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Belgian experience with direct acting antivirals in people who inject drugs

Belgian Experience with Direct Acting Antivirals in People Who Inject Drugs.

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ABSTRACT

Background and aim

Hepatitis C viral infection (HCV) has become a curable disease due to the development of direct acting antivirals (DAA). The WHO has set a target to eliminate HCV completely. Therefore, people who inject drugs (PWID) also need to be treated. In this study, we compared the real-life uptake and outcome of DAA treatment for HCV in PWID and non-PWID.

Methods

We performed a nation-wide, retrospective cohort study in 15 hospitals. All patients who were treated with simeprevir-sofosbuvir, daclatasvir-sofosbuvir, or ombitasvir/paritaprevir ritonavir – dasabuvir between December 2013 and November 2015 were included.

Results

The study population consisted of 579 patients: 115 PWID (19.9%) and 464 non-PWID (80.1%). Of the PWID 18 were active PWID (15.6%), 35 still received opiate substitution therapy (OST) (30.4%) and 62 were former PWID without OST (53.9%). PWID were more infected with genotype 1a and 3 (p=0.001). There were equal rates of side-effects (44.7% vs. 46.6%; p=0.847), similar rates of treatment completion (95.7% vs 98.1%; p=0.244) and SVR (93.0% vs 94.8%; p=0.430) between PWID and non-PWID, respectively.

Conclusion

PWID, especially active users, are underserved for DAA treatment in real life in Belgium. Reimbursement criteria based on fibrosis stage make it difficult to treat PWID. Treatment adherence is similar in PWID and the general population, even in patients with active abuse. DAA were safe and effective in PWID despite the higher prevalence of difficult-to-treat genotypes. Based on these data more efforts to treat PWID are needed and policy changes are necessary to reach the WHO targets.

KEY WORDS

Direct acting antiviral therapy, hepatitis c virus, intravenous drug use, people who inject drugs, treatment uptake.

1. INTRODUCTION

Hepatitis C viral infection (HCV) remains one of the main causes of chronic liver disease and mortality worldwide. The hepatitis C virus (HCV) infects approximately 70-85 million people according to the latest data of the Polaris observatory, published by Gower et al. in 2014.(Gower et al., 2014) People who inject drugs (PWID) are one of the largest risk groups for HCV infection and it is estimated that worldwide about 10 million PWID are infected with the virus.(Nelson et al., 2011) In high-income countries, injection drug use is the primary mode of HCV transmission.(Grebely et al., 2015; Nelson et al., 2011) In Belgium, the seroprevalence of HCV antibodies is estimated to be 50-70% in PWID.(Matheï et al., 2005) Furthermore, recent modeling efforts suggest that PWID account for nearly half of the new infections.(Matheï C, 2015) In total, approximately 2.970 PWID are estimated to be infected with HCV(Matheï C, 2015).

Due to the development of Direct Acting Antivirals (DAA), HCV treatment has become very effective.(Feld et al., 2014; Kowdley et al., 2014; Lawitz et al., 2014; Sulkowski et al., 2014) Therefore, the World Health Organization (WHO) has set a target to reduce the incidence of HCV with 90% and liver-related mortality with 65% by 2030, while increasing diagnosis and treatment eligibility.(WHO, 2016) To reach these targets, PWID should be treated. Multiple studies have provided data that PWID could be treated effectively and safely in the interferon-era.(Arain and Robaeys, 2014; Aspinall et al., 2013; Evon et al., 2011; Grebely et al., 2016a; Robaeys G, 2005; Robaeys et al., 2006; Sylvestre and Clements, 2007) This has also been studied

for the first generation DAAs.(Arain et al., 2015) Pharmacological data state that there are no important drug-drug interactions between the second generation of DAAs and opiate substitution therapy (OST).(Ogbuagu et al., 2016) More recently, Dore et al. reported in an interventional study similar sustained virologic response (SVR) in people in a OST cohort and with active drug use treated by Grazoprevir-Elbasvir.(Dore et al., 2016) However, these findings were not generalizable to people not being treated with OST, and also not in genotype 3 patients, a genotype with a higher prevalence in PWID.(Robaeys et al., 2016) Grebely et al. published the results of people on OST who were treated by sofosbuvir/velpatasvir in the phase III Astral trial.(Grebely et al., 2016b) They saw no interactions nor a different treatment outcome in patients receiving OST in this pharmaceutical driven trial. Current treatment guidelines state that PWID should not be excluded from HCV treatment.(Pawlotsky JM, 2015) However, only 10% was willing to treat active PWID in a questionnaire obtained from 108 prescribing physicians at the Liver Meeting in 2014.(Asher et al., 2016) Reinfection rates and treatment costs were the main concerns when determining candidacy. Thus the populations at greatest risk for new infections, are also at greatest risk of not receiving treatment due to stigmatization. The aim of this trial was to evaluate the uptake and outcome of therapy in PWID versus the general population in a real-life setting in Belgium.

