INCIDENCE OF HEPATITIS C REINFECTION FOLLOWING SUSTAINED VIROLOGICAL RESPONSE

SEVEN-YEAR FOLLOW-UP OF NORWEGIAN PATIENTS INFECTED THROUGH INJECTING DRUG USE

Håvard Midgard¹, Benedikte Bjøro², Arild Mæland³, Zbigniew Konopski⁴, Hege Kileng⁵, Jan K Damås⁶, Jørn Paulsen⁷, Lars Heggelund⁸, Per K Sandvei⁹, Jetmund O Ringstad⁹, Lars N Karlsen¹⁰, Kathrine Stene-Johansen¹¹, John H-O Pettersson¹¹, Dagny H Dorenberg¹¹ and Olav Dalgard¹.

¹Department of Infectious Diseases, Akershus University Hospital, Norway; ²Department of Transplantation Medicine, Oslo University Hospital; ³Department of Infectious Diseases, Oslo University Hospital; ⁴Department of Gastroenterology, Oslo University Hospital; ⁵Section of Gastroenterology, University Hospital of North Norway; ⁶Department of Infectious Diseases, St. Olav's Hospital; ⁷Section of Gastroenterology, Telemark Hospital Trust; ⁸Section of Infectious Diseases, Vestre Viken Hospital Trust; ⁹Department of Medicine, Østfold Hospital Trust; ¹⁰Department of Medicine, Stavanger University Hospital; ¹¹Department of Virology, The Norwegian Institute for Public Health, Norway.
Background

- Given the lack of protective immunity, on-going risk behaviours can lead to hepatitis C virus (HCV) reinfection after successful treatment.

- Incidence of reinfection following treatment in a meta-analysis of 5 studies among people who inject drugs (PWID)\(^1\):
  - 2.4/100 PY among patients with a history of injecting drug use (IDU)
  - 6.4/100 PY among patients with on-going IDU after treatment

- Risk of reinfection 5-years after SVR was 8% a in meta-analysis of 16 studies among PWID or prisoners\(^2\)

- Tolerable DAAs will likely increase HCV treatment uptake among PWID and reinfection will probably emerge as an increasingly important topic.

---

Aims of the study

In a population of PWID who previously had achieved SVR following at least six months of abstinence from drug use prior to HCV treatment, we aimed to assess

1. The long-term incidence of persistent HCV reinfection
2. The frequency of relapse to IDU
Materials

North-C RCT 2004-2006 (n=428)\(^1\)

- Mono-infected GT 2/3 patients in Norway, Sweden and Denmark
- RVR: Randomized to 14 or 24 weeks pegIFN + RBV (SVR\(_{24}\) 76%)
- 68% infected through IDU – 6 months abstinence required
- Standard of care information about risk reduction
- Patients were not followed prospectively

This follow-up study was performed in 2012-2014 at all 22 Norwegian study sites

All patients who had achieved SVR (n=161) were eligible for inclusion

Methods

Data collection

- Patients were scheduled for a follow-up visit at local site
- Clinical, demographical and drug behavioural data were collected

Laboratory methods

- *HCV RNA*: COBAS AmpliPrep/TaqMan HCV Test v2.0
- *Genotyping*: Versant INNO-LiPA HCV 2.0
- *Viral sequencing*:
  - ~1500 bp fragment covering Core, E1, HVR1 and E2 was amplified by a nested RT-PCR using universal and subtype-specific primers\(^1\)
  - The PCR product was sequenced using the Sanger method
  - Maximum-likelihood phylogenetic tree of the Core-E2 fragment

Study definitions of HCV reinfection

Confirmed reinfection
  • Recurrence of HCV RNA post SVR with a viral strain different from strain(s) detected in the baseline sample prior to treatment

Probable reinfection
  • Recurrence of HCV RNA post SVR with lacking sequence data, but occurring in a patient who relapsed to IDU after treatment
Overview of the study population

Patients who achieved SVR (n=161)

