Uptake of hepatitis C virus screening and treatment in persons under opioid substitution therapy between 2008 and 2013 in Belgium

D. Busschots[1,2], A. Arain[1,2], R. Bielen[1,2], Ö.M. Koc[1-3], L. Bruckers[4], T. Rakhmawati[4], K. Corten[1], C. Lebbe[5], K. Cornelis[6], C. Mathei[7,8], F. Buntinx[9], N. Hens[4,10], G. Robaeys[1,2,11]

(1) Faculty of Health and Life Sciences, University Hasselt, Diepenbeek, Belgium ; (2) Department of Gastroenterology and Hepatology, Ziekenhuis Oost-Limburg, Genk, Belgium ; (3) Medical Microbiology, School of NUTRIM, Maastricht University Medical Centre, Maastricht, the Netherlands ; (4) Faculty of Science, Interuniversity Institute for Biostatistics and statistical Bioinformatics, Hasselt University, Diepenbeek, Belgium ; (5) Medical Direction, Christian Health Insurance Fund (CM), Brussels, Belgium ; (6) Department of Research and Development, Christian Health Insurance Fund (CM), Brussels, Belgium ; (7) Free Clinic, Antwerp, Belgium ; (8) Department of Public Health and Primary Care KULeuven, Leuven, Belgium ; (9) Department of General Practice, KU Leuven, Belgium and Maastricht University, The Netherlands ; (10) Centre for Health Economic Research and Modelling Infectious Diseases, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium ; (11) Department of Gastroenterology and Hepatology, University Hospitals KU Leuven, Belgium.

Abstract

Background : **Hepatitis C is a viral infection caused by the hepatitis C virus (HCV) with people who inject drugs as the main group at risk worldwide.**

Aim : **This study investigated the differences in uptake for HCV screening and treatment between persons in opioid substitution therapy (OST) and the other members of the Christian Health Insurance Fund in Belgium.**

Methods : **Invoice data were retrospectively collected from the Christian Health Insurance Fund, representing 42% of the healthcare users. Information on demographics, screening, diagnostic tests, treatment and disease progression was obtained from 2008 till 2013. All people in this study were aged 20-65 year. Persons in the OST group were identified as having at least one prescription reimbursed for methadone. This group was compared to the other members of the Insurance Fund not on OST (NOST).**

Results : **The Insurance Fund registered 8,409 unique OST and 3,525,190 members in the general group. HCV RNA screening rate was higher in the OST group after correction for age and gender (4.3% vs. 0.2%). Ribavirin reimbursement, did not differ between the OST and NOST group screened for HCV RNA (16.9% vs. 14.4%), though the probability of having ribavirin reimbursed was smaller for females than for males. Procedures concerning disease progression were reimbursed less frequently in the HCV RNA screened OST group compared to the NOST group (0.3% vs. 1.2%).**

Conclusion : **People on OST were screened more often for HCV RNA. However, the general uptake for HCV screening and treatment in both populations remained suboptimal.** (Acta gastroenterol. belg., **2021**, 84, **311-316**).

Keywords : hepatitis c, substitution treatment, ribavirin, Belgium.

Abbreviations : Ab : Antibody ; CI : Confidence Intervals ; CM : Christian Health Insurance Fund ; DAA : Direct-Acting Antiviral ; HCV : Hepatitis C Virus ; OR : Odds Ratio ; OST : Opioid Substitution Therapy ; PWID : Persons Who Inject drugs ; PWUD : People Who Use Drugs ; PY : Person Years ; SVR : Sustained Virologic Response ; WHO : World Health Organization.

Introduction

Worldwide, hepatitis C virus (HCV) infection related morbidity and mortality continues to increase (1). According to the most recent estimates in 2013 1.1% of the global population (71 million) was chronically infected with HCV (2,3). HCV is primarily transmitted through blood-to-blood contact and is nowadays mainly associated with intravenous drug use. Persons who inject drugs (PWID) are therefore categorized by the World Health Organization (WHO) as the main risk group for HCV infection in Western countries. Previous studies in Flanders (Belgium) estimated an HCV prevalence of 0.87% in the general population in 1997 and ranged between 0.22% and 0.57% in 2015 (4-8). In 2015, there were an estimated 9,080 PWID in Belgium of whom 32.7% were HCV-infected (9).

