS5A RAVs</td>
<td>9.9 (29/294)</td>
<td>65.5 (19/29)</td>
<td>87.5 (14/16)</td>
<td>38.5 (5/13)</td>
</tr>
<tr>
<td>No baseline NS5A RAVs</td>
<td>90.1 (265/294)</td>
<td>98.1 (260/265)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Genotype 1b RAVS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline NS5A RAVs</td>
<td>13.3 (23/173)</td>
<td>95.7 (22/23)</td>
<td>100 (1/1)</td>
<td>95.5 (21/22)</td>
</tr>
<tr>
<td>No baseline NS5A RAVs</td>
<td>86.7 (150/173)</td>
<td>99.3 (149/150)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

†The resistance analysis population includes all patients from the full analysis set who have sequencing data available and who either achieved SVR12 or met criteria for virologic failure.

N = number of patients who achieved SVR12

m = number of patients with evaluable baseline sequence

n = number of patients with or without a baseline RAV

Signature NS5A loci included the substitutions M28T/V/A, Q30E/H/R/G/K/L/D, L31M/V/F, H58D, and Y93C/H/N/S for GT1a and the substitutions L28T/V/A, R30E/H/G/K/L/D, L31M/V/F, P58D and Y93C/H/N/S for GT1b.

Based on the available GT1a replicon data, the following variants are considered to have >5-fold resistance to EBR: M/L28T/A, Q/R30E/H/R/G/K/L/D, L31M/V/F, H58D, Y93C/H.

#AIDS2016 | @AIDS_conference
Daclatasvir + Asunaprevir: High SVR across all patient types without baseline L31 and/or Y93H polymorphisms

Korea and Taiwan combined (N = 124)

<table>
<thead>
<tr>
<th>Category</th>
<th>L31 and/or Y93H</th>
<th>No L31 or Y93H</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>37.5</td>
<td>91.7</td>
</tr>
<tr>
<td>Treatment-naive</td>
<td>75.0</td>
<td>97.1</td>
</tr>
<tr>
<td>Prior non-responders</td>
<td>20.0</td>
<td>88.9</td>
</tr>
<tr>
<td>IFN ineligible/intolerant</td>
<td>28.6</td>
<td>89.2</td>
</tr>
</tbody>
</table>

Proportion with SVR12 (%)

#AIDS2016 | @AIDS_conference

SVR to Sofosbuvir/Ledipasvir According to NS5A RAVs (513 cirrhotic patients)

Sarrazin et al., EASL 2015
Impact of Baseline GT1a NS5A Class RAVs and Ombitasvir-specific RAVs on SVR Rate

Similar SVR rates were observed irrespective of the presence or absence of baseline variants

Can a resistance test guide treatment decision making in patients with prior failure of DAA based therapy?
### Retreatment of Patients Who Failed 8 or 12 Weeks of LDV/SOF-Based Regimens With LDV/SOF for 24 Weeks

#### SVR according to baseline parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Cirrhosis</th>
<th>Yes Cirrhosis</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>No Baseline</th>
<th>Yes Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of NS5A RAVs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior HCV treatment duration, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 weeks</td>
<td>68</td>
<td>74</td>
<td>80</td>
<td>46</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>Presence of NS5A RAVs</td>
<td>19</td>
<td>15</td>
<td>30 (73)</td>
<td>30 (73)</td>
<td>19 (63)</td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>11</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Study Details

Mean HCV RNA, log_{10}IU/mL (range) 6.2 (4.5-7.4)

Lawitz E, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O005.
Results and Analysis

• Prior to re-treat
  – No NS5B resistance associated (S282T) or treatment-emergent (L159F, V321A) variants were detected

• At second virologic failure
  – 4 of 12 (33%) patients had NS5B variants detected
    • S282T (n=2)
    • L159F (n=1)
    • Double-mutant S282T + L159F (n=1)

SVR12 by Baseline NS5A RAVs
GT 1 Retreatment

SVR12 (%)
Re-treatment after failure to LDV/SOF

- 9 patients without SVR in ION-4 after 12 weeks of LDV/SOF

<table>
<thead>
<tr>
<th>GT</th>
<th>NS5A RAVs Before Primary Study (%)</th>
<th>NS5A RAVs at Virologic Relapse After Primary Study (5)</th>
<th>SRV12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>1a</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>1a</td>
<td>L31M (&gt;99), H58D (92)</td>
<td>L31M (&gt;99), H58D (92)</td>
<td>Yes</td>
</tr>
<tr>
<td>1a</td>
<td>Y93F (1), Y93N (10)</td>
<td>Y93N (&lt;99)</td>
<td>Yes</td>
</tr>
<tr>
<td>1a</td>
<td>L31M (&gt;99), Y93N (&lt;25)</td>
<td>L31M (&gt;99), Y93N (&gt;99)</td>
<td>Yes</td>
</tr>
<tr>
<td>1a*</td>
<td>None</td>
<td>Y93N (&gt;99)</td>
<td>Yes</td>
</tr>
<tr>
<td>1b</td>
<td>Y93H (&gt;99)</td>
<td>L31I (11), Y93H (&gt;99)</td>
<td>Yes</td>
</tr>
<tr>
<td>1b</td>
<td>None</td>
<td>L31V (&gt;99)</td>
<td>Yes</td>
</tr>
<tr>
<td>1a</td>
<td>None</td>
<td>L31M (&gt;99)</td>
<td>No</td>
</tr>
</tbody>
</table>