IDU (n=106)
- Deaths (n=5)
- Lost to follow-up (n=7)
- Included (n=94) 89%

Non-IDU (n=55)
- Deaths (n=4)
- Lost to follow-up (n=7)
- Included (n=44) 80%
### Patient characteristics (n=138)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IDU (n=94)</th>
<th>Non-IDU (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at treatment (years), median (IQR)</td>
<td>36 (12)</td>
<td>39 (14)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>57 (61)</td>
<td>25 (57)</td>
</tr>
<tr>
<td>Low education level, n (%) (secondary school or lower)</td>
<td>45 (48)</td>
<td>13 (31)</td>
</tr>
<tr>
<td>Unemployed or welfare benefits, n (%)</td>
<td>36 (38)</td>
<td>17 (39)</td>
</tr>
<tr>
<td>Short treatment (14 weeks)</td>
<td>35 (37)</td>
<td>17 (39)</td>
</tr>
<tr>
<td>IDU before treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100 lifetime injections</td>
<td>19 (20)</td>
<td>NA</td>
</tr>
<tr>
<td>≥ 100 lifetime injections</td>
<td>75 (80)</td>
<td></td>
</tr>
<tr>
<td>Follow-up time (years), median</td>
<td>7.1</td>
<td>7.5</td>
</tr>
</tbody>
</table>
## Patient characteristics (n=138)

<table>
<thead>
<tr>
<th></th>
<th>IDU (n=94)</th>
<th>Non-IDU (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at treatment, median (IQR)</strong></td>
<td>36 (12)</td>
<td>39 (14)</td>
</tr>
<tr>
<td><strong>Male gender, n (%)</strong></td>
<td>57 (61)</td>
<td>25 (57)</td>
</tr>
<tr>
<td><strong>Low education level, n (%)</strong></td>
<td>45 (48)</td>
<td>13 (31)</td>
</tr>
<tr>
<td>(secondary school or lower)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unemployed or welfare benefits, n (%)</strong></td>
<td>36 (38)</td>
<td>17 (39)</td>
</tr>
<tr>
<td><strong>Short treatment (14 weeks)</strong></td>
<td>35 (37)</td>
<td>17 (39)</td>
</tr>
<tr>
<td><strong>IDU before treatment, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100 lifetime injections</td>
<td>19 (20)</td>
<td>NA</td>
</tr>
<tr>
<td>≥ 100 lifetime injections</td>
<td>75 (80)</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up time, median years</strong></td>
<td>7.1</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>Recurrence of HCV RNA, n (%)</strong></td>
<td>12 (13)</td>
<td>0</td>
</tr>
</tbody>
</table>
Timelines for 12 recurrent cases: baseline

Timelines for 12 recurrent cases: baseline

1 2 3 4 5 6 7 8 9 10 11 12

BL EOT SVR24 1 2 3 4 5 6 7 8

Years

1a 2a 2b 3a Not genotyped HCV RNA negative
Timelines for 12 recurrent cases: follow-up

- **1a**: Orange
- **2a**: Yellow
- **2b**: Green
- **3a**: Blue
- **Not genotyped**: Black
- **HCV RNA negative**: White

**Blind (BL)**, **End of Treatment (EOT)**, **SVR24**
Timelines for 12 recurrent cases: outcome

BL, EOT, SVR24, Persistence, Uncertain, Clearance

- 1a: Orange
- 2a: Yellow
- 2b: Green
- 3a: Blue
- Not genotyped: Black
- HCV RNA negative: White
Persistent reinfections: Confirmed or probable

1. Probable
2. Probable
3. Confirmed
4. Probable
5. Probable
6. Confirmed
7. Probable
8. Confirmed
9. Confirmed
10. Confirmed
11. Probable
12. Probable

BL, EOT, SVR24, Years

1a, 2a, 2b, 3a, Not genotyped, HCV RNA negative
Incidence of persistent HCV reinfection