The WHO emphasizes the importance of screening and treatment within this PWID population (10). Additionally, Belgium has had a 'Hepatitis C Plan' since 2014 to reduce transmission, increase the awareness of their diagnosis and to enhance HCV infected patients' care pathway and quality of life (11). However, screening and treatment uptake among PWID remains low, despite evidence that an increased treatment uptake rather than improved sustained virologic response (SVR) profiles will be the key driver in avoiding future infections (12-14). Between 2008 and 2015, 61.1% (18,880/30,905) PWUD where screened at least once for HCV in Belgium. However, regular screening is necessary to achieve the WHO targets (reducing new infections by 90% and mortality by 65%) by 2030 (15,16). In Belgium, reimbursement for direct-acting antiviral (DAA) treatments only started in 2015 (17). Before, all HCV infected patients were treated with an interferon based therapy, potentially supplemented with ribavirin.

The aim of this study was to compare the uptake for HCV screening and treatment in persons under opioid substitution therapy (OST) group with the remaining members of the Christian Health Insurance Fund (CM) not on OST in Belgium.

The most common treatment, in combination with psychosocial interventions, to treat opioid dependent

Correspondence to : Dana Busschots, Faculty of Health and Life Sciences, Agoralaan Gebouw D, 3590 Diepenbeek, Belgium. Phone : +32 (0)89 21 20 61. Email : dana.busschots@uhasselt.be

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persons is OST. More than half of the opioid users are receiving OST. Therefore we can suggest that all persons on OST are people who use drugs (PWUD) (18,19).

Materials and methods

Healthcare insurance is compulsory in Belgium and is provided through several major agencies to organize the reimbursement of medical fees or prescribed medication. This allows collecting and managing of data concerning medical tests, prescribed medications, treatments and demographic characteristics. The largest sickness fund is the CM which represents 42% of the Belgian population (20).

In this study OST was identified as having at least one prescription of methadone, Subutex® or Subuxone® reimbursed per year. In this study the OST group was compared to the group with no OST reimbursement that year (NOST group). All people in this study were aged 20-65 year and to study the age effect the group subdivided in two age groups (20-40 year and 41-65 year).

In this study, invoice data were retrospectively collected from the CM between 2008 and 2013. The following topics were investigated for the OST group and NOST group : demographics, uptake for HCV screening, antiviral treatment, diagnostic procedures and therapies related to disease progression. To ascertain that all used data were relevant to HCV infection, data from diagnostic procedures, antiviral treatment and therapies related to disease progression were only used in the analysis if the person was screened for HCV RNA. Before June 2008, HCV RNA testing was performed in specialized centers and was not reimbursed by the health insurance fund. Therefore, the data represent a time span from 2008 to 2013. All data were extracted from the CM databases.

Screening uptake was studied by analyzing the number of tests reimbursed for HCV RNA (quantitative, qualitative or genotyping) between 2008 and 2013. To map the disease progression, reimbursements for medications or procedures used to treat the common complications associated with advanced chronic liver disease such as cirrhosis, ascites and esophageal varices were used as a proxy. The number of liver transplants is a measure for decompensated end-stage liver disease. When ascites is non-responsive to diuretics, an evacuating ascites puncture is performed. A liver biopsy is used to assess the histological changes in the liver and grade this according to the METAVIR score (21). In order to measure the patients treated for portal hypertension and bleeding varices, the number of patients reimbursed for sclerotherapy was counted. CM does not have data about the results of the reimbursed tests or procedures.

Antiviral treatment uptake was investigated by studying the number of reimbursed ribavirin prescriptions as ribavirin was almost unique to HCV treatment (the only other indication was Ebola viral infection) and was part of every antiviral HCV therapy plan available during this study period.

The patient numbers per year were unique numbers, meaning that reimbursement from one patient was only counted once, even if it encompassed multiple years.

