Acute hepatitis C reinfection and late relapse

Thomas Martin
ACF ID/MM Guy’s and St Thomas’ NHS Foundation Trust
Overview

• Definitions
• Late relapse
• Reinfection
• HCV quasispecies and relapse
• Late relapse vs. reinfection
HCV infection relapse definitions

- Null or partial response
- Early Relapse
- Late Relapse

Treatment period:
- EOT
- 24 weeks (SVR)
HCV multiple infection definitions

- No formal definitions
- Coinfection
  - Infection with more than 1 genetically distinct virus on initial exposure
- Superinfection
  - Infection with a genetically distinct virus upon re-exposure
- Reinfection
  - Detection of HCV viraemia following exposure to HCV in an individual who has either previously spontaneously cleared or has been treated for HCV infection
- Late relapse
  - Re-remergence of a pre-existing HCV viraemia 24 weeks or more following the end of treatment
HCV reinfection and late relapse

• No formal definitions
• Coinfection
  – Infection with more than 1 genetically distinct virus on initial exposure
• Superinfection
  – Infection with a genetically distinct virus upon re-exposure
• Reinfection
  – Detection of HCV viraemia following exposure to HCV in an individual who has either previously spontaneously cleared or has been treated for HCV infection
• Late relapse
  – Re-remergence of a pre-existing HCV viraemia 24 weeks or more following the end of treatment
Overview

• Definitions
• Late relapse
• Reinfection
• HCV quasispecies and relapse
• Late relapse vs. reinfection
HCV late relapse is rare

- In long-term prospective follow up of patients enrolled in phase III trials for pegylated IFN/Rib
- N=1343; mean duration of follow up post-SVR was 47 months (range 10-87 months)
- Relapses were seen in only 0.9%
- Durable SVR found for HIV/HCV coinfected patients (N=100) (99%)
- Relapses occurred at mean of 666 days (95 weeks)

Swain MG et al. Gastroenterology 2010;139:1593-1601
HCV late relapse is rare among HIV infected individuals

- Retrospective analysis of 77 HIV/HCV coinfected patients
- Mean follow up following SVR 58 months +/- 28 months (4466 patient-months f/u)
- GT1 – 19%; GT 2+3 – 54%; GT4 – 4%
- Mean CD4 508
- No HCV re-emergence

Soriano et al. Antiviral Ther 2004; 9:987-992
Relapse following treatment mostly occurs within 12 weeks of EOT

- 270 individuals treated for chronic HCV infection with an EOT response
  - 143 of these HIV coinfected

3 very late relapses

Late relapse could be confused with reinfection

• Of the 3 late relapses
  – 2 were HIV positive
    • One had distantly related virus at relapse (gt1b)
    • One had closely related viral sequences (gt3)
  – 1 was HIV negative
    • Had distantly related viral sequences pre-post- (gt1b)

• In a follow-up case series of 4 patients with late relapse (36-48wk) 50% had genetically similar virus pre- and post-treatment

Overview

• Definitions
• Late relapse
• Reinfection
• HCV quasispecies and relapse
• Late relapse vs. reinfection
HCV reinfection is possible among chimpanzees

Challenges performed with same or different virus

Periods of viraemia in black box

HCV reinfection is possible among chimpanzees

Chimp 1: challenged with same virus develops new viraemia and hepatitis

HCV reinfection is possible among chimpanzees

Chimp 2: challenged with a different virus develops new viraemia and hepatitis

HCV reinfection is possible among chimpanzees


Chimp 4: develops viraemia after each new challenge except for last challenge where it relapses with the penultimate virus into chronic infection
## HCV reinfection among chimpanzees

Peak ALT appeared to decline with later challenges; however, necroinflammatory change consistent with hepatitis present after each episode.