2. METHODOLOGY

2.1. Study Design

We performed a national, retrospective cohort study in 15 hospitals, distributed across the country. All patients treated with DAA therapy between December 2013 and December 2015 were included. Patients with DAA treatment were enlisted, and a database was filled out based on the electronic health record (EHR). This was done by the study nurse of the participating centers, or by one PhD student who collected data on-site. All correspondence between the hospital and the general practitioner was hand-searched for the different parameters such as drug use, comorbidity, etc. to minimize the risk of missing data. In case antiviral treatment was started and if data were available on SVR status, data were collected in a central database. Permission was given from the ethical committee of ZOL Genk to collect data retrospectively.

At that time, only physicians affiliated to tertiary centers could prescribe DAA therapy. Almost all these centers participated in this trial, therefore, we have a good overview of the prescription of DAA in Belgium between from 2013 to 2015. We have collected data on interferon free regimens: all patients who were treated with simeprevir-sofosbuvir, daclatasvir-sofosbuvir, or ombitasvir/paritaprevir ritonavir – dasabuvir were included. Sofosbuvir-ledipasvir was not yet available in Belgium in this period, and therefore could not be used for this study. Data of patients treated in compassionate use programs were also collected.

2.2. Applied definitions and criteria.

A PWID was defined as someone who used intravenous drugs at least once. An active PWID was defined as someone who used drugs during DAA treatment. A former PWID was defined as someone who used drugs at least once, but not during this treatment. These were subdivided into

patients receiving opiate substitution therapy (OST) during the HCV therapy and patients without any treatment concerning drug use.

The Belgian reimbursement criteria were applicable on all these patients (until the end of 2016). As such, only patients with F3 or F4 fibrosis, based on either a liver biopsy (Metavir score) or a combination of non-invasive testing (1) elastography and (2) biological fibrosis score could be treated (if not in a compassionate use program). Treatment completion was defined when patients presented at the outpatient clinic at the end of treatment to discuss end-of-treatment (EOT) results.

Diagnosis of the comorbidities were made by the treating physicians, and filled out in the database. Depression was based on the DSM-IV criteria. Alcohol use was stated as a comorbidity when excessive use was present (> 2 units for women, > 3 units for men). The presence of hepatocellular carcinoma (HCC) was defined as a comorbidity if there was a HCC in the patient history.

2.3. Study population:

In total, 579 patients were included in the study: 115 were PWID (19.9%) and 464 were non-PWID (80.1%). These were later subdivided in 18 active PWID (15.7%), 35 former PWID who still receive OST (30.4%) and 62 former PWID without any OST (53.9%). Active PWID used heroin and/or methamphetamine and/or cocaine and/or marihuana during treatment. Most of them were also in follow-up in a OST treatment program. Only 3 of the active PWID did not receive OST. The different subgroups of PWID were analyzed.

2.4. Endpoints of the study:

First of all, we wanted to study the treatment uptake of PWID in Belgium. Next, the primary endpoints were treatment completion and viral clearance with sustained virologic response after

12 weeks of treatment (SVR12). Patient characteristics and side effects of antiviral treatment were also studied.

2.5. Statistical analysis

Descriptive statistics of patient characteristics are presented: for continuous variables, means and standard deviation, for categorical variables proportions and percentage are given. A logistic regression model was used to compare the SVR ratio between PWID and the control group. A non-inferiority hypothesis was tested for each subgroup with a 5% margin. To compare patient subgroups, regression methodology was used for continuous variables (such as age and BMI), and Chi-square test for categorical variables (such as fibrosis score, treatment completion). A *P*-value <0.05 was considered statistically significant.

