Research Article

The Belgian experience with triple therapy with boceprevir and telaprevir in genotype 1 infected patients who inject drugs†

Running title: Treatment of genotype 1 HCV infection in persons who inject drugs

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ABSTRACT

Background
No data have been reported yet on treatment outcome in persons who inject drugs (PWID) infected with hepatitis C virus treated with boceprevir or telaprevir in combination with peginterferon (Peg IFN) and ribavirin (RBV). Additionally, there are concerns about the safety of boceprevir and telaprevir in some subgroups of patients with hepatitis C (HCV).

Methods
In a cohort of HCV patients infected with genotype 1 in Belgium, treatment outcome of patients infected due to IV drug use was analyzed and compared with patients who have no history of substance use.

Results
The study population consisted of 179 patients: 78 PWID and 101 controls treated with boceprevir (n=79) or telaprevir (n=100) additional to Peg IFN and RBV; 53 (30%) had advanced disease (F3, F4) and 79 (44%) had an antiviral therapy previously. There were no significant differences in the baseline characteristics between both groups, except that PWID patients were more frequently infected with genotype 1a (67% vs 21%), were younger and were predominantly male. Psychiatric complaints during follow-up occurred more frequently in the PWID patients: 24% vs 11% (p=0.02). Treatment failure for other reasons than absence of viral response was 70% and 64% in PWID and non-PWID respectively. The sustained viral response (SVR) rates were similar in both groups (71% in PWID vs 72% in non-PWID); with a non-inferiority test with -5% margin there is a difference of -1% (95% CI [-15%, 13%]) and p= 0.30.

Conclusions
There are no reasons to exclude PWID from treatment with boceprevir, telaprevir and novel antiviral therapies. This article is protected by copyright. All rights reserved

Key words
Hepatitis C, direct acting antivirals, telaprevir, boceprevir, persons who inject drugs.

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INTRODUCTION

Worldwide 130-150 million people are chronically infected with hepatitis C virus (HCV) and every year more than 350 000 people die because of HCV-related diseases [WHO, 2014]. During the past decade therapy with Peg IFN and RBV for 48 weeks was the standard of care for treating HCV genotype 1 infection. This dual treatment was successful in 40-50% of the patients [EASL, 2011; Ghany et al., 2011]. In 2011 the direct acting antivirals (DAAs) boceprevir (BOC) and telaprevir (TVR) were approved to be used in combination with Peg IFN and RBV for adult patients chronically infected with HCV genotype 1 [EASL, 2014; FDA, 2011; FDA, 2014]. This therapy results in increased viral clearance but is a serious burden for the patients (medication intake, side effects) and BOC and TVR can interfere with a lot of medications [The, 2014]. New generation DAAs are now becoming available, which are characterized by very high SVR rate, a short treatment period and almost no side effects [Feeney and Chung, 2014]. However, the cost of treatment is extremely high and the medications are therefore only reimbursed in a limited number of countries.

Substance users are an important group of HCV infected patients in the developed world and have become the main source of new HCV infections all over the world [Nelson et al., 2011; Shepard et al., 2005]. We previously reported excellent outcome of antiviral therapy without DAA in this group of patients [Robaeys et al., 2009; Robaeys et al., 2006]. However, this population is thought to be less compliant and at high risk of drug toxicity because of the concomitant use of various chemical substances. Currently there is some reluctance to prescribe the DAAs to those PWID patients. Treatment is also deferred due to the misconception that there is a high risk for reinfection in this population. The rate of HCV reinfection among PWID is low, at approximately 1%-5% per 100 person-years, even among persons who continue injection drug use during and after treatment [Grady et al., 2013].

At this moment there are no published trials on the outcome of BOC and TVR in PWID. Therefore we performed a study during which we compared the outcome of antiviral therapy including BOC or TVR in PWID and non-PWID.
MATERIALS AND METHODS

Study design
This is a national retro/prospective, interventional cohort study conducted between 2008 and 2013 in 11 Belgian centres during which patients infected with genotype 1 were treated with BOC or TVR in combination with Peg IFN and RBV. All centres were experienced in treating HCV infected patients who were infected due to substance use. PWID were part of a substitution programme and if necessary, they received daily methadone or other substitution medications. When enrolling patients in this programme, they were questioned about their risk behaviours and tested for infectious diseases such as HCV, HBV and HIV. Patients who tested positive for HCV infection were referred to a gastro-enterologist/ hepatologist to consider antiviral treatment. The addiction care physician and specialized nurses were involved in further HCV related care of the patient. In case antiviral treatment was started data were collected in a central database.

In parallel the centres were asked to collect also the same data in the patients they treated with DAAs during the same period but without a history of drug use. Patients with decompensated cirrhosis were excluded.