<table>
<thead>
<tr>
<th>Chimpanzee</th>
<th>First challenge</th>
<th>Second challenge</th>
<th>Third challenge</th>
<th>Fourth challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Source of HCV inoculum</td>
<td>Baseline ALT</td>
<td>Peak ALT</td>
<td>Source of HCV inoculum</td>
</tr>
<tr>
<td>963</td>
<td>Chronic PTH, strain F, third chimpanzee passage (1)</td>
<td>30</td>
<td>220 (12)</td>
<td>Chronic PTH, strain F, third chimpanzee passage (1)</td>
</tr>
<tr>
<td>793</td>
<td>Acute PTH, strain K, first chimpanzee passage (1)</td>
<td>23</td>
<td>418 (12)</td>
<td>Chronic PTH, strain F, third chimpanzee passage (1)</td>
</tr>
<tr>
<td>502</td>
<td>Chronic PTH, strain F, third chimpanzee passage (1)</td>
<td>21</td>
<td>412 (13)</td>
<td>Acute PTH, strain H (1)</td>
</tr>
<tr>
<td>189</td>
<td>Acute PTH, strain K (3)</td>
<td>19</td>
<td>219 (15)</td>
<td>Chronic PTH, strain F (5)</td>
</tr>
<tr>
<td>196</td>
<td>Chronic PTH, strain G (75)</td>
<td>17</td>
<td>62 (13)</td>
<td>Chronic PTH, strain F (5)</td>
</tr>
</tbody>
</table>

*ALT fluctuated between 43 and 59 U/liter during the duration of the study, in parallel with the persistence of HCV viremia.
HCV reinfection among PWID

<table>
<thead>
<tr>
<th>Study populations</th>
<th>Number of new infections during follow-up</th>
<th>Median follow-up (years)</th>
<th>Incidence rate per 100 person-years</th>
<th>Crude incidence rate ratio</th>
<th>Adjusted ratio (95% CI)</th>
<th>p value</th>
<th>Median HCV RNA testing interval for patients previously infected (months)</th>
<th>Clearance of reinfection in patients whose infection had previously cleared</th>
<th>Reinfecion in prevalent or incident cases?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehta et al.</td>
<td>Not infected (n=164) vs HCV clearance (n=98)</td>
<td>35 vs 12</td>
<td>2.4 vs 2.1</td>
<td>0.45</td>
<td>0.23 (0.23–0.88)†</td>
<td>0.02</td>
<td>6.3 (6)</td>
<td>6 of 9 (67%)‡</td>
<td>Prevalent</td>
</tr>
<tr>
<td>Grebely et al.</td>
<td>Not infected (n=926) vs HCV clearance (n=152)</td>
<td>172 vs 14</td>
<td>2.8 vs 2.2</td>
<td>0.22</td>
<td>0.23 (0.10–0.51)$</td>
<td>&lt;0.001</td>
<td>15.6</td>
<td>4 of 14 (29%)</td>
<td>Prevalent</td>
</tr>
<tr>
<td>Micallif et al.</td>
<td>Not infected (n=423) vs HCV clearance (n=18)</td>
<td>114 vs 13</td>
<td>1.0 vs 1.2</td>
<td>2.40</td>
<td>1.11†</td>
<td>0.80</td>
<td>5.0 (6)</td>
<td>3 of 7 (43%)</td>
<td>Incident</td>
</tr>
<tr>
<td>Aitken et al.</td>
<td>Not infected (n=55) vs HCV clearance (n=50)</td>
<td>10 vs 23</td>
<td>NA</td>
<td>3.0</td>
<td>2.54 (1.11–5.78)‡</td>
<td>0.027</td>
<td>3.8 (3)</td>
<td>9 of 22 (41%)</td>
<td>Prevalent and incident</td>
</tr>
<tr>
<td>van de Laar et al.</td>
<td>Not infected (n=168) vs HCV clearance (n=24)</td>
<td>58 vs 9</td>
<td>3.6 vs 0.5</td>
<td>1.9</td>
<td>NA</td>
<td>NA</td>
<td>7.3 (4–6)</td>
<td>3 of 9 (33%)</td>
<td>Incident</td>
</tr>
<tr>
<td>Page et al.</td>
<td>Not infected (n=380) vs HCV clearance (n=27)</td>
<td>132 vs 7</td>
<td>NA</td>
<td>0.92</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3 of 7 (100%)</td>
<td>Incident</td>
</tr>
<tr>
<td>Osburn et al.</td>
<td>Not infected (n=179) vs HCV clearance (n=22)</td>
<td>62 vs 11</td>
<td>NA</td>
<td>1.11</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10 of 12 (83%)</td>
<td>Incident</td>
</tr>
<tr>
<td>Currie et al.</td>
<td>HCV clearance (n=29)</td>
<td>0</td>
<td>5.5</td>
<td>0.0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Differs from 0.9 of 29 (30%)</td>
<td>Prevalent</td>
</tr>
<tr>
<td>Grebely et al.</td>
<td>HCV clearance (n=30)</td>
<td>2</td>
<td>1.1</td>
<td>6.1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2 of 2 (100%)</td>
<td>Incident</td>
</tr>
</tbody>
</table>

HCV=hepatitis C virus. NA=not available. *Scheduled interval given in parentheses when available. †Hazard ratio. ‡Restricted to HIV-negative participants. $Odds ratio. †Incidence rate ratio. ||Data taken from van den Berg et al. **Data taken from Cox et al.

