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Chronic hepatitis C in Swedish subjects receiving opiate substitution therapy – factors associated with advanced fibrosis

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Abstract

Background Opiate substitution therapy (OST) reduces the risk of death from directly drug related causes in heroin users, allowing other chronic health problems to emerge. People who inject drugs (PWID) are exposed to HCV, with an associated risk of chronic liver disease. We investigated HCV prevalence and liver-related morbidity in a cohort of OST recipients, and analyzed factors associated with significant hepatic fibrosis.

Methods All patients registered on April 1st 2008 in four clinics providing OST in the three largest cities in Sweden were eligible for inclusion. HCV viremic subjects were evaluated for fibrosis stage by liver biopsy, transient elastometry (TE) and/or a biochemical fibrosis index (Göteborg University Cirrhosis Index; GUCI). Factors associated with severity of fibrosis were determined with logistic regression analysis.

Results Out of 524 eligible patients, 277 consented to enrolment. 236 subjects (88%) were anti-HCV positive, and 162 of these were viremic (69%). Significant liver fibrosis (defined as Ishak stages F3-F6, TE value ≥ 8.85 kPa or GUCI >0.33) was found in 69 out of 103 (67%) tested viremic patients, and was associated with alcohol intake (p=0.03), higher body mass index (BMI; p=0.04) and presence of anti-HBc antibodies (indicating exposure to hepatitis B virus [HBV]; p=0.02).

Conclusions Significant liver fibrosis was detected in two thirds of HCV viremic OST recipients in this cohort, and was associated with alcohol use, high BMI and exposure to HBV. These findings indicate that management of HCV and associated risk factors should be emphasized in Swedish OST programs.

Introduction

Chronic hepatitis C is a leading cause of end-stage liver disease in North America and Europe (1, 2). In Sweden, as in most industrialized countries, injection drug use is the predominant route of infection.

Although some studies suggest a marked increase in the incidence of serious liver disease with rising age among people who inject drugs (PWID) (3-7), the natural course of HCV infection and its impact on morbidity and mortality in this population is complex and remains controversial.

Despite high prevalence of HCV infection, the risk of HCV related death among active opiate users is low (10), and the dominant causes of excess mortality are drug overdose, suicide, trauma and in some populations also HIV/AIDS (3, 8-10). However, directly drug related mortality is reduced in patients receiving OST, (11, 12). This might allow for other chronic conditions, such as HCV infection, to emerge as important causes of morbidity and mortality. Yet, factors with a potential influence on the course and outcome of HCV infection are frequent among PWID, irrespective of OST. These factors, such as heavy alcohol intake, co-infection with HIV or HBV and low HCV treatment uptake, might both obscure and aggravate the course of HCV infection in this population..

The emergence of new and more effective antiviral therapies necessitates better understanding of the characteristics of HCV infection among persons infected through injection drug use to enable optimal use of such regimens in this population.

We have investigated the prevalence of HCV infection, the burden of HCV-related chronic liver disease and factors associated with advanced fibrosis among Swedish OST recipients.

Methods

Setting

OST was introduced in Sweden in the 1960s (13). Methadone was the first widely used substance for OST, but since the late 1990s buprenorphine has been used as an alternative. Currently, it is estimated that 30-40% out of 10 000 heroin users in Sweden receive OST(14)

Design and study population

All patients receiving treatment in four public clinics providing OST in three metropolitan areas of Sweden (Stockholm, Gothenburg, Malmö) on April 1st 2008 were eligible for inclusion in this cross-sectional study. Visits for inclusion occurred between April 1st 2008 and January 29th 2010.

National criteria for OST at the time of inclusion were: at least 2 years of documented opiate abuse, a minimum age of 20 years, a history of several failed attempts of detoxification without substitution therapy, absence of advanced poly-drug abuse, Swedish citizenship and permanent housing. Written informed consent was obtained (separately for HCV testing and for liver disease investigation). No exclusion criteria were applied.

Procedures

Study subjects were interviewed by a physician specialized in addiction medicine following a structured questionnaire, with details concerning demographics, main drug of use, year of first illicit drug injection, year of OST initiation and type of substitution therapy. In order to estimate alcohol consumption, patients were asked to state their current monthly alcohol consumption by frequency of intake and number of standard units on each occasion. They were also asked for history of conviction for alcohol related crime and admission to facilities

for treatment of alcohol abuse. In addition, addiction clinic staff were asked to provide information on problematic alcohol use following registration in the respective clinics. Lifetime regular use of cannabis for a period greater than one year was recorded. Patients were also interviewed regarding symptoms possibly related to HCV infection and prior investigation and/or treatment of HCV infection. The "time at risk" for HCV acquisition was calculated by subtracting time in OST from time period since first reported illicit drug injection.

