Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

All-cause and liver-related mortality in hepatitis C infected drug users followed for 33 years: A controlled study☆

Knut Boe Kielland[1,*], Kjell Skaug[2,†], Ellen J. Amundsen[3], Olav Dalgard[4]

[1]*Innlandet Hospital Trust, Centre for Addiction Issues, PO Box 104, N-2381 Brumunddal, Norway;* [2]*Norwegian Institute of Public Health, Division of Infectious Disease Control, Department of Virology, PO Box 4404 Nydalen, N-0403 Oslo, Norway;* [3]*Norwegian Institute for Alcohol and Drug Research, PO Box 565 Sentrum, N-0105 Oslo, Norway;* [4]*Akershus University Hospital, N-1478 Lørenskog, Norway*

Background & Aims: The course of chronic hepatitis C virus (HCV) in injecting drug users (IDUs) has not been well described. The aim of this study was to compare long-term all-cause and liver-related mortality among anti-HCV positive IDUs with and without persisting HCV infection.

Methods: A retrospective–prospective controlled cohort design was applied. All IDUs admitted to resident drug treatment (1970–1984) and with available stored sera were screened for anti-HCV antibody. Anti-HCV positive individuals were further tested for the presence of HCV RNA. All-cause and liver-related mortality was compared between HCV RNA positive (n = 328) and HCV RNA negative individuals (n = 195). The observation was accomplished through register linkage to national registers. Mean observation time was 33 years.

Results: All-cause mortality rate was 1.85 (95% CI 1.62–2.11) per 100 person-years, male 2.11 (95% CI 1.84–2.46), female 1.39 (95% CI 1.07–1.79). Mortality rates were not influenced by persisting HCV infection. Main causes of death were intoxications (45.0%), suicide (9.1%), and accidents (8.2%). Liver disease was the cause of death in 7.5% of deaths among HCV RNA positive subjects. Five of 13 deaths among male IDUs with persisting HCV infection occurring after the age of 50 years were caused by liver disease.

Conclusions: The all-cause mortality in IDUs is high and with no difference between HCV RNA positive and HCV RNA negative individuals, the first three decades after HCV transmission. However, among IDUs with chronic HCV infection who have survived until 50 years of age, HCV infection emerges as the main cause of death.

Keywords: Liver disease; Drug abuse; Overdose; Cohort; Hepatitis B.

Received 24 May 2012; received in revised form 22 August 2012; accepted 27 August 2012; available online 4 September 2012

☆ The work was done mainly at Centre for Addiction Issues, Innlandet Hospital Trust, and Department of Virology, Division of Infectious Disease Control, Norwegian Institute of Public Health.

* Corresponding author. Address: Klinkenbergvn. 14, N-2860 Hov, Norway. Tel.: +47 95128190; fax: +47 61126515.

E-mail addresses: knkiella@online.no, knut.boe.kielland@sykehuset-innlandet.no (K.B. Kielland).

† Died during the final work with this study.

Abbreviations: HCV, hepatitis C virus; IDU, injecting drug user; HCC, hepatocellular carcinoma; SKN, Statens Klinikk for Narkomane (National Clinic for Drug Abuse); RNA, ribonucleic acid; NIPH, National Institute of Public Health in Norway; anti-HCV, anti-hepatitis C antibody; HBV, hepatitis B virus; anti-HBc, anti-hepatitis B core antibody; HBsAg, hepatitis B surface antigen; PCR, polymerase chain reaction; PY, person-years; SD, standard deviation; CI, confidence interval; SMR, standard mortality ratio; IQR, interquartile range.

Introduction

Hepatitis C virus (HCV) infection is common worldwide. In most Western countries, including Scandinavia, injecting drug users (IDUs) constitute the main group of HCV patients [1,2]. The natural course of HCV infection the first two decades after exposure has been described for blood product-associated hepatitis. There is paucity in unbiased prospective studies illuminating the course of chronic HCV infection in IDUs. Most HCV-related deaths seem to occur after more than 25 years of infection. But, there are very few studies with such a long time of observation in any group of patients. More knowledge on long-term occurrence of end-stage liver disease, hepatocellular carcinoma (HCC) and mortality is essential for both decision-making in individual cases and health care planning [3].