HCV Reinfection among HIV MSM

• Jones et al. 2010 studied 22 individuals with re-emergent HCV
  • Of these, 9 individuals had paired, amplifiable HCV RNA
    • 1 had a genotype switch at 19 months following EOT
    • 6 of remaining 8 had genetically divergent samples when comparing pre- and post-treatment strains
  • Of these 6, 2 had re-emergent viraemia within 24 weeks of EOT
• Further 3 individuals without paired samples demonstrated a genotype switch with re-emergent HCV

Phylogenetics suggest that re-emergent viraemia represents reinfection
But in some cases a relapse is more probable
There appears to be high reinfection among HIV MSM in Europe: Amsterdam

- 56 patients HIV MSM negative at EOT
- 16 had re-emergent viraemia
- 5 with the same virus as pre-treatment: definite relapse
- 3 reinfected with ‘different’ virus but same genotype
- 8 were genotype switches

Reinfection rate of 15.2/100py

HCV Reinfection Incidence

- Overall reinfection rate: 7.8 per 100 py (95% CI 5.8-10.5 per 100py)
- Post-treatment: 9.6 per 100py (95% CI 6.6-14.1/100py)
- Post-spontaneous clearance: 4.2 per 100py (95% CI 1.7-10/100py)

Comparing reinfection post-treatment versus post-spontaneous clearance: p=0.15
HCV Reinfection Incidence HIV MSM

Second reinfection: 23.2 per 100 py (95%CI 11.6-43.4 per 100py)
Overall reinfection outcomes are good (N=47)

- No treatment N=1
- Spontaneous clearance N=13 (20%)
- Treatment failure N=7
- SVR N=26 (73% GT 1+4; 100% GT 2+3)
Reinfection across Europe

- 553 patients from 7 NEAT centres with cured acute HCV since 2001
- 141 with at least one re-infection (25.5%)
- 1509 patient years of follow-up; median 2.1 years
- Incidence rate: 7.82/100 patient years

Ingilitz P et al. on behalf of NEAT. EASL 2014
## Factors associated with spontaneous clearance

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous Clearance N=19</th>
<th>No Clearance N=94</th>
<th>Univariate p-value</th>
<th>Odds ratio</th>
<th>95% -CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age [years]</td>
<td>39</td>
<td>40</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median baseline CD4-cells [ / µl ] (IQR)</td>
<td>491 (382-686)</td>
<td>541 (401-716)</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HIV-RNA &lt;50cop/ ml [% ]</td>
<td>50</td>
<td>54</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAART [% ]</td>
<td>58</td>
<td>67</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL28B CC genotype [% ]</td>
<td>71</td>
<td>44</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HCV-RNA [IU/ ml] (IQR)</td>
<td>1.7x10^5 (5910-2x10^6)</td>
<td>3.5x10^5 (44000-2.5x10^6)</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV genotype 1 vs. non-1 (%)</td>
<td>64</td>
<td>75</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV genotype switch (%)</td>
<td>42</td>
<td>47</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearance of precedent episode (%)</td>
<td>32</td>
<td>9</td>
<td>0.02</td>
<td>4.6</td>
<td>1.3-15.9</td>
</tr>
<tr>
<td>Median maximum ALT [U/ I] (IQR)</td>
<td>489 (160-1179)</td>
<td>312 (172-543)</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration between episodes [weeks] (IQR)</td>
<td>129 (94-218)</td>
<td>145 (102-230)</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAG positivity [% ]</td>
<td>0</td>
<td>0</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ingilitz P et al. Oral presentation EACS 2013
Overview

- Definitions
- Late relapse
- Reinfection
- HCV quasispecies and relapse
- Late relapse vs. reinfection
Pre-treatment, multiple strains of HCV often coexist