Applied definitions or criteria:
In case of non-response during treatment the antiviral therapy was interrupted, as defined by the guidelines [EASL, 2014]. Diagnosis of depression was made by the clinicians according to the DSM criteria. Treatment completion was defined as return to the outpatient clinic at the end of treatment. The stage of fibrosis was scored before treatment initiation on the liver biopsies according to the Metavir criteria [Bedossa and Poynard, 1996].

Study population
In total one hundred and seventy-nine patients were included in the study: 78 patients were PWID and 101 were non-substance users. Thirty-seven percent (n=29) of the PWID were treated with substitution therapy (28 with methadone and 1 with suboxone) during the antiviral treatment. Twenty-one (27%) and twenty-nine (37%) patients were active substance and benzodiazepine
users, respectively. Active users used heroin and/or cocaine and/or cannabis during the antiviral treatment period.

Endpoints of the study
The primary endpoints were treatment completion and viral clearance: early virological response at 3 months and SVR 24 weeks after the end of treatment. In addition to these also patient characteristics, addiction treatment and side effects of antiviral HCV treatment were studied.

Statistics
In order to characterize the patients in the study, descriptive statistics of patient characteristics are presented. For continuous variables means and standard deviation are presented. For categorical variables, proportions and percentage are given.

Regression methodology was used to compare patient groups (PWID and non-PWID) in terms of continuous responses or continuous patient characteristics (such as age and body mass index). Comparison of patient groups for a categorical variable (such as fibrosis stage, treatment completion, viral response) was performed by means of the Chi-square test. A p-value <0.05 was considered as statistically significant.

For the primary endpoints of this study (SVR and treatment completion) a non-inferiority hypothesis with a 5% margin was specified to compare the PWID and non-PWID group.

RESULTS

Baseline characteristic
PWID were significantly younger, were predominantly male and had a significantly lower BMI compared to controls (table 1). Most patients in the two groups were Caucasian.
The prevalence of infection with HCV genotypes 1a and 1b was different between the two groups. In the PWID group significantly more patients were infected with genotype 1a HCV (67%) compared to controls (21%) (table 1). Approximately 70% of the patients had a high viral load (HCV RNA level >800,000 IU per milliliter) at baseline. The viral load was similar in both groups. There was no significant difference in the stage of fibrosis between PWID and controls. Thirty percent (n=53) had an advanced stage of liver disease (F3, F4). Fifty six percent (n=100) were naïve for treatment. This percentage was higher in the PWID group (64%) but not significantly different from the control group (50%).

Antiviral Treatment

There was no difference in the number of patients treated with BOC and TVR in both groups (table 2). In both groups slightly more patients were treated with TVR. In general, the occurrence of side effects was not different between the two groups, although the development of psychiatric complaints (depression, etc.) was significantly higher in the PWID group (24% in PWID vs 11% in control group (p= 0.02)) with a higher need to start antidepressants (p= 0.06). Dermalogic side effects such as rash, dry skin did occur in 31% of PWID vs 37% of non-PVID (p=0.41). Anemia did occur in 35% of PWID and 46% of non-PWID (p=0.11).

In PWID and controls the antiviral treatment was modified due to side effects in respectively 28% and 45% (p=0.03). This was mostly due to dose adjustment of RBV because of anemia (respectively 77 and 69%) (p=not significant (NS)).

Interruption of the treatment due to viral non-response (see table 3) during the treatment was 8/27 (30%) vs 8/22 (36%) in PWID and non-PVID respectively. The difference in treatment interruption equals - 6% (95% CI [-33%, 20%]). The p-value when using a non-inferiority test with a +5% margin is 0.19. Interruption of the treatment in case of naïve patients was 11/50 (22%) in PWID vs 7/50 (14%) in non-PVID. There is a difference of 8% (95% CI [-7%, 23%]), and the p-value when tested in a non-inferiority setting (with a margin of +5%) is 0.65. Failure of treatment completion for other reasons than viral non-response was: 19/27 (70%) and 14/22 (64%) respectively in the PWID and non-PVID group (p= NS). In the PWID group this was particularly due to side effects (n=8), financial reasons (n=1), substance abuse (n=1), non-compliance (n=1) and mortality of unknown
cause during treatment (n=2). One non-substance user died during antiviral treatment due to myasthenia gravis. SVR (table 3) was 49/69 (71%) in the PWID patients and 68/94 (72%) in the control group. A non-inferiority statistical test with -5% margin, resulted in a p-value of 0.30. The difference in SVR between PWID and non-PWID group is -1% (95% CI [-15%, 13%]).