Blood samples were collected at this study visit. Anti-HCV antibodies were detected using standard laboratory procedures (different enzyme- or chemiluminescence immunoassays). Seroreactive samples were further tested for HCV RNA by polymerase chain reaction (PCR). HCV genotype was determined for all viremic samples using an in-house nested PCR and sequencing of the NS5B region (15). Patients with a previous registered positive result for HCV RNA were not retested. Patients with undetectable HCV RNA were re-tested after an interval of at least six months; subjects with persistently negative HCV RNA were considered to have spontaneously resolved HCV infection.

Viremic patients were then offered structured assessment for liver disease including medical history, history of alcohol and drug use, details regarding OST, smoking habits and physical examination, performed at departments of infectious diseases. Weight and height were obtained to calculate the body mass index (BMI; weight in kilograms divided by height in square meters). Fibrosis stage was determined using liver biopsy and/or transient elastometry. Blood samples for haematological parameters, liver, renal and metabolic function tests, and markers of HBV (HBsAg, anti-HBc and anti HBs) and HIV infection were collected. The study was approved by the Regional Ethical Review Board in Lund, Sweden.

Assessment of liver fibrosis

Liver biopsies were centrally scored for fibrosis stage by two experienced observers blinded for clinical information (J.W and M.L) according to the Ishak protocol (16) in a dual observer consensus fashion (17, 18). . Biopsies containing fewer than four portal tracts or measuring less than 1.5 cm were excluded. Significant fibrosis was defined as Ishak stages F3-F6. For statistical analysis of factors associated with fibrosis, Ishak F0-2 was defined as low-grade fibrosis, F3-4 as intermediate and F5-6 as high-grade fibrosis/cirrhosis.

Transient elastometry (TE; Fibroscan®) for measurement of liver stiffness was performed on the right liver lobe through intercostal access. Ten valid measurements with an interquartile range (IQR) less than 30% were required, using the median value for analysis. Significant fibrosis was defined as a stiffness value of ≥8.85 kPa and cirrhosis as a value of ≥10.05 kPa, using threshold levels derived by comparison with Ishak fibrosis staging according to Cross et al (19). These cut-off values were used to categorize patients into low, intermediate and high-grade fibrosis for statistical analysis.

Göteborg University Cirrhosis Index (GUCI) score, a biochemical fibrosis index shown to be highly correlated to the Ishak fibrosis stage (20, 21) was calculated from the following formula: GUCI = (normalized AST x prothrombin-INR x 100)/platelet count (x 10^9). Cut-off levels of 0.33 and 1.11 were used to categorize patients into low, intermediate and high-grade fibrosis for statistical analysis.

Patients were categorized into three groups according to their degree of fibrosis defined either by liver biopsy, TE or GUCI score. For this purpose, liver biopsy was preferred over TE and GUCI score, and TE over GUCI score (in case measurements by several methods were available).

Patients with clinical or histological signs of cirrhosis were screened for hepatocellular carcinoma (HCC) using liver ultrasonography.

Statistical methods

Differences among groups with regard to categorical variables were compared by the Chi square test and continuous variables by the Mann-Whitney U test or Kruskal-Wallis 1-way ANOVA. Factors potentially associated with advanced fibrosis and cirrhosis (age, gender, BMI, years since start of injection drug use, cannabis use, smoking, anti-HBc positivity, indicators of problematic alcohol use) were evaluated by trend tests (for continuous variables the Jonckheere-Terpstra test and for binary variables the linear by linear associations test) and multivariate analysis of factors showing a p-value for trend <0.20, was performed by logistic regression, entering data in a single step. All calculations were performed using the SPSS statistical software package, version 20.0.

Results

Patient characteristics

On April 1st 2008, 524 patients were receiving treatment in the four OST clinics. Among these, 277 (53%) consented to inclusion in the first part of the study (Figure 1). Inclusion visits occurred between April 1st 2008 and January 29th 2010. Characteristics of included subjects are shown in Table I. Among the 247 eligible patients not included, 182 declined participation, 42 had been discharged from treatment, 7 had moved from the uptake area and 16 had died. Median age (45 years) and gender distribution (71% men), as well as duration of OST, did not differ significantly from included subjects.

Previous investigation for HCV-related liver disease was reported by 73 participants (26%); 18 (6%) and 10 (4%) patients respectively reported having started or completed antiviral therapy, respectively.