3. RESULTS

3.1. Baseline characteristics

Patient characteristics are described in Table 1. PWID were significantly younger and predominantly male. They had a lower BMI, and less diabetes mellitus. PWID used more benzodiazepines, and presented with more excessive use of alcohol. Furthermore, PWID were much more infected with genotype 1a and 3, whereas genotype 1b was the most prevalent in non-PWID. There was no significant difference in viral load, nor fibrosis stage. The latter could be explained by the reimbursement criteria in Belgium, as only patients within the F3-F4 stage could be treated. Only 79 patients (14%) were treated through compassionate use programs, and did not yet have severe fibrosis. These were predominantly former PWID and non-PWID. There was no difference in treatment experience between the subgroups. Only one patient was re-infected. There were no significant differences between the subgroups for HIV- or HBV-coinfection.

From the active PWID, 5 did not receive OST during DAA treatment. All patients had ever used heroin or cocaine. The active use of drugs was obtained from the EHR-files. The kind of drugs used during treatment was in most cases not specified.

3.2. Antiviral treatment

Details of antiviral treatment are described in Table 2. Patients were treated according to the latest guidelines following the rules of good clinical practice. All patients used one of the following regimens: simeprevir 150mg + sofosbuvir 400mg, daclatasvir 90mg + sofosbuvir 400mg, or ombitasvir 12.5mg + paritaprevir 75mg + ritonavir 50mg ± dasabuvir 250mg. The choice of these regimens was based on the availability for real-life use, which was dependent on the Belgian reimbursement policy. As ombitasvir/paritaprevir/ritonavir ± dasabuvir became only available at the end of 2015, less patients were treated with this regimen. There were no differences in the probability to reach SVR between the treatment regimens as visualized in Figure 1. This was verified by the logistic regression model, which could not show differences of SVR between simeprevir-sofosbuvir and daclatasvir-sofosbuvir (p=0.423) nor simeprevir-sofosbuvir and ombitasvir- paritaprevir-ritonavir ± dasabuvir (p=0.598). There were no significant differences in the rate of side effects between PWID and non-PWID. Gastro-intestinal complaints were more noted in non-PWID. PWID did more often have a history of depression, and did develop more psychological side effects during the treatment. However, although PWID did use more antidepressants before the start of therapy, there was no difference in starting new antidepressants during therapy in PWID vs non-PWID. Ribavirin was more often used in PWID, resulting from the higher prevalence of genotype 1a and 3 in this subgroup. There were no significant differences in treatment duration.

3.3. Factors affecting outcome in PWID

Details of outcome of antiviral treatment are provided in Figure 2. Treatment completion was similar in both groups. In 2.4% (14/579) of the patients, treatment was stopped. In 5 PWID treatment was not completed: 2 patients developed severe liver decompensation, 1 patient was diagnosed with end-stage HCC, 1 had psychological side effects, and 1 died during treatment (unknown cause). Also in 9 non-PWID treatment was not completed: 2 patients developed severe liver decompensation, 2 patients were diagnosed with end-stage HCC, 2 were stopped due to incompliance, 2 due to severe vertigo and 1 patient due to lung empyema.

In another 33 patients, treatment was adjusted. In 90.9% (30/33), ribavirin was lowered in dosage or stopped completely due to side effects. In 9.1% (3/33), treatment with DAA was adjusted. One patient (active PWID) incorrectly used 2 pills of daclatasvir per day, and was adjusted to the normal dosage. One patient (ex-PWID) had subjective intolerance to daclatasvir, and dosage was lowered from 60mg to 30mg per day. The last patient (non-PWID) was switched from simeprevir to daclatasvir due to insufficient response at 12 weeks, and reimbursement problems.

There were no significant differences in the rate of SVR between PWID and non-PWID. If we analyze the outcome of therapy for PWID in the 3 subgroups of active users, the OST group and former PWID, there is also no statistical significant difference as shown in figure 3. Furthermore, from the 3 patients not reaching SVR in the active PWID group, 2 patients were EOT, but died before reaching SVR. One patient died due to a car accident, the other due to a cerebral hemorrhage. Only one patient did develop acute on chronic liver failure during therapy, and therefore therapy was stopped before reaching EOT.

