Efficacy of response-guided pegylated interferon and ribavirin therapy for people who inject drugs with HCV genotype 2/3 infection: the ACTIVATE study

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HCV therapeutic evaluation among PWID

**Issues**

- PWID initially excluded from HCV treatment guidelines
- Ongoing concern from some HCV clinicians, re safety, efficacy (including re-infection), and competing morbidity
- Increasing evidence of favorable HCV treatment outcomes, from observational studies, although heterogeneous and small
- Exclusion of PWID from HCV phase II/III protocols
- Need for PWID-specific HCV therapeutic evaluation
Treatment outcomes: History of injecting - PEG-IFN/RBV

56% (95% CI, 51%, 60%)

Mauss 2004
Schaefter 2007
Guadagnino 2007
Grebely 2007
Krook 2007
Jeffrey 2007
Hallinan 2007
Jovanovic 2007
Fried 2008
Bruggmann 2008
Bonkovsky 2008
Bonkovsky 2008
Dimitroulopoulos 2008
Litwin 2009
Gazdik 2009
Ebner 2009
Belfiori 2009
Alvarez-Uria 2009
Wilkinson 2009
Jack 2009
Melin 2010
Harris 2010
John-Baptiste 2010
Tait 2010
Schulte 2010
Mauss 2010
Manolakopoulos 2010
Waizmann 2010
Grebely 2010
Curcio 2010
Curcio 2010
Papadopoulos 2010
Sasadeusz 2011
Lindenburg 2011
Taylor 2011
Martinez 2011

Dimova R, et al Clinical Infectious Diseases 2013
Treatment outcomes: Active injecting - PEG-IFN/RBV

56% (95% CI, 50%, 61%)

- Wilkinson 2009
- Jack 2009
- Papadopoulos 2010
- Sasadeusz 2011
- Lindenburg 2011
- Jafferbhoy 2012

Aspinall E, et al Clinical Infectious Diseases 2013
ACTIVATE study: Aims

• To establish an international network to evaluate HCV therapy among PWID

• To evaluate safety and efficacy of PEG-IFN-alfa2b and RBV for treatment of chronic HCV genotype 2/3 among active PWID and those receiving opioid substitution therapy

• To evaluate shortened therapy (12 weeks) for individuals with a rapid virological response
ACTIVATE study: Participants

• 17 sites, 7 countries
• Participants recruited between May 2012 and Sept 2014
Inclusion criteria

- Chronic GT 2/3 HCV treatment naïve patients
- Active injection drug use (defined as injection drug use within the 24 weeks prior to consent) OR currently receiving opioid substitution therapy
- Compensated liver disease (Child-Pugh class A)
- 93 participants initiated therapy
ACTIVATE study: Endpoints and Analysis

- SVR was the primary efficacy endpoint (intent-to-treat)
  - HCV RNA undetectable at post-treatment week 12

- Questionnaires were administered to obtain information on injecting drug use risk behaviours

- Detailed information on adverse events

- Logistic regression analyses used to identify predictors of SVR
### ACTIVATE study: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>PEG-IFN/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=93</td>
</tr>
<tr>
<td>Mean age, year ± SD</td>
<td>42 ± 9</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>77 (83)</td>
</tr>
<tr>
<td>Caucasian ethnicity, n (%)</td>
<td>84 (90)</td>
</tr>
<tr>
<td>Privately owned or rented accommodation, n (%)</td>
<td>71 (74)</td>
</tr>
<tr>
<td><strong>Opioid Substitution Therapy (OST)</strong></td>
<td></td>
</tr>
<tr>
<td>OST with no injecting in the previous 12 weeks</td>
<td>23 (25)</td>
</tr>
<tr>
<td>OST with injecting in the previous 12 weeks</td>
<td>16 (17)</td>
</tr>
<tr>
<td>No OST</td>
<td>54 (58)</td>
</tr>
<tr>
<td><strong>Recent injecting</strong></td>
<td></td>
</tr>
<tr>
<td>Injecting in the previous month (4 weeks)</td>
<td>57 (61)</td>
</tr>
<tr>
<td>Injecting in the previous 4-12 weeks</td>
<td>13 (14)</td>
</tr>
<tr>
<td>No injecting in the previous 12 weeks</td>
<td>23 (25)</td>
</tr>
<tr>
<td><strong>HCV genotype at screening</strong></td>
<td></td>
</tr>
<tr>
<td>Genotype 2</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>82 (88)</td>
</tr>
<tr>
<td><strong>HCV RNA levels at screening, log IU/mL, median (IQR)</strong></td>
<td>6.0 (5.3, 6.7)</td>
</tr>
</tbody>
</table>
ACTIVATE study: Disposition and Outcomes