Observational studies of transfusion-associated hepatitis C mostly in older patients indicated that about 20% developed cirrhosis within 20 years after transmission [4–6]. Later prospective studies in young healthy women exposed to HCV through contaminated immunoglobulin provided evidence of a more benign course in these patients [7–9]. In presence of established cirrhosis, there is a 5–10% risk per year of developing hepatocellular carcinoma (HCC) and/or decompensated liver disease [10]. Risk of rapid progression to cirrhosis is increased with metabolic syndrome, male gender, advanced age at time of exposure, and high alcohol consumption [11].

IDUs are often infected at a young age, which could imply a slow development of cirrhosis. On the other hand, unhealthy behaviour, including high alcohol consumption, may be frequent among IDUs; the majority are males and HCV treatment uptake may be particularly low in this group [12]. Therefore, studies on the course of HCV infection in this vulnerable group are needed.

The epidemic of injection drug use was established in Western Europe in the late 1960s and has since sustained. Viral hepatitis is transmitted mainly by syringe sharing, and hepatitis A, B, and C

Research Article

have been rapidly introduced into the IDU population also in Norway [13]. The first wave of drug users in Western Europe is now in their fifties and early sixties. As they were most probably infected by HCV in their teens or early twenties, the survivors from other hazards typical of injection drug use, have been living with HCV infection for more than 30 years. How will this influence their mortality?

The aim of this study is to explore this in three ways: (1) compare long-term all-cause mortality among anti-HCV positive IDUs with and without persisting HCV infection, (2) compare causes of death in the same groups, (3) compare long-term liver-related mortality in the same groups.

Patients and methods

Study design

The study has a retrospective–prospective controlled cohort design. All 523 patients admitted to resident drug abuse treatment at Statens Klinikk for Narkomane (SKN) 1970–1984 who had tested positive for anti-HCV were included. Cases were those who had chronic hepatitis C defined as being found HCV RNA positive at any time. Controls were those who had evidence of exposure to HCV (anti-HCV positive) and who persistently tested negative for HCV RNA. The cohort has been followed-up through register linkage until December 31, 2008. End points were death, liver transplantation, and HCC.

Participants

Of the 864 individuals admitted to SKN as inpatients during the period 1970–1984, frozen sera, mainly drawn at the time of admission, could be retraced for 635 patients at the Norwegian Institute of Public Health (NIPH). NIPH also received sera obtained from the same patients at other treatment centres, mostly after, but in some cases also prior to, the index admissions at SKN. Sera have since been stored at −20 °C at NIPH and never thawed. The median number of sera available from each patient was four, varying between one and 30. The median time between first and last serum was 5.8 years, quartiles 0.7 and 16.4.

Anti-HCV was detected in 535/635 (84.1%) cases, and it was possible to analyse HCV RNA with polymerase chain reaction (PCR) technique in the serum of 523/535 subjects. HCV RNA could not be analysed in 12/535 cases for technical and logistical reasons. The 523 IDUs constitute the participants in the study, including both HCV RNA positive and negative individuals.

SKN was the main institution for resident drug abuse treatment in Norway during most of the period 1970–1984, and patients in that period consisted to a large extent of young, opiate dependent IDUs.

Virological assessment

Sera were analysed for HCV by the following algorithm: first, the most recently drawn serum was tested for anti-HCV antibody. Anti-HCV positive sera were analysed for HCV RNA. Then the oldest available serum from patients who were anti-HCV positive, was tested for anti-HCV to establish the earliest documented time of HCV infection. If the oldest serum was anti-HCV negative, later sera were tested, if available, to find the first anti-HCV positive one.

A similar algorithm was followed concerning HBV-infection: the latest available serum was tested for anti-hepatitis B core antibody (anti-HBc). Positive sera were tested for hepatitis B surface antigen (HBsAg). Then the oldest available serum for those positive for anti-HBc was analysed for anti-HBc.

