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Hepatitis C infection among Dutch haemophilia patients: a nationwide cross-sectional study of prevalence and antiviral treatment

D. POSTHOUWER*, I. PLUG†, J. G. VAN DER BOM†, K. FISCHER*, F. R. ROSENDAAL† and E. P. MAUSER-BUNSCHOTEN*

**Van Creveldkliniek, University Medical Center, Utrecht; and †Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands*

Summary. Hepatitis C is a major co-morbidity among patients with haemophilia who received inadequately or non-virus-inactivated clotting factor concentrates before 1992. The objectives of this study were to investigate the prevalence of hepatitis C and the use of antiviral therapies during the last decade among patients with haemophilia in the Netherlands. We performed a cross-sectional study and a questionnaire was sent to all 1519 patients known with haemophilia in the Netherlands between 2001 and 2002. The study population for the present study consisted of 771 patients who had received clotting factor products before 1992 of whom 638 reported their hepatitis C status. In total, 441 of the 638 (68%) patients ever had a positive test for hepatitis C virus (HCV); 344 patients (54%) had a current infection, and 97 (15%) had cleared the virus. Among 344 patients currently HCV infected, 111 (32%) had received treatment for hepatitis C, while 34% (33/97) of patients with an infection in the past had been treated for hepatitis C. In 2002 the prevalence of hepatitis C among patients with haemophilia who received clotting factor products before 1992 was 54%. The majority of patients with a current HCV infection had not been treated with antiviral therapy.

Keywords: haemophilia, hepatitis C, prevalence, survey, treatment

Introduction

Haemophilia is an X-linked bleeding disorder caused by a partial or complete lack of clotting factor activity: factor VIII in haemophilia A and factor IX in haemophilia B. Since the 1960s haemophilia patients have received intravenous factor VIII and IX replacement therapy [1]. In the following years it became apparent that viruses like human immunodeficiency virus (HIV) and hepatitis C virus (HCV), formerly known as non-A non-B hepatitis, were transmitted due to transfusion of infected plasma products [2,3]. Patients treated with large pool products were infected with HCV in 98%, whereas patients treated with cryoprecipitate were infected in 66% of the cases [4]. In the early 1990s, methods were developed to adequately inactivate HCV and subsequently donor screening for HCV was introduced, resulting in HCV safe clotting products [4–6].

Once infected, about 10–20% of the patients are able to clear the virus spontaneously, while the others develop a chronic carrier state [7–9]. Untreated HCV infection may progress to liver fibrosis, cirrhosis or hepatocellular carcinoma [10,11]. Liver disease caused by HCV is now recognized as an important cause of morbidity in haemophilia patients [12]. Treatment for non-A non-B hepatitis became available in 1986 [13,14]. Today pegylated interferon (Peg-IFN) in combination with ribavirin is the most effective therapy for hepatitis C [15]. Success of therapy is mainly dependent on genotype and viral load [16]. Antiviral drugs cause side effects like anaemia, neutropenia, depression and flu-like symptoms in the majority of the patients [17–19].

Correspondence: Dirk Posthouwer, Van Creveldkliniek, C.01.425, University Medical Center Utrecht, Heidelberglaan 100, PO Box 85500, 3508 GA Utrecht, The Netherlands.
Tel.: +31 30 250 1709; fax: +31 30 250 5438;
e-mail: d.posthouwer@azu.nl

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Little or no information is available on the current prevalence of hepatitis C and antiviral treatment history among patients who have received inadequately or non-virus inactivated clotting factor concentrates before 1992. We therefore investigated the prevalence of hepatitis C infection and assessed the use of antiviral therapy among patients with haemophilia in the Netherlands.

Materials and methods

Setting

Data for the present study were collected within the last survey of a series initiated by Veltkamp in 1972 [20]. Since then nationwide surveys were repeated in 1978, 1985, 1992 and in 2001 [21–24]. These studies aimed at assessing the medical and social consequences of haemophilia in the Netherlands. In 2001, postal questionnaires were sent to all 1519 patients known with haemophilia in the Netherlands, who were either registered at the Netherlands Hemophilia Patients Society, at the haemophilia treatment centres or known from previous surveys. In this last survey items on hepatitis C were added for the first time.