Drug use details

Although most patients (264/277; 95%) reported heroin as their main drug of use, use of additional illicit drugs was common; 8 (3%) stated use of cocaine, 71 (26%) amphetamine, 73 (26%) benzodiazepines and 197 (71%) cannabis.

A substantial proportion of the patients had a history of alcohol related problems: 63 (23%) had been convicted for alcohol related crime; OST clinic staff reported excessive use of alcohol in 46 patients (17%) and 18 persons (7%) had received treatment for alcohol abuse. Despite this, most patients (n=179; 66%) claimed their current alcohol consumption to be modest (none or less than once a month). Ninety-five percent were current or former tobacco smokers (84% and 11% respectively).

Concomitant diseases

Apart from 27 (25%) patients with psychiatric disease (most commonly depression; n=22), few participants reported significant concomitant disease [heart disease (n=16), airway disease (n=16), diabetes (n=5)].

HCV markers

Among 269 persons tested, anti-HCV was detected in 236 (88%) individuals. Those without HCV antibody had a shorter time at risk of HCV compared to seroreactive participants (4 vs. 13 years, respectively; $p<0.0001$). There was no significant difference in age and gender distribution between these groups.

HCV PCR was performed for 234 out of 236 anti-HCV-positive subjects; 162 of these (69%) were viremic. Among the 72 (31%) persons without viremia, 9 individuals had received antiviral therapy, and the remaining 63 subjects showed spontaneous HCV resolution. Spontaneous clearance was significantly more common in women than in men (38% vs. 22%; p=0.02).

The distribution of genotypes was: 1a 44%, 1b 7%, 2b 13% and 3a 32%. No mixed infections were detected.

HBV and HIV markers

Two patients were HIV-positive (previously known) and 2 patients were HBsAg-positive. Sixty-five out of 106 patients (61%) were anti-HBc positive; among these 36 (55%) had both anti-HBc and anti-HBs antibodies, whereas 29 of these (45%) did not have detectable anti-HBs(anti-HBc alone). Nineteen patients (18%) had signs of previous HBV vaccination (anti-HBs alone).

Liver disease

Symptoms and clinical findings

Symptoms potentially related to hepatitis C were reported by 184/277 (66%) subjects before results of anti-HCV testing were released (fatigue 132 [48%], muscular pain 77 [28%], abdominal discomfort 76 [27%] and nausea 57 [21%]), however, the presence of these symptoms was neither associated with HCV viremia nor with fibrosis severity.

Among the 162 viremic patients, 106 (65%) consented to further evaluation of liver disease. Physical findings suggesting chronic liver disease were detected in a minority of patients (spiders [n=25], palmar erythema [n=11], hepatomegaly [n=6], and splenomegaly [n=1]).

Body mass index (BMI) was determined for 92 (87%) patients. The median BMI was 27 kg/m^2 (range 19-42). Forty patients (43%) were overweight (BMI 25-29.9) and of these 22 (24%) were obese.

Liver fibrosis

The degree of fibrosis could be categorized for 103 patients with any of the three techniques (45 by biopsy, 26 by TE and 32 by GUCI only). The number of patients in each category of fibrosis by diagnostic method is shown in Table II.

Forty-eight patients underwent liver biopsy. Two biopsies were of inadequate size and one biopsy specimen could not be retrieved, leaving 45 biopsies for central scoring.
Twenty-three (51%) patients had significant fibrosis (Ishak stage >F2) and 6 of these (13%) patients had cirrhosis.

TE was performed in 34 participants. The median stiffness value was 10.6 kPa (range 4-75). According to our definitions, 16 (47%) patients had significant fibrosis/cirrhosis. All 16 had a stiffness value >10.5 kPa, which is the cut-off value for cirrhosis recommended by Cross et al and 13 had a stiffness value >12.5 kPa (cut-off value for cirrhosis recommended by Castera et al (22)).

GUCI score could be calculated for 99 patients. The median GUCI score was 0.84 (range 0.19-12.2); 90 (91%) patients had a GUCI score >0.33 and 40 (40%) had a GUCI score >1.11. Since the proportion of advanced fibrosis was higher in patients who were only assessed by GUCI score, we compared the GUCI results in participants who had been investigated with an additional method. There was no significant difference in GUCI score distribution among

patients categorized by biopsy, TE or GUCI, within the categories low, intermediate or high grade fibrosis.

Ultrasound

Abdominal ultrasound was performed in 61 subjects (58%). Twelve patients had splenomegaly, 2 had ascites, and in 4 focal lesions were detected. Further investigations confirmed the diagnosis of hepatocellular carcinoma (HCC) in 2 of these cases.