SVR in 8/9; 1 relapse 4 weeks after EOT: GT1a, no cirrhosis

#AIDS2016  | @AIDS_conference
Retreatment of Patients Who Failed DAA-combination Therapies - Real-world Experience From a Large Hepatitis C Resistance Database

- Subset of the European resistance database (n=3549) with persons who failed DAAs outside of clinical trials (N=310) – drug-class specific RASs (NS3, NS5A, NS5B) associated with > 2-fold increase in EC50
- Assess HCV guidelines approach to re-treatment:
  1. Use active DAAs
  2. Add RBV
  3. Longer duration

<table>
<thead>
<tr>
<th>N = 310</th>
<th>SMV/S OF ± RBV N=55</th>
<th>LDV/SOF ± RBV F=114</th>
<th>DCV/SOF ± RBV F=51</th>
<th>RTV/OB V ± RBV n=30</th>
<th>SOF + RBV n=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>58 (43-75)</td>
<td>57 (34-77)</td>
<td>55 (31-71)</td>
<td>55 (34-58)</td>
<td>52 (27-65)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>43 (78)</td>
<td>94 (82)</td>
<td>42 (82)</td>
<td>26 (87)</td>
<td>47 (78)</td>
</tr>
<tr>
<td>Cerrhosis, n (%)</td>
<td>37 (71)</td>
<td>62 (57)</td>
<td>33 (70)</td>
<td>11 (37)</td>
<td>21 (44)</td>
</tr>
<tr>
<td>+RBV, n (%)</td>
<td>10 (55)</td>
<td>39 (34)</td>
<td>8 (16)</td>
<td>19 (63)</td>
<td>60 (100)</td>
</tr>
<tr>
<td>Prior IFN Therapy</td>
<td>39 (76)</td>
<td>67 (67)</td>
<td>20 (76)</td>
<td>21 (70)</td>
<td>27 (63)</td>
</tr>
<tr>
<td>G, n (%)</td>
<td>1</td>
<td>49 (89)</td>
<td>90 (79)</td>
<td>29 (57)</td>
<td>27 (90)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 (2)</td>
<td>15 (13)</td>
<td>20 (39)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5 (9)</td>
<td>9 (8)</td>
<td>2 (4)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Treatment duration 8/12/24 weeks, n</td>
<td>-/53/1</td>
<td>12/80/20</td>
<td>-/25/26</td>
<td>-/29/1</td>
<td>-/26/29</td>
</tr>
</tbody>
</table>
Retreatment after DAA Failure

- 22 of 119 patients with **G1 and NS5A treatment failure** (DCV or LDV + SOF)
- Retreatment with PI containing regimen
  - SMV/SOF +/- RBV or 3D +/- RBV for 12 or 24 weeks
  - SVR12 in 6 of 7 patients (limited data)
- 27 of 49 patients with **G1 and SMV/SOF treatment failure**
- Retreatment with NS5A containing regimen
  - LDV/SOF (n=23) or 3D (n=4) +/- RBV
  - SVR12 in 20 of 22 patients
Retreatment after DAA Failure (cont’d)

• 5 of 27 patients with **G1** and **3D** treatment failure
  – Retreatment with SOF based regimen
  – No data on outcomes

• 14 of 23 patients with **genotype 3** and SOF/RBV treatment failure
  – Retreatment with DCV (n=13) or LDV (n=1) + SOF +/- RBV
  – SVR12 in 7 of 7

Vermehren J, et al. 51st EASL; Barcelona, Spain; April 13-17, 2016. Abst. PS103.
Summary

• After IFN-free treatment failure, HCV variants resistant to protease inhibitors progressively disappear by population sequencing, replaced by wild-type virus.

• In contrast, viruses resistant to NS5A inhibitors and to NNIs persist for years.

• In most patients who fail to achieve an SVR on an IFN-free regimen, viruses that are resistant to one or more of the DAAs administered are present as the dominant species at the time of relapse.

• By means of population sequencing, HCV RAVs at baseline may have an impact on the rate of SVR with IFN-free regimens in patients with negative host factors.

• The addition of ribavirin and extending treatment duration appears to minimize the impact of pre-existing RAVs on SVR.