- **HCV mono-infection**
  - 10% coinfected with multiple incident genotypes
  - Among PWID, superinfection occurs leading to further viral diversity
  - Superinfection incidence similar to primary infection incidence

- **Acute hepatitis C virus infection among HIV infected individuals**
  - Upwards of 40% of HIV/HCV coinfected subjects have multiple strains of HCV
  - Recent study conducted a Study of 15 individuals performing deep sequencing on pre-treatment samples of acute HCV
    - all had multiple strains, subtypes or genotypes
    - All had 2-6 strains of genotype 1a
    - 6 had more than 1 viral subtype (eg 1a and 1b)
    - 1 had more than 1 genotype

Virological failure may be due to emergence of minority strains in HCV/HIV pts

- Next-generation sequencing on 15 patients who failed to achieve SVR
  - 6 null response
  - 3 partial response
  - 6 relapsed

- Study compared RNA from the E2 HVR-1 region pre- and post-treatment with potential outcomes being:
  - Persistent infection same dominance
  - Persistent infection new dominance
  - Persistent infection new variant detected

Persistence of the dominant strain is the cause of treatment failure in 5 of 15 cases.

<table>
<thead>
<tr>
<th>ID</th>
<th>Clinical outcome</th>
<th>Pairwise distance (Sanger)</th>
<th>Pairwise distance (NGS)</th>
<th>New Dominance</th>
<th>New Variants</th>
<th>Cleared Variants</th>
<th>Final conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>P38</td>
<td>Null response</td>
<td>0.19</td>
<td>0.08</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P63</td>
<td>Null response</td>
<td>0.03</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>1</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P67</td>
<td>Null response</td>
<td>0.04</td>
<td>0.04</td>
<td>-</td>
<td>0</td>
<td>2</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P81</td>
<td>Null response</td>
<td>0.48</td>
<td>0.06</td>
<td>13%</td>
<td>1</td>
<td>3</td>
<td>Persistent infection (New dominance and new variant detected)</td>
</tr>
<tr>
<td>P112</td>
<td>Null response</td>
<td>0.17</td>
<td>0.01</td>
<td>-</td>
<td>0</td>
<td>3</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P118</td>
<td>Null response</td>
<td>0.47</td>
<td>0.01</td>
<td>3%</td>
<td>0</td>
<td>5</td>
<td>Persistent infection (New dominance)</td>
</tr>
<tr>
<td>P21</td>
<td>Partial response</td>
<td>0.27</td>
<td>0</td>
<td>NA</td>
<td>1</td>
<td>2</td>
<td>Persistent infection (New dominance and new variant detected)</td>
</tr>
<tr>
<td>P31</td>
<td>Partial response</td>
<td>0.08</td>
<td>0.08</td>
<td>-</td>
<td>0</td>
<td>3</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P105</td>
<td>Partial response</td>
<td>0.46</td>
<td>0</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P75</td>
<td>Relapse</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P76</td>
<td>Relapse</td>
<td>0.24</td>
<td>0.05</td>
<td>3.2%</td>
<td>0</td>
<td>4</td>
<td>Persistent infection (New dominance)</td>
</tr>
<tr>
<td>P101</td>
<td>Relapse</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>3</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P57</td>
<td>Relapse</td>
<td>0.33</td>
<td>0.03</td>
<td>9%</td>
<td>0</td>
<td>2</td>
<td>Persistent infection (New dominance)</td>
</tr>
<tr>
<td>P131</td>
<td>Relapse</td>
<td>0.27</td>
<td>0.05</td>
<td>-</td>
<td>2</td>
<td>3</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P141</td>
<td>Relapse</td>
<td>0.24</td>
<td>0.01</td>
<td>3.0%</td>
<td>0</td>
<td>3</td>
<td>Persistent infection (New dominance)</td>
</tr>
</tbody>
</table>

5 of 15 had evidence of persistent infection of the dominant strain. The majority occurred among null responders.
In 6 cases, a previous minority variant became dominant following treatment.