Sera were not tested for HIV infection due to our inability to follow-up on those who eventually would test positive.

Serum specimens were examined for anti-HCV (Ortho-Clinical Diagnostics HCV 3.0 Elisa), HBsAg, and anti-HBc (Bio-Rad Monolisa HBsAg Ultra and anti-HBc PLUS). HCV RNA was detected by an "in-house" PCR to detect viral RNA (detection limit 500 virus copies per ml corresponding to 100 IU per ml) [14].

Since reinfection was a possibility in those who were initially found HCV RNA negative, we traced more recently drawn sera at Oslo University Hospital, retested them for HCV RNA and found that 5/23 (22%) were HCV RNA positive. In our analyses, those five have been categorised as HCV RNA positive. Their time of HCV transmission is set at the estimated time of reinfection. Information on possible reinfection lacks for most of the HCV RNA negative subjects.

The median year of the first serum sample was 1981, quartiles 1977 and 1983. The median year of the serum sample for HCV RNA analysis was 1986, quartiles 1982 and 1999.

Time point of estimated HCV transmission

As acute HCV infection was not registered in any of the patients, the time point of HCV transmission had to be estimated. All patient case records at SKN were studied by one of the authors (KBK) to establish the age of first drug injection. Case records for most patients contained direct information about this, and, for most of the others, it was possible to establish the age of first injection with reasonable certainty through circumstantial information. The time point of HCV transmission was estimated mainly based on the year of first drug injection (Table 1). HCV transmission was estimated to occur during the first 2 years following initiation of drug injection for 82% of the cohort [15].

Register data and information on anti-viral HCV treatment

Data about status of living, including information on emigration, was obtained from the National Register of Demographic Data, and about causes of death from the Causes of Death Registry (Statistics Norway). Information about HCC was supplied by the Cancer Registry of Norway and about liver transplantation by the Oslo University Hospital Rikshospitalet, where all liver transplants in Norway are performed.

Data on HCV antiviral medical treatment anterior to 2004 were obtained by linkage to Scandinavian research trials on antiviral HCV treatment and from 2004 through the Norwegian Prescription Database (Norwegian Institute of Public Health), which was in operation from that year and included all treated cases in Norway in that period. We estimate that one in four treated before 2004 was treated in clinical trials.

Statistics

Mortality rates were calculated as number of deaths per 100 person-years (PY). Standard mortality rates were calculated by sex and age groups using death rates in the population by the middle of the follow-up period. The death rates in the population decreased linearly during the whole follow-up.

In Kaplan–Meier analysis, the 18 individuals (3.4%) who emigrated during follow-up have been censored at the date of emigration. HCV RNA positive cases have been censored when antiviral treatment has led to sustained virologic response. In the analysis of mortality caused by liver disease, the starting point was defined as time point of estimated HCV-transmission even if in most patients there was no observation during the time from HCV transmission to admission at resident drug abuse treatment (Table 2). Log rank tests were used for comparison of mortality trends in Kaplan–Meier analysis, and Fisher's exact test for comparison of liver mortality rates according to age. Pearson's Chi-squared test was used for comparison of causes of death in two groups. Confidence interval (CI) levels were set to 95%. For statistical analysis, the Statistical Package for the Social Sciences (SPSS) version 18.0 and Stata version 11.2 (StataCorp LP) have been employed.

Ethics

The study has been approved by the National Committee for Research Ethics. No consent was collected from the participants at the time of admission to resident treatment, and in accordance with the National Committee for Research Ethics no attempt was done to collect later consent.

Results

Characteristics of the cohort

This cohort of anti-HCV positive individuals consisted mainly of the first wave of IDUs in Norway initiating drug use by injection in the late 1960s or during the 1970s. 180/523 (65.6%) subjects were males (Table 2).

Of the 523 anti-HCV positive subjects, 328 (62.7%) were HCV RNA positive, indicating chronic infection, with HCV clearance in