4. DISCUSSION

Multiple clinical trials have shown the efficacy of the second generation of DAA against HCV.(Ferenci et al., 2014; Garimella et al., 2015; Jacobson et al., 2014; Lawitz et al., 2014;

Manns et al., 2014; Sulkowski et al., 2014; Zeuzem et al., 2014) Real life data are also starting to be published, with equal results.(Pol et al., 2016; Willemse et al., 2016) Up to now, no real-life data on the use of DAA in PWID were published. In this retrospective trial, there is no evidence to suggest that there is a difference in outcome between PWID and non-PWID, even in patients with severe fibrosis or even cirrhosis. Thus, (former) drug use itself does not influence SVR in this cohort. If we analyze the data for PWID in different subgroups, we notice a non-significant decline in the SVR rate of active PWID (see figure 3). However, two out of three patients who did not reach SVR, already reached EOT, and died due to reasons unrelated to the HCV treatment. It would be reasonable to expect that these patients would also reach SVR. If we withhold them from the analysis (modified intention to treat analysis), 93.8% (15/16) of the patients reached SVR. Thus the difference disappears completely. Also, treatment completion rates were similar between these subgroups. However, further research remains necessary, as only 18 active PWID were treated during the last two years in these centers. Only 5 out of these 18 patients did not receive OST treatment. Thus, also this population is still selected, and further efforts should be made to reach out to the active PWID population.

Treatment adherence, based on the rates of treatment completion, was similar between PWID 95.7% (110/115) and non-PWID 98.1% (455/462) p=0.302. Direct observed adherence could not be assessed due to the retrospective study design. However, previous studies with (peg)interferon and first generation DAA have proven similar treatment adherence between PWID and non-PWID multiple times.(Arain et al., 2015; Dimova et al., 2013; Robaeys et al., 2006)

Multiple pharmacokinetic studies have investigated the interactions between antiviral agents and substitution therapy.(Garimella et al., 2015; Lalezari et al., 2015; Ogbuagu et al., 2016) These studies state no clinical significant interactions occurred between antiviral therapy and substitution therapy, and there was no need to adjust dosage. In this setting, there were no reasons

to suspect clinical interaction of substitution therapy and antiviral therapy. Active PWID used heroin, cocaine, methamphetamine, cannabis. No clinical evidence of interaction between drug use and antiviral therapy was clear from the medical files. However, due to small numbers of active PWID treated, no definite statements can be made.

As the WHO has set a target to reduce HCV incidence with 90% by 2030, treatment of PWID should be prioritized.(WHO, 2016) Furthermore, multiple models have supplied theoretical evidence that treatment of HCV in PWID, in combination with harm reduction programs, is cost-effective and necessary to reach the goal of prevention through treatment.(Hickman et al., 2015; Martin et al., 2011; Martin et al., 2012; Matheï C, 2015) Specifically for the Belgian situation, it is estimated that > 10% of the population of active PWID (>297 patients) should be treated annually.(Matheï C, 2015) In this study, only 18 active PWID were treated with DAA therapy between November 2013 and November 2015.

This could be biased by the reimbursement criteria in Belgium at that time, which required F3 or F4 fibrosis. As (active) PWID in this study were younger as non-PWID, this could have an impact on fibrosis stage and thus treatment uptake. However, structural underlying problems at patient level (lack of knowledge and screening), and at doctor level (selection of patients, stigmatization) are also responsible.(Arain and Robaeys, 2014; Asher et al., 2016) Based on the patient files, only 2.5% (1/40) of the ex-PWID who were treated in the past with interferon were re-infected. This is comparable to earlier studies who also have shown low reinfection rates.(Aspinall et al., 2013; Dalgard et al., 2002; Grady et al., 2013; Midgard et al., 2016; Valerio et al., 2015) However, due to the shift to the target of viral elimination, the potential risk of reinfection should not influence the physicians' judgement, as these patients are the key targets to treat in order to achieve viral elimination. Therefore, continued efforts should be made to reach PWID for treatment of HCV.

5. CONCLUSION

PWID, especially active users, are underserved for DAA treatment in real life in Belgium. Reimbursement criteria based on fibrosis stage make it nearly impossible to treat young injection drug users. Nevertheless, treatment adherence is similar in PWID and the general population, even in our patients with active abuse. DAA were safe and effective in PWID despite the higher prevalence of difficult-to-treat genotypes. Based on these data more efforts to reach out and treat PWID are needed. Policy changes are necessary if we want to reach the WHO targets.

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7. FIGURE LEGENDS

Figure 1: SVR rates according to treatment regimen.

SVR=sustained virologic response 12 weeks after treatment completion.

Figure 2: Outcome of antiviral therapy between PWID and non-PWID.

SVR = sustained virologic response 12 weeks after treatment completion.

Figure 3: Outcome of antiviral therapy between active PWID, OST PWID, Former PWID.

SVR = sustained virologic response 12 weeks after treatment completion.
*P-value is marginally not significant, however after correction for non-treatment related causes for loss to follow-up, little evidence remains to suggest that active drug use influences SVR. (cfr. discussion)