<table>
<thead>
<tr>
<th>ID</th>
<th>Clinical outcome</th>
<th>Pairwise distance (Sanger)</th>
<th>Pairwise distance (NGS)</th>
<th>New Dominance</th>
<th>New Variants</th>
<th>Cleared Variants</th>
<th>Final conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>P38</td>
<td>Null response</td>
<td>0.19</td>
<td>0.08</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P63</td>
<td>Null response</td>
<td>0.03</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>1</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P67</td>
<td>Null response</td>
<td>0.04</td>
<td>0.04</td>
<td>-</td>
<td>0</td>
<td>2</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P81</td>
<td>Null response</td>
<td>0.48</td>
<td>0.06</td>
<td>13%</td>
<td>1</td>
<td>3</td>
<td>Persistent infection (New dominance and new variant detected)</td>
</tr>
<tr>
<td>P112</td>
<td>Null response</td>
<td>0.17</td>
<td>0.01</td>
<td>-</td>
<td>0</td>
<td>3</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P118</td>
<td>Null response</td>
<td>0.47</td>
<td>0.01</td>
<td>3%</td>
<td>0</td>
<td>5</td>
<td>Persistent infection (New dominance)</td>
</tr>
<tr>
<td>P21</td>
<td>Partial response</td>
<td>0.27</td>
<td>0</td>
<td>NA</td>
<td>1</td>
<td>2</td>
<td>Persistent infection (New dominance and new variant detected)</td>
</tr>
<tr>
<td>P31</td>
<td>Partial response</td>
<td>0.08</td>
<td>0.08</td>
<td>-</td>
<td>0</td>
<td>3</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P105</td>
<td>Partial response</td>
<td>0.46</td>
<td>0</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P75</td>
<td>Relapse</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P76</td>
<td>Relapse</td>
<td>0.24</td>
<td>0.05</td>
<td>3.2%</td>
<td>0</td>
<td>4</td>
<td>Persistent infection (New dominance)</td>
</tr>
<tr>
<td>P101</td>
<td>Relapse</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>3</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P57</td>
<td>Relapse</td>
<td>0.33</td>
<td>0.03</td>
<td>9%</td>
<td>0</td>
<td>2</td>
<td>Persistent infection (New dominance)</td>
</tr>
<tr>
<td>P131</td>
<td>Relapse</td>
<td>0.27</td>
<td>0.05</td>
<td>-</td>
<td>2</td>
<td>3</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P141</td>
<td>Relapse</td>
<td>0.24</td>
<td>0.01</td>
<td>3.0%</td>
<td>0</td>
<td>3</td>
<td>Persistent infection (New dominance)</td>
</tr>
</tbody>
</table>

6 of 15 had evidence of new dominance of a previously minority variant.
In 6 cases there was a new variant detectable following treatment.

6 of 15 had evidence of a new variant post-treatment not present pre-treatment.

<table>
<thead>
<tr>
<th>ID</th>
<th>Clinical outcome</th>
<th>Pairwise distance (Sanger)</th>
<th>Pairwise distance (NGS)</th>
<th>New Dominance</th>
<th>New Variants</th>
<th>Cleared Variants</th>
<th>Final conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>P38</td>
<td>Null response</td>
<td>0.19</td>
<td>0.08</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P63</td>
<td>Null response</td>
<td>0.03</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>1</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P67</td>
<td>Null response</td>
<td>0.04</td>
<td>0.04</td>
<td>-</td>
<td>0</td>
<td>2</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P81</td>
<td>Null response</td>
<td>0.48</td>
<td>0.06</td>
<td>13%</td>
<td>1</td>
<td>3</td>
<td>Persistent infection (New dominance and new variant detected)</td>
</tr>
<tr>
<td>P112</td>
<td>Null response</td>
<td>0.17</td>
<td>0.01</td>
<td>-</td>
<td>0</td>
<td>3</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P118</td>
<td>Null response</td>
<td>0.47</td>
<td>0.01</td>
<td>3%</td>
<td>0</td>
<td>5</td>
<td>Persistent infection (New dominance)</td>
</tr>
<tr>
<td>P21</td>
<td>Partial response</td>
<td>0.27</td>
<td>0</td>
<td>NA</td>
<td>1</td>
<td>2</td>
<td>Persistent infection (New dominance and new variant detected)</td>
</tr>
<tr>
<td>P31</td>
<td>Partial response</td>
<td>0.08</td>
<td>0.08</td>
<td>-</td>
<td>0</td>
<td>3</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P105</td>
<td>Partial response</td>
<td>0.46</td>
<td>0</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P75</td>
<td>Relapse</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P76</td>
<td>Relapse</td>
<td>0.24</td>
<td>0.05</td>
<td>3.2%</td>
<td>0</td>
<td>4</td>
<td>Persistent infection (New dominance)</td>
</tr>
<tr>
<td>P101</td>
<td>Relapse</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>3</td>
<td>Persistent infection</td>
</tr>
<tr>
<td>P57</td>
<td>Relapse</td>
<td>0.33</td>
<td>0.03</td>
<td>9%</td>
<td>0</td>
<td>2</td>
<td>Persistent infection (New dominance)</td>
</tr>
<tr>
<td>P131</td>
<td>Relapse</td>
<td>0.27</td>
<td>0.05</td>
<td>-</td>
<td>2</td>
<td>3</td>
<td>Persistent infection (New variant detected)</td>
</tr>
<tr>
<td>P141</td>
<td>Relapse</td>
<td>0.24</td>
<td>0.01</td>
<td>3.0%</td>
<td>0</td>
<td>3</td>
<td>Persistent infection (New dominance)</td>
</tr>
</tbody>
</table>
Viral relapse with same strain of virus but elimination of minority strains

