Prevalence of HCV resistance associated substitutions in Europe

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Erasmus Medical Center
On behalf of the HEPVIR working group
Introduction

- Direct-acting antivirals (DAAs) cure >95% of hepatitis C infected patients

- Presence of a resistance associated substitutions (RAS) can jeopardize cure rates
Different forms of RAS

- Naturally occurring
  - If present: reduce cure rate from 95% to 70%
    - Genotype
    - Drug
    - Mutation(s)

Different forms of RAS

▪ Naturally occurring
  ▪ If present: reduce cure rate from 95% to 70%
    • Genotype
    • Drug
    • Mutation(s)

▪ Treatment emerging
  ▪ Remain present for months until years
  ▪ Challenge for retreatment
    • Reduces cure rate

The aims of our study are:

1. Prevalence of natural occurring NS5A RAS
2. Prevalence of treatment emerging NS3 and NS5A RAS
Collaboration is key

- Virological failure is rare (<5%)

- Real-life sample sizes are small
HepCare

- European surveillance of Hepatitis C patients

- Collected demographic, clinical, and virological data
HepCare

- European surveillance of Hepatitis C patients

- Collected demographic, clinical, and virological data
Methods

Included

- Adults with PCR positive HCV infection
- Failure sequences available
  And/or
- Baseline sequence available

Excluded

- Chimeric genotypes
Methods

- Genotype and subtype provided by the submitter
  - in-house assays
- Reassessed with geno2pheno tool
- Aligned to reference sequence
- Trimmed to equal length
Covered RAS positions

NS5A - naturally occurring

- Based on clinically relevant RAS in literature
- All changes at the position was recorded

Kalahatgi, Sikorski et al. 2016; Sarrazin 2016; Lontok, Harrington et al. 2015; Sorbo, Cento et al. 2018
Covered RAS positions

**NS5A - naturally occurring**

Based on clinically relevant RAS in literature
All changes at the position were recorded

**NS3 – treatment emerging**

**NS5A – treatment emerging**

Kalahatgi, Sikorski et al. 2016; Sarrazin 2016; Lontok, Harrington et al. 2015; Sorbo, Cento et al. 2018
The results of our studies:

1. Prevalence of natural occurring NS5A RAS
2. Prevalence of treatment emerging NS3 and NS5A RAS
Genotype distribution baseline

838 individuals
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Total RAS prevalence (%) (95% Confidence interval)</th>
<th>RAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>14 (11.1 – 18.1)</td>
<td>M28V/L/T, Q30D/H/E/R, L31M, Y93C/H/L</td>
</tr>
<tr>
<td>1b</td>
<td>17 (12.6 – 22.8)</td>
<td>L28M, R30Q, L31M/V, Y93H</td>
</tr>
<tr>
<td>2c</td>
<td>42 (19.3 – 68.0)</td>
<td>F28C, L31M</td>
</tr>
<tr>
<td>3a</td>
<td>23 (17.4 – 30.4)</td>
<td>M28V, A30K/M/Q/S/T/V, L31I/P, Y93H</td>
</tr>
<tr>
<td>4a</td>
<td>29 (13.8 – 50.0)</td>
<td>L28M/S/V, L30F/H, M31I/L</td>
</tr>
<tr>
<td>4d</td>
<td>14 (7.2 – 24.9)</td>
<td>R30L, M31V, Y93H</td>
</tr>
</tbody>
</table>
# NS5A RAS prevalence from 14-42% at baseline

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<td>M28V/L/T, Q30D/E/H/R L31M, Y93C/H/L</td>
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**RAS >100-fold resistance NS5A inhibitors**

P.Halfon et al Hepatology 2016
Prevalence of natural occurring RAS

- Natural variation of RAS over genotype

- Prevalence varies between 14 and 42% for NS5A RAS in Europe
The aims of our study are:

1. Prevalence of natural occurring NS5A RAS
2. Prevalence of treatment emerging NS3 and NS5A RAS
Genotype distribution failure sequences