Factors affecting outcome in the PWID patients

Substitution treatment did not affect treatment completion: 20/29 (69%) vs 31/49 (63%), (p= NS); neither modification of medication: 8/29 (28%) vs 14/49 (29%), (p= NS); nor viral clearance at week 12: 24/26 (92%) vs 40/49 (82%), (p= NS); nor SVR: 18/24 (75%) vs 31/45 (69%), (p= NS). However, significantly more patients in a substitution program started antidepressants: 8/9 (89%) vs. 6/13 (46%) (p=0.04) during the treatment compared to patients not on substitution treatment.

Active use of substances such as heroin, cocaine, cannabis in 21/78 (27%) of the cases and the use of benzodiazepines in 29/78 (37%) of the patients neither affected treatment completion nor viral clearance at week 12 or SVR, reasons for non-completion, start of antidepressants or modification of medication.

DISCUSSION

This study demonstrates that, as for previous combination therapy with Peg IFN and RBV, combination therapy with BOC or TVR yielded similar SVR rates in PWID and in non-PWID patients.

Three patients died before an SVR test was performed,10 patients were lost to follow-up, for 3 patients SVR test was not performed because of early treatment stop (2 patients) and nonresponse (1 patient) during the treatment. The SVR results were comparable to the registration trials reporting SVR rates between 60-80 percent [Bacon et al., 2011; Hezode et al., 2009; Jacobson et al., 2011; Kumada et al., 2012; Kwo et al., 2010; McHutchison et al., 2009;
McHutchison et al., 2010; Poordad et al., 2011]. There were significantly more treatment naïve patients in the PWID group. There were more genotype 1a infected patients in the PWID group. This was also shown in other studies [Love et al., 1996; Silini et al., 1995].

The triple treatment with DAA is challenging for HCV infected drug users. The treatment consists of oral intake of antiviral medication during food intake twice or thrice a day, and always at the same time besides the intake of ribavirin twice a day and subcutaneous administration of Peg IFN once a week. This might be very difficult in substance users and could cause a lack in treatment adherence.

Adherence to treatment is important for a successful treatment. A recent study demonstrated adherence over 80% with Peg IFN/RBV in substance users [Lewis et al., 2012]. A pooled Peg IFN/RBV treatment completion rate of 83% among drug users was reported in a meta-analysis [Dimova et al., 2013]. There are currently no published studies reporting treatment completion among substance users on TVR/BOC. In our study, treatment completion rate in PWID was 65%, which is not significantly different from non-PWID. It corresponds to the non-difference in adherence found in interferon and ribavirin based studies in PWID [Robaeys et al., 2006]. In registration trials with first generation DAA in combination with Peg IFN and RBV 63-75% of treatment-naive and 59-66% of treatment-experienced patients achieved an SVR [Bacon et al., 2011; Jacobson et al., 2011; Poordad et al., 2011; Zeuzem et al., 2011].

Pharmacokinetic studies performed on TVR and BOC with Opioid Substitution Therapy (methadone and buprenorphine) found no clinically important interactions [Hulskotte et al.; Luo et al., 2012; van Heeswijk et al., 2013]. In this real life study, active substance users did use heroin, cocaine, cannabis, and benzodiazepine. There were no arguments for clinical interaction of substitution therapy in the DAA metabolism since the patients treated with substitution therapy had similar viral clearance and side effects as non-PWID.

It was suggested that the ongoing use of substances might influence the metabolism of TVR and BOC on Cytochrome p450 3A family and have an influence on the availability of these medications in the body and consequently the viral clearance [Mauss and Klinker, 2013]. In this study, we noticed that in patients actively using those substances (21/78) there was no influence
on viral clearance. Major side effects were not reported. However, two substance users died because of an unknown reason not related to substance overdose.

Recently, a lower SVR rate (42%) has been found in post-marketing studies [Maasoumy et al., 2014]. One of the possible predictive factors in the latter study was the high baseline HCV RNA being more than 800 000 IU/ml [Vierling et al., 2014]. We could not confirm this in our study.

The use of substances did not influence the adherence ratio in this TVR/BOC based treatment study. This is comparable to the previous interferon and ribavirin based studies in PWID [Robaeys et al., 2006]. The most common reason for treatment non-completion other than viral nonresponse was side effects in both PWID and non-PWID. The reasons for non-completion were not significantly different between PWID and non-PWID (p=0.48) suggesting that PWID do not end treatment early due to their drug addiction and other life style related issues.

In the present study a large number of genotype 1 infected patients was studied. This is quite unique since in substance users in some regions genotype 3 infected HCV patients are predominantly diagnosed.

There were some limitations of these data including the small number of patients. Due to the small number of patients there was not enough statistical power. In treatment experienced patients it was often not reported whether they were previous non-responders or relapsers. This is why we could not compare treatment outcome and completion in naïve, non-responders and relapsers.