Factors associated with fibrosis/cirrhosis

There was a trend towards increasing fibrosis severity with increasing age, increasing BMI, presence of anti-HBc antibody and amount of alcohol intake per month (Table III). These factors were tested by logistic regression, with the patients dichotomized as high vs. intermediate/low or low vs. intermediate/high fibrosis stage. When comparing high and intermediate/low fibrosis categories, high stage fibrosis was associated with alcohol intake (HR 0.33, p=0.03) and presence of anti-HBc antibody (p=0.02). For comparison between low and intermediate/high fibrosis stages, an association was found for increasing BMI and higher stage of fibrosis (HR 1.13, p=0.04) (Table III).

Discussion

HCV infection was highly prevalent in this cohort of Swedish PWID receiving OST and a majority of these subjects had significant liver fibrosis. Despite enrolment in OST programs, only a minority of patients had previously been assessed for HCV, a phenomenon that has been described from other countries (23, 24). Subjects without anti-HCV antibodies were characterized by a shorter duration between their first illicit drug injection and OST initiation,

suggesting that early enrolment for OST could contribute to the reduction of HCV infection among injecting heroin users (25).

To our knowledge, this is the first investigation of liver fibrosis in HCV-infected Swedish OST recipients. In most subjects with severe fibrosis this condition had not been recognized previously. How can identification of such patients – who are also in need of antiviral therapy - be improved in OST clinics?

Few of our participants showed signs of liver disease on physical examination. Similarly, the frequency of self-reported "liver related symptoms" did not differ with regard to HCV viremia status or fibrosis severity.

However, GUCI score - a fibrosis index based on simple biochemical markers – indicated advanced fibrosis in 40% of the participants. This method has been validated for non-invasive estimation of fibrosis(26), and could be considered for initial screening in an OST setting to detect subjects in need of further investigation.

Several patients had previously described risk factors for liver fibrosis progression such as obesity(27, 28), use of cannabis(29), smoking(30), exposure to HBV (31) and excessive intake of alcohol(32). We found associations between advanced liver fibrosis and alcohol consumption, increased BMI and the presence of anti-HBc antibodies.

Both alcohol abuse and obesity are important to recognize, especially since these conditions are also linked to other health problems. Using different approaches to estimate alcohol consumption, we found a high prevalence of problematic alcohol use in this cohort, in agreement with earlier studies showing alcohol dependence in 13-31% of OST recipients(33, 34).

Similarly, both overweight and obesity are common in patients on OST(35). In a Swedish autopsy study of 1180 intravenous drug addicts, 43.1% of methadone treated subjects had BMI>25 kg/m^2 (36).

Exposure to HBV was detected in 65 individuals, but only 2 of these fulfilled criteria for chronic hepatitis B. The association between anti-HBc positivity and advanced fibrosis in multivariate analysis could indicate the presence of so-called occult chronic hepatitis B, which has recently been shown to be an independent risk factor for cirrhosis, HCC and mortality(37).

This finding highlights the importance of HBV prevention, which has to target PWID more effectively in countries where HBV immunization is not included in infant vaccination programs.

Most studies on HCV in persons receiving OST have focused on aspects of delivery and outcomes of antiviral therapy. For this study, we chose to include all patients receiving OST on a specific date in order to gather representative information on the burden of HCV and characteristics of liver disease in this population. Furthermore, findings from other regions may not be applicable for Sweden; both due to the restricted access to OST and the low prevalence of HIV co-infection (which has an accelerating impact on fibrosis progression (38, 39)).

There are some limitations to this study. First, only 53% of eligible patients consented to inclusion, and among viremic subjects, 36% did not complete investigation for liver disease. Patients who did not accept participation did not differ from included subjects regarding age and gender distribution or time on substitution therapy. The main reason for non-participation was unstable psycho-social situation; we consider it unlikely that a bias with regard to liver disease severity occurred.

For patients with a prior result indicating HCV viremia we did not repeat PCR testing; they were assumed to have chronic HCV infection. We cannot exclude that some of these cases may have represented acute infection with subsequent spontaneous clearance; this may have led to some overestimation of the proportion of chronic infection in the population.

A further limitation is that we used three different methods for categorization of liver fibrosis. The degree of liver fibrosis can be misclassified by all available techniques. Although liver biopsy is considered to be the gold standard method for staging of liver fibrosis, sampling error can occur, leading to underestimation of cirrhosis (40). In order to compare results of these three methods we used cut-off values validated in previous studies (19, 21). The proportions of patients with significant fibrosis were similar using either biopsy or TE. Among the 32 patients who were only assessed by GUCI score, the proportion was considerably higher (91%). Although overestimation of fibrosis by GUCI score in this group cannot be excluded, GUCI values were similar for each category of fibrosis assessed by biopsy, TE or by GUCI alone.