<table>
<thead>
<tr>
<th>Time at risk after SVR (PY)</th>
<th>All patients (n=138)</th>
<th>IDU ever (n=94)</th>
<th>IDU post SVR (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent reinfections</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Incidence per 100 PY</td>
<td>1.2</td>
<td>1.8</td>
<td>5.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.6–2.2</td>
<td>0.9–3.3</td>
<td>2.6–9.5</td>
</tr>
</tbody>
</table>
7-year risk of persistent HCV reinfection

- All patients (n=138): 8%
- IDU ever (n=94): 12%
- IDU post SVR (n=37): 30%
Injecting risk behaviours post SVR

Relapse to IDU*

- No IDU: 61%
- Short term/sporadic (<100 injections): 19%
- Dependent/frequent (>100 injections): 20%

Sharing of drug equipment§

- No sharing: 65%
- Needles or syringes: 15%
- Water, cookers or cotton: 20%

*Among 94 patients with a history of IDU prior to treatment
§Among 20 patients who responded completely to the behavioural survey
Predictors of reinfection and relapse to IDU

• All cases of reinfection occurred among those who had relapsed to IDU after treatment

• Reinfection was not associated with any baseline variables and was not associated with post treatment injecting risk behaviours

• Relapse to IDU was associated with
  • **Low age at treatment:** aOR 0.89 per year (95% CI 0.83-0.95)
  • **Low education level:** aOR 4.10 (95% CI 1.56-10.8)
Conclusions and implications

• The incidence of HCV reinfection after SVR among PWID was moderate, but lower than reported rates of primary infection

• At the individual level, reinfection might compromise long-term benefits of treatment for patients with on-going risk behaviours

• At the population level, treating patients at high risk of reinfection may have great prevention potential as these patients are being “kept out of the pool” for a period and prevented from transmitting the virus

• Strategies to prevent reinfection should be addressed and evaluated in future studies
Acknowledgements

Study participants

Supervisors
Olav Dalgard
John W Haukeland

Norwegian Institute of Public Health
K Stene-Johansen
J H-O Pettersson
D H Dorenberg

Oslo University Hospital, Dpt of Microbiology
M Holberg-Petersen
AB Kran
K Jakobsen

Funding
Norwegian ExtraFoundation for Health and Rehabilitation

The Norwegian North-C group
B Bjøro
A Mæland
Z Konopski
H Kileng
J K Damås
J Paulsen
L Heggelund
P K Sandvei
J O Ringstad
L N Karlsen
J Almark
B Andersen
K Bjøro
K Bø
T F Engan
S Ertesvåg
J Florholmen
O Hope

T H Henriksen
M Gangsøy-Kristiansen
B Hiåsen
V Høeg
K Landrø
O Lange
J Langtind
I Melkeraaen
E Melsom
O S Moen
G Noraberg
E Reinertsen
I Slørdal
H Steinum
F Strøm
R Torp
K Wesenberg

Norwegian Institute of Public Health

Oslo University Hospital
Backup slides
Viral sequencing of the core-E2 region

- 18/24 samples were available for sequencing
- Adequate sequences were obtained in 10/18 samples
  - Old samples
  - Suboptimal storage
  - Low viral load
  - Primer mismatch
- Results also depend on line probe assays
Limitations of the study

1. Lengthy follow-up intervals – spontaneously cleared reinfections may be missed
   • Persistent reinfections are the most clinically significant endpoint

2. Incomplete HIV status at follow-up
   • HIV infection is infrequent in the Norwegian IDU-population (1%)¹

2. Suboptimal methods/conditions for viral sequencing
   • Late viral relapse of coexisting unresponsive strains?
   • Late viral relapse in patients with recurrence of the same genotype?
   • However,
     • All viral recurrences occurred in patients with IDU post SVR
     • Late relapse post SVR₂⁴ is a very rare event (< 1%)²

¹ Dalgard O. et al. Tidsskr Nor Laegeforen 2009