Patient demographics were summarized using mean ± standard deviation for continuous characteristics and by proportions for categorical characteristics. Pearson's chi-square statistic was used to evaluate differences between the OST and NOST group in terms of categorical patient characteristics and by means of a t-test for continuous characteristics.

Logistic regression models were employed to evaluate differences in screening (HCV RNA screening, genotyping) and disease progression (mortality) between the OST and NOST group. Age, gender and calendar year were included as explanatory variables in the logistic models. As a result, the obtained odds ratio (OR) quantifying the difference between the OST and NOST group, and the statistical significance are corrected for age, gender and calendar year. A significance level of 5% was used in all models.

Result

The CM registered 8,409 unique persons with at least one invoice for OST and 3,525,190 other unique members without an invoice for OST from 2008 to 2013 (data not shown).

In the OST group the majority of the members were male (75%) whereas gender was equally divided in the NOST group (50%). The average age for the NOST group was 43±13 years and 37±10 years for the OST group. The proportion of young persons in the OST

Table 1. — **Results for the logistic regression models used to evaluate differences in screening and disease progression between OST and the NOST population**

	OST (2008-2013 N=8,409)	NOST (2008-2013 N=3,525,190)	P-value	OR 95% CI
Mortality	376 (4.5%)	42,303(1.2%)	**<0.001**	4.65 (2.61;8.29)
HCV RNA testing	642 (4.3%)	5,705 (0.2%)	**<0.001**	76.09 (61.01;94.41)
HCV genotyping*	270 (42.1%)	1,619 (28.4%)	**<0.001**	117.80 (99.08;140.05)
Ascites punction*	4 (0.6%)	106 (1.8%)	**<0.001**	0.34 (0.21;0.56)
Sclerotherapy*	2 (0.3%)	45 (0.8%)	**0.010**	0.39 (0.12;0.80)
Liver transplant*	1 (0.2%)	64 (1.1%)	**<0.001**	0.14 (0.37;0.05)

*Among the persons who were screened for HCV RNA

group (63%) was higher than in the NOST group (46%). The all cause death rate during the study period was 4.5% in the OST and 1.2% in the NOST group. The results of a logistic regression model indicated that this difference was significant (Table 1).

HCV RNA screening

Between 2008 and 2013, a higher proportion of OST were screened for HCV RNA (4.3% vs. 0.2%, Table 1). In 2008, 58 (1.5%) of the OST group received reimbursement for an HCV RNA test. This number increased to 178 in 2013 (4.4%, data not shown). Furthermore, the odds were significantly higher for the OST group, the older age group and for males.

HCV genotyping

A significantly higher proportion of the screened OST group was genotyped (42.1% vs. 28.4%, Table 1) compared to the NOST group. Additionally, the probabilities for the older age group and males to be genotyped were higher compared to the younger aged group and females.

Liver biopsy

In persons who were screened for HCV RNA, the probability to undergo a liver biopsy did not differ (p=0.940) between the OST and NOST group (12.6% vs. 13.6%). In contrast, the probability of undergoing a liver biopsy was significantly higher for the older age group compared to the younger aged group and for males compared to females (data not shown).

Disease progression procedures

An evacuating ascites punction was performed in 0.6% of the screened OST group and in 1.8% of the screened NOST group between 2008 and 2013 and this difference was significant (Table 1). Of the persons who have got HCV RNA reimbursed, sclerotherapy for esophageal varices was reimbursed in 0.3% of the OST group and 0.8% of the NOST group during the study period. This difference in the probability of receiving sclerotherapy in the HCV screened OST compared to the NOST group was statistically significant (Table 1). The HCV screened OST group had a significant lower probability of undergoing a liver transplantation compared to the NOST group (0.2% vs. 1.1%, Table 1).

Ribavirin reimbursement

Of the persons who have got HCV RNA reimbursed, ribavirin reimbursement, was not significantly different in the OST group compared to the NOST group between 2008 and 2013 (p=0.3963, Figure 1). The odds of receiving HCV treatment was significantly higher for the older age group compared to the younger aged group and for male compared to female (data not shown).