**Total**
- *n=93*

**ETR**
- *n=73 (78%)

**Treatment failure**
- *n=20 (22%)
  - Virological response failure: *n=3*
  - Treatment stopped due to side effects: *n=9*
  - Patient unwillingness to continue: *n=3*
  - Patient lost to follow-up: *n=4*
  - Other: *n=1*

**SVR12**
- *n=59 (63%)

**Post-treatment failure**
- *n=14 (19% of ETR)
  - HCV relapse: *n=5 (7% of ETR)*
  - Patient lost to follow-up or no available data: *n=9 (12% of ETR)*
Total n=93

Standard treatment (no RVR) n=27 (29%)
- Treatment failure n=13 (48%)
  - ETR n=14 (52%)
    - SVR12 n=10 (37%)
      - Post-treatment failure n=4 (29% of ETR)
        • HCV relapse: n=2 (14% of ETR)
        • Patient lost to follow-up or no available data: n=2 (14% of ETR)

Shortened treatment (RVR) n=60 (65%)
- ETR n=59 (98%)
  - SVR12 n=49 (82%)

Withdrew before week 4 n=6 (6%)
- Treatment failure n=1 (2%)
  - Post-treatment failure n=10 (17%)
    • HCV relapse: n=3 (5% of ETR)
    • Patient lost to follow-up or no available data: n=7 (12% of ETR)
## Predictors of SVR in those reaching W4 (n=87)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Number with SVR12 (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>-</td>
<td>0.98 (0.93, 1.03)</td>
<td>0.41</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (73)</td>
<td>1.00</td>
<td>-</td>
<td>0.73 (0.21, 2.52)</td>
<td>0.62</td>
</tr>
<tr>
<td>Male</td>
<td>48 (67)</td>
<td>0.73 (0.21, 2.52)</td>
<td>-</td>
<td>0.62</td>
<td>-</td>
</tr>
<tr>
<td>OST and recent injecting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OST</td>
<td>23 (68)</td>
<td>1.00</td>
<td>-</td>
<td>2.87 (0.31, 26.84)</td>
<td>0.35</td>
</tr>
<tr>
<td>No OST, injecting in the past 4-12 weeks</td>
<td>6 (86)</td>
<td>0.73 (0.21, 2.52)</td>
<td>-</td>
<td>0.90 (0.35, 2.30)</td>
<td>0.82</td>
</tr>
<tr>
<td>No OST, injecting in the past month</td>
<td>30 (65)</td>
<td>0.68 (0.12, 3.60)</td>
<td>-</td>
<td>0.65</td>
<td>-</td>
</tr>
<tr>
<td>HCV genotype at screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 2</td>
<td>6 (75)</td>
<td>1.00</td>
<td>-</td>
<td>0.86 (0.12, 2.30)</td>
<td>-</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>53 (67)</td>
<td>0.86 (0.12, 2.30)</td>
<td>-</td>
<td>0.65</td>
<td>-</td>
</tr>
<tr>
<td>HCV RNA levels at screening, log IU/mL</td>
<td>-</td>
<td>0.82 (0.53, 1.26)</td>
<td>0.36</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Rapid Virologic Response (RVR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RVR (Standard treatment)</td>
<td>10 (37)</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
<td>0.01</td>
</tr>
<tr>
<td>RVR (Shortened treatment)</td>
<td>49 (82)</td>
<td>7.57 (2.73, 20.97)</td>
<td>&lt;0.01</td>
<td>9.02 (2.94, 27.70)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Conclusions

- Among PWID with chronic HCV genotypes 2/3, SVR12 was 63%
  - SVR12 was 82% in those with an RVR and 37% in those who did not achieve an RVR

- On-treatment RVR was a strong predictor of SVR in patients receiving a 12 week course of PEG-IFN/RBV therapy

- The response to therapy was similar among people receiving OST and those with active injecting drug use

- Support for HCV treatment in active PWID and the use of innovative shorter therapies in this context
ACTIVATE network: Future directions

- **SIMPLIFY (Gilead)**: Phase IV study of SOF/VEL in PWID
  - n=100; pangenotypic; treatment naive
  - on OST +/- active injecting drug use
  - 21 sites

- **D3FEAT (Abbvie)**: Phase IV study of PTV/OBV/DBV/ RBV in PWID
  - n=100; genotype 1; treatment naïve
  - on OST +/- active injecting drug use
  - 20 sites
Acknowledgements

Project Steering Committee

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