As these treatments with BOC and TVR are more challenging both in terms of medical follow-up, compliance and costs, our feasibility, efficacy and compliance results show that there are no reasons to exclude PWID from treatment with BOC and TVR and novel antiviral strategies. There is no need to withhold HCV treatment due to concerns about reinfection alone because the rate of HCV reinfection is low after HCV antiviral treatment.

In some countries the new generation DAAs will not be available/ reimbursed and TVR and BOC base triple therapy will therefore be the alternative for the newer all-oral treatments. However, more studies are required to study more the side effects related to substances use in detail.
Acknowledgments

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Table 1. Demographic and HCV related characteristics

<table>
<thead>
<tr>
<th></th>
<th>PWID (n=78)</th>
<th>Non-PWID (n=101)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>44.7 ± 9.1</td>
<td>52.5 ± 11.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male gender</td>
<td>60 (77%)</td>
<td>54 (54%)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>75 (96%)</td>
<td>96 (95%)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>24.6 ± 3.6</td>
<td>26.3 ± 4.8</td>
<td>0.0152</td>
</tr>
<tr>
<td>HCV genotype (1a)</td>
<td>52 (67%)</td>
<td>21 (21%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Viral load (&gt;800000IU/ml)</td>
<td>49/77 (64%)</td>
<td>75 (74%)</td>
<td>NS</td>
</tr>
<tr>
<td>Stage of fibrosis (biopsy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- F0</td>
<td>4/74 (5%)</td>
<td>15/89 (17%)</td>
<td></td>
</tr>
<tr>
<td>- F1</td>
<td>27/74 (37%)</td>
<td>26/89 (29%)</td>
<td></td>
</tr>
<tr>
<td>- F2</td>
<td>21/74 (28%)</td>
<td>17/89 (19%)</td>
<td></td>
</tr>
<tr>
<td>- F3</td>
<td>9/74 (12%)</td>
<td>11/89 (12%)</td>
<td></td>
</tr>
<tr>
<td>- F4</td>
<td>13/74 (18%)</td>
<td>20/89 (23%)</td>
<td></td>
</tr>
<tr>
<td>Treatment history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- naive</td>
<td>50 (64%)</td>
<td>50 (50%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
### Table 2. Antiviral HCV treatment related characteristics

<table>
<thead>
<tr>
<th>Antiviral treatment</th>
<th>PWID (n=78)</th>
<th>Non-PWID (n=101)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of treatment:</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>- Boceprevir</td>
<td>37 (47%)</td>
<td>42 (42%)</td>
<td></td>
</tr>
<tr>
<td>- Telaprevir</td>
<td>41 (53%)</td>
<td>59 (58%)</td>
<td></td>
</tr>
<tr>
<td>Occurrence of side effects</td>
<td>68 (87%)</td>
<td>90 (89%)</td>
<td>NS</td>
</tr>
<tr>
<td>- Psychiatric complaints</td>
<td>19 (24%)</td>
<td>11 (11%)</td>
<td>0.02</td>
</tr>
<tr>
<td>- Skin rash</td>
<td>24 (31%)</td>
<td>37 (37%)</td>
<td>NS</td>
</tr>
<tr>
<td>- Anaemia</td>
<td>27 (35%)</td>
<td>47 (47%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 3. Results of non-inferiority statistical analysis comparing endpoints between PWID and non-PWID

<table>
<thead>
<tr>
<th></th>
<th>PWID (n=78)</th>
<th>Non-PWID (n=101)</th>
<th>Difference</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of treatment completion</td>
<td>27 (35%)</td>
<td>22 (22%)</td>
<td>13</td>
<td>[0;26]</td>
<td>0.87</td>
</tr>
<tr>
<td>Reasons for non-completion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Absence of viral response</td>
<td>8/27 (30%)</td>
<td>8/22 (36%)</td>
<td>-6</td>
<td>[-33;20]</td>
<td>0.19</td>
</tr>
<tr>
<td>- Other reasons*</td>
<td>19/27 (70%)</td>
<td>14/22 (64%)</td>
<td>6</td>
<td>[20;33]</td>
<td>0.55</td>
</tr>
<tr>
<td>SVR</td>
<td>49/69** (71%)</td>
<td>68/94** (72%)</td>
<td>-1</td>
<td>[-15;13]</td>
<td>0.30</td>
</tr>
<tr>
<td>- Naïve patients</td>
<td>39/49 (80%)</td>
<td>40/48 (83%)</td>
<td>3.7</td>
<td>[-19.2; 11.7]</td>
<td>0.44</td>
</tr>
</tbody>
</table>

* Other reasons were substance or alcohol use, side effects, comorbidities, socio-financial situation, non-compliance, death, lost to follow-up or decision of the patient.

** 69 and 94: These are the total number of PWID and non-PWID with known result for SVR (yes or no) and in other patients SVR result was missing due to death, lost to follow-up etc.