Discussion

The main finding of this study is that the OST group was more frequently screened for HCV RNA than the NOST group. The uptake for HCV antiviral treatment did not differ between the two groups as we take ribavirin reimbursement as a proxy for antiviral HCV treatment. In the OST group there were less prescriptions for therapies concerning the common complications associated with advanced liver failure.

Most studies on HCV screening reported an infection rate reflecting the percentage of HCV antibody (Ab) or RNA positive subjects in the tested population. In this study we reported the rate of reimbursed HCV RNA tests as prevalence for persons tested for HCV RNA. In total, 4.3% of the OST group and 0.2% of the NOST group was screened for HCV RNA between 2008 and 2013. These results were expected as a RNA test was only performed to confirm HCV infection after a positive HCV Ab test and HCV Ab prevalence in the general population is low (5,7,8,22-25). Moreover, our results are in line with another study conducted in PWUD in Belgium. The authors estimated the number of PWUD tested for HCV by using national nomenclature codes for HCV tests between 2008 and 2015. Of the PWUD in this study 4.4% was tested for HCV RNA. (15) This is similar to 4.3% we found. In addition, an HCV Ab prevalence of 1.31% and an HCV RNA prevalence of 0.57% were reported at the emergency department of Ziekenhuis Oost-Limburg in 2015 (26). The prevalence of HCV Ab in the general population between 2013 and 2015 was estimated to be 0.22% and the HCV RNA 0.12% (8). However, our NOST group also contains drug users, the risk factors related to HCV will be limited and the entire NOST population will resemble the general Belgian population more than the OST group. Nevertheless, testing rates were suboptimal in both OST and NOST group. The Centers for Disease Control and Prevention even recommends a universal HCV screening of at least once in a lifetime for all adults aged 18 years or older and a routine periodic testing for people with ongoing risk factors (e.g. PWID) (27). A study carried out at the emergency department of a large non-university hospital in Belgium concluded that screening should be offered at least to men born in 1955-1974 (26).

A systematic review of HCV treatment uptake among PWID in the European Region demonstrated that the treatment uptake for people who were HCV RNA positive and who were under OST ranged from 10% to 47% (28). Treatment uptake within the OST population seems to be inadequate in this study looking at the prescriptions for ribavirin (16.9%). Although, we can only speculate because we do not know the results of the HCV RNA screening. Nevertheless, a suboptimal uptake could be explained on the one hand by the frequent side-effects

related to interferon-toxicity. Anxiety for the side effects of therapy in the interferon era was the main reason to interrupt follow-up and refusal of treatment in a study by Keymeulen *et al*. in Belgium (29). Further, a lack of HCV treatment infrastructure or on the other hand a low prevalence of HCV RNA testing and low prevalence of HCV RNA positive tests during the study period could have led to suboptimal treatment uptake. Other health and social problems were likely to play a role as symptomatic illnesses and stable housing often take priority (30). Since 2015, DAA treatments are available in Belgium and these well-tolerated and highly effective (SVR >95%) drugs could facilitate treatment uptake especially since it is reimbursed for every HCV infected person since January 2019. In fact, one of the main reasons for non-eligibility to DAA treatment was that the regimen was not reimbursed (access limitation) (31,32).

In our study, we also assessed the proportions of performed liver biopsies in the OST group and NOST group. Our results indicated that liver biopsy was performed equally in both groups (13%). Nevertheless, no clear increasing or decreasing trend could be observed in the rate of liver biopsies. We expected a decreasing trend due to the growing use of alternative, patient-friendly and non-invasive methods such as a transient elastography to determine the stage of fibrosis (33-35). However these non-invasive methods did not affect the rate of liver biopsies. At that time, a liver biopsy was compulsory in Belgium for most genotypes to receive a reimbursement for HCV antiviral therapy, which may have been a disincentive to the start the treatment. International guidelines and the Belgian Hepatitis C Plan have plead to allow the above mentioned alternative and patient-friendly methods to be accepted as an equivalent to liver biopsies regarding reimbursement (11, 36, 37). They succeeded because nowadays only a FibroScan® and blood sample are obligatory to start treatment (17). These interventions are less invasive and could therefore facilitate treatment uptake.