Same strain dominant pre- and post-treatment

3 minority variants detectable pre-treatment but not post-treatment
Viral relapse with emergence of 2 new variants post-treatment (undetectable or superinfection)

Persistence of low levels of previously dominant strain post-treatment

Elimination of 3 minority strains post-treatment

Emergence of 2 new strains post-treatment
If only looking at dominant strains we can’t differentiate reinfection/relapse

- Jones et al. 2010 studied 22 individuals with re-emergent HCV
- Of these, 9 individuals had paired, amplifiable HCV RNA
  - 1 had a genotype switch at 19 months following EOT
  - 6 of remaining 8 had genetically divergent samples when comparing pre- and post-treatment strains
- Of these 6, 2 had re-emergent viraemia within 24 weeks of EOT
- Further 3 individuals without paired samples demonstrated a genotype switch with re-emergent HCV

Some patients included may in fact be late relapses

- 56 patients HIV MSM negative at EOT
- 16 had re-emergent viraemia
- 5 with the same virus as pre-treatment: definite relapse
- 3 reinfected with ‘different’ virus but same genotype
  - 2 of these within 24 weeks of EOT
- 8 were genotype switches

Definitions

Reinfection
• Any newly positive HCV RNA PCR 24 weeks or more following end of treatment or clearance of the virus; or
• Newly positive HCV RNA PCR within 24 weeks of end of treatment or clearance if reinfeated with a different genotype

Following treatment

Following spontaneously clearance
Time to first reinfection (N=44) is long following EOT
Reinfection (wk 24-48) outcomes are consistent with treatment of primary infections

- Successfully treated: 78%
- Relapse: 17%
- Spontaneous clearance: 17%

Number of individuals (N=12)
What about late relapse?

• Reinfection
  – Detection of HCV viraemia following exposure to HCV in an individual who has either previously spontaneously cleared or has been treated for HCV infection

• Late relapse
  – Re-remergence of a pre-existing HCV viraemia 24 weeks or more following the end of treatment

• No published studies to date looking at emergence of minority strains in late relapse period

• New viraemia after 24 weeks post-EOT could represent either reinfection or late relapse

• May have an impact on reinfection studies to date
Late relapses do not explain the scale of re-emergent virus post-SVR

- Late relapse among HIV/HCV
  - Swain: 0.9% after 95 weeks (N=100)
  - Medrano: 1.4% after 48 weeks (N=143)
  - Soriano: 0% after 58 months (N=77)

- Reinfection among HIV/HCV MSM post-treatment
  - Lambers: 33% at 48 weeks
  - Martin: 25% at 48 weeks
  - Ingilitz: 25.1% with median f/u 2.1 years
Conclusions

• Re-emergent virus post-SVR occurs in a significant proportion of HIV infected individuals
• Likely to represent predominantly reinfection rather than late relapse; however, further studies are required
• Re-treatment following re-emergence is possible and is effective
Questions yet to be answered

• Will the advent of DAAs lead to an increase in risk behaviour and therefore reinfection?
• Is there a late relapse rate associated with IFN free DAA regimens?
• Does recurrent infection have a more deleterious effect on liver disease progression?
• Are there risk associations with reinfection? (eg drug use, sexual risk behaviours, STIs)
Acknowledgements

- St Stephen’s AIDS Trust
- National Institute for Health Research (NIHR)
- Medical Research Council (MRC)