Chronic hepatitis C is a frequent but hitherto largely neglected health problem among Swedish OST recipients. We show that the burden of advanced liver disease in this population is high. In the current era of improving antiviral therapy, management of HCV needs to be integrated within OST programs. Systematic testing with routine referral for further hepatologic assessment of viremic individuals could result in earlier identification of patients with significant liver disease, who should be prioritized for antiviral therapy.

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Table I

Characteristics of OST recipients tested for anti-HCV antibodies, and for patients with HCV viremia.

	All included patients	**Viremic patients, assessed for liver fibrosis**	**Viremic patients, not assessed for liver fibrosis**
Number of patients	277*	103	59
Median age in years (range)	44 (22-64)	44 (26-61)	43 (22-58)
Men n, (%)	187 (68)	73 (71)	41 (70)
Median number of years, since first illicit drug injection (range)	20 (1-44)	22 (4-42)	22 (5-43)
Median number of years in OST (range)	5 (0.2-20)	4.9 (0.1-22)	5.9 (0.2-30)
Type of substitution therapy Methadone Buprenorphine Missing data	 154 (56%) 114 (41%) 9 (3%)	 57 (55%) 45 (44%) 1(1%)	 33 (56%) 24 (41%) 2 (3%)

OST, Opiate substitution treatment. *Subjects included (269 tested for anti-HCV antibodies; 236 anti-HCV positive)

Table II

Patients in each category of fibrosis by diagnostic method.

	Biopsy[1] **n (%)**	**Transient elastometry[2]** **n (%)**	**GUCI[3]** **n (%)**	**Total**
Low	21 (47)	12 (46)	1 (3)	34
Intermediate	18 (40)	0 (0)	17 (53)	35
High	6 (13)	14 (54)	14 (44)	34

For categorization of patients, liver biopsy was preferred over TE (transient elastometry) and GUCI (Göteborg University Cirrhosis Index) score, and TE over GUCI score (in case measurements by more than one technique were available). The degree of fibrosis was designated low, intermediate or high and cut off values were defined for each fibrosis assessment technique as below.

1. Low: Ishak F0-F2, Intermediate: F3-F4, High: F5 -F6
2. Low: <8.85 kPa, Intermediate: 8.85 -10.04 kPa, High: ≥10.05 kPa
3. Low: <0.33, Intermediate: 0.33-1.11, High: >1.11

Table III

Factors associated with degree of liver fibrosis

	Low grade fibrosis (N=34)	Intermediate grade fibrosis (N=35)	High grade fibrosis (N=34)	Trend (p-value)	Multivariate (Low vs. Intermediate+High) HR; 95% C. I., (p-value)	Multivariate (Low+Intermediate vs. High) HR; 95% C. I., (p-value)
Age (years; median)	39.5	44	47	0.02	1.05; 0.96-1.2 (0.3)	1.10; 0.99-1.2 (0.08)
Male gender (%)	21 (62)	25 (71)	27 (79)	0.1	0.94; 0.31-2.9 (0.9)	1.52; 0.44-5.2 (0.5)
BMI (kg/m^2; median)	25,2	28.3	28.0	0.05	1.14; 1.01-1.28 (0.04*)	1.05; 0.94-1.2 (0.4)
Interval since first illicit drug injection (years; median)	19	16.5	26.5	0.06	0.95; 0.88-1.0 (0.3)	0.94; 0.87-1.0 (0.2)
Reported use of cannabis N (%)	24 (71)	24 (69)	26 (76)	0.8	-	-
Smoking N (%)	25 (78)	31 (89)	26 (76)	0.5	-	-
Alcohol use less than once monthly N (%)	23 (72)	26 (74)	15 (44)	0.02	0.75; 0.27-2.1 (0.6)	0.33; 0.12-0.92 (0.03*)
Report of alcohol related crime N (%)	7 (21)	9 (26)	10(29)	0.9	-	-
Report of alcohol abuse by OST clinic N (%)	4 (12)	7 (20)	5(15)	0.9	-	-
Previous admission to facility for treatment for alcohol abuse N (%)	1 (3)	2 (6)	2(6)	0.3	-	-
Presence of anti-HBc antibody N (%)	17 (52)	19 (56)	28(82)	0.009	1.98; 0.65-6.1 (0.2)	4.38; 1.2-15.6 (0.02*)

OST, Opiate substitution treatment; HR, hazard ratio

Figure legends

Figure 1

Overview of study participation