Novel in this study is that the therapies concerning decompensated (end-stage) liver disease were more reimbursed in the NOST group. This could indicate that the OST group experienced less severe liver damage or were undertreated. Several factors could explain this finding. First, the OST group is screened for HCV more often and at a younger age which benefits prevention of liver damage if antiviral treatment is initiated. Second, the OST group died at a younger age which may have led to a shorter infection period and thus less time for liver damage to occur. Third, due to social marginalization, mistrust of the healthcare system and financial problems, it is possible that persons from the OST group did not seek medical attention when needed and thus liver disease progression may remain undiagnosed (38).

We found a significant difference in mortality between the OST and the NOST group. The OST group has a higher probability to die compared to the NOST group. These results are in line with a meta-analysis suggesting that drug users have higher risk for death. This higher risk could be attributed to directly drug-related factors such as an overdose, HIV co-infection and alcohol abuse. In addition, also indirect factors such as an inability to perceive health issues due to an intoxicated mental state could facilitate the higher mortality in the OST group (39). In a Norwegian study all-cause mortality in PWID was high with no difference between HCV RNA positive and HCV RNA negative individuals, in the first three decades after HCV transmission (40). A Danish study demonstrated that HCV-infected patients had lower income levels and more comorbidities, psychiatric illnesses, and substance and alcohol abuse than the age- and sex- matched cohort. An Australian study comparing mortality in more than 75,000 HCV infected patients with standardized mortality rates, also reported an increased risk of drug-related death, especially in younger individuals (41). These studies suggested that the increased mortality resulting mainly among HCV infected patients can be explained by the increased presence of comorbidity, alcohol abuse, drug use, and poor socioeconomic status. Thus antiviral HCV treatment will only be a partial solution and needs to be combined with harm reduction such as OST and needle/syringe programs.

Limitations

This was a descriptive study and not directly comparable to other studies due to the differences in study population and/or study methods. Based on the received data we could not make the distinction if the OST was prescribed for injecting drug users or not. Therefore we considered the OST population to be PWUD and not PWID. In addition, the CM data contained only information of 8,409 out of an estimated 31,000 PWUD (15). Our numbers may therefore be an underestimate, as we only have data on just over a quarter of the Belgian PWUD. Further, in most studies that report screening or treatment uptake, the study population often consists of participants of organizations providing care to substance users. Moreover in these studies the rate of treatment uptake is the percentage of persons starting treatment among persons who tested positive for HCV RNA. In contrast, in our study the denominator was the number of persons screened (reimbursed) for HCV RNA. Not all of the HCV RNA screened persons will test positive because some might have spontaneously cleared the virus or were previously treated and do not need HCV treatment. We only had information whether a test was reimbursed. Thus, there is no information on how many persons tested positive for HCV RNA between 2008 and 2013. There is also no information on HCV screening before 2008.

In addition, the data in this study only describes the members of the CM and it is unsure if they represent the entire Belgian population due to a lack of demographic data. Other limitations could be that there is an under- or

even overestimation of some data because sclerotherapy is not equal to portal hypertension and liver transplantation is not equal to (end-stage) liver failure. This study also lacks data on factors that could affect screening, treatment and disease outcome such as PWID, liver transaminases, alcohol abuse and co-infections.

Finally, the study was carried out in a period when HCV was treated with interferon usually supplemented with ribavirin in Belgium. However, since 2015 HCV is always treated with DAA therapy and this treatment is reimbursed for everyone since January 2019 in Belgium. Therefore a new study with data starting from 2015 would have a great added value to this study.

Conclusion

Our findings suggest that persons on OST were screened more often for HCV. Thereby, the uptake for HCV screening and treatment in Belgium was still suboptimal in both groups. People on OST died at a younger age and suffered less from decompensated (end-stage) liver failure or were less tested.

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Statement of Ethics

Ethical approval was not required due to the retrospective nature of the research..

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Author's contributions

A.A. and G.R., conception and design of the study, and data collection. L.B., T.R. and K.C. analysis of data. D.B. drafting of the article and finalizing the article. R.B., O.M., C.L., K.C., C.M., F.B. and N.H. : critical revision of draft and approval of the final version of the article and author list.

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