720 individuals
DAA treatment during failure

- **SOF/LDV**: 34%
- **3D**: 18%
- **SOF/DAC**: 15%
- **SOF/SIM**: 10%
- **BOC or TEL/PEG**: 8%
- **SOF/PEG**: 6%
- **GZR/ELB**: 3%
- **Other**: 3%
- **SOF/VEL**: 2%

LDV = ledipasvir, 3D = paritaprevir/ritonavir/ombitasvir, SOF = sofosbuvir, DAC = daclatasvir, SIM = simeprevir, BOC = boceprevir, TEL = telaprevir, GZR = grazoprevir, ELB = elbasvir, VEL = velpatasvir, PEG = pegylated interferon
NS3 and NS5A failures

424 failed an NS5A
NS3 and NS5A failures

424 failed an NS5A

264 failed an NS3
### 33-100% RAS in NS5A after failure

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<th>Genotype</th>
<th>Total prevalence % (95% confidence interval)</th>
<th>RAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>79 (71.4 – 84.8)</td>
<td>M28L/T/V, Q30A/D/E/H/K/R L31F/I/M/V, H58C/D/G/N/P/Y, A92P/T, Y93C/H</td>
</tr>
<tr>
<td>1b</td>
<td>86 (78.5 – 91.0)</td>
<td>L28G/M/V, R30K/Q, L31E/I/M/V, P58A/S/T, A92K/T/V, Y93C/H</td>
</tr>
<tr>
<td>2c</td>
<td>100 (51 – 100)</td>
<td>F28C, L31M, P58S, C92S</td>
</tr>
<tr>
<td>3a</td>
<td>75 (65.5 – 82.6)</td>
<td>M28L, A30K/S/T/V, L31F/I/M, P32R, P58R/S, E92A, Y93H</td>
</tr>
<tr>
<td>4a</td>
<td>66 (20.8 – 93.9)</td>
<td>L30H</td>
</tr>
<tr>
<td>4d</td>
<td>33 (23.1 – 46.6)</td>
<td>R30L, M31V, P58A/L/T, Y93H</td>
</tr>
</tbody>
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## 25–75% RAS in NS3 after failure

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Total prevalence % (95% confidence interval)</th>
<th>RAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>75 (66 – 83)</td>
<td>V36M/L, T54S, Y56H, Q80K/L, R155K, D168A/R/V, I170V</td>
</tr>
<tr>
<td>1b</td>
<td>74 (65.5 – 80.7)</td>
<td>V36I/M, Y56F/H/V, Q80D/L/R, R155Q, A156S, D168V, V170I/T</td>
</tr>
<tr>
<td>2c</td>
<td>67 (20.8 – 93.9)</td>
<td>L36V, V158M</td>
</tr>
<tr>
<td>3a</td>
<td>40 (11.8 – 76.9)</td>
<td>L36V, Q80K</td>
</tr>
<tr>
<td>4a</td>
<td>Not treated with NS3 compounds</td>
<td></td>
</tr>
<tr>
<td>4d</td>
<td>26 (13.2 – 44.7)</td>
<td>Y56H, Q80R, A156G, D168A/E/V</td>
</tr>
<tr>
<td>Genotype</td>
<td>Total prevalence % (95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>87 (75.2 – 93.5)</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>61 (64.4 – 92.1)</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>50 (15 – 85)</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>Not treated with NS3 compounds</td>
<td></td>
</tr>
<tr>
<td>4d</td>
<td>0 (0 – 65.8)</td>
<td></td>
</tr>
</tbody>
</table>
Prevalence treatment emerging RAS

- Prevalence is high among failures
  - 33-100%
  - NS5A > NS3

- Varies over geno-and subtype
  - GT1a/b > GT4

- Multiclass RAS (NS3 and NS5A)
  - Prevalence varies per genotype (0-90%)
  - Difficult for retreatment
Identifying RAS after failure is important

- Retreatment can be tailored according to presence of RAS

- Sequence NS3/NS5A and NS5B
  - Take naturally occurring mutations into account
Discussion

- To establish baseline testing recommendations
  - Clinical treatment outcome data is required

- A surveillance program is important to monitor further European RAS prevalence
  - Baseline and failure
Acknowledgements

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