Data

The study population consisted of patients who were treated with clotting factor products before 1992 and who reported their hepatitis C status. These patients were potentially at risk for HCV infection because they were treated with non-virus inactivated or inadequately inactivated clotting factor concentrates. Severity of haemophilia was defined by the percentage of factor VIII or factor IX clotting activity: severe haemophilia <1%, moderate haemophilia 1–5%, and mild haemophilia 5–40% clotting factor activity. Reported type and severity of haemophilia were verified with information from the treatment centres. In addition, data on haemophilia type and severity of non-responders were obtained from treatment centres or from the previous questionnaire performed in 1992. Haemophilia type and severity of 346 non-responders were similar to those in the study population. Items on hepatitis C and HIV were obtained from the questionnaire. Information on the hepatitis B status was not collected.

To assess the validity of the self-reported items on hepatitis C, a random sample of 92 patients (14%) was taken from the two largest participating centres verifying their reported hepatitis C status with information from their treating haematologist.

Statistics

Infection with HCV was defined as three possible status: never infected with HCV, HCV infection cleared and chronic hepatitis C. 'Never infected with HCV' was defined as negative for both HCV antibodies and HCV-RNA in serum. A 'cleared HCV infection' or 'infection in the past' was defined as positive for HCV antibodies but negative for HCV-RNA. 'Chronic hepatitis C' was defined as positive for both HCV antibodies and HCV-RNA. In addition, 'ever infected with HCV' was defined as positive for HCV antibodies, regardless of the HCV RNA result.

To study risk of infection according to period of treatment, a sub-analysis was performed comparing infection rates between patients first treated before 1985 with patients first treated between 1985 and 1992. Patients with incomplete treatment history were excluded for this sub-analysis.

The HCV status according to type and severity of haemophilia was compared by using the chi-square test. Mean values with 95% confidence intervals of age according to severity of haemophilia and HCV infection status were calculated.

Results

A flow chart of the selection of patients for this study is shown in Fig. 1. The response to the questionnaire was 1066 of 1519 (70%). General characteristics of the participants are shown in Table 1.

Hepatitis C

Patients treated with clotting products before 1992

A total of 771 patients were at risk for HCV infection (i.e. treated before 1992); 599 were already treated with clotting products before 1985, 136 were treated exclusively between 1985 and 1992, whereas 36 patients reported to have been treated before 1992 but not whether they were also exposed to clotting products before 1985. 638 of these 771 patients reported their HCV status. Among the 133 patients at risk without a HCV test result, 68% had mild haemophilia.

In the verification sample, 92% (85/92) reported their hepatitis C status correctly; 96% of patients with an HCV infection and 88% of patients with a cleared infection or those who where never infected.

Among 638 patients treated with clotting factor products before 1992 and tested for HCV, 441 (68%) ever had an anti-HCV positive test; 344 (54%) reported to be currently infected with HCV, 97 (15%) reported an infection in the past and

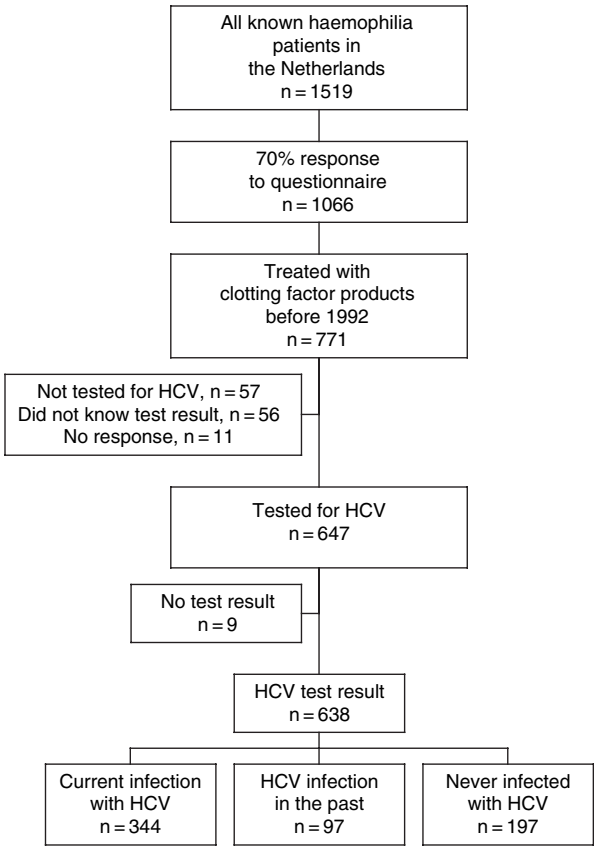

Fig. 1. Flowchart of selection of study population.

Table 1. Patient characteristics.*

Total number of patients	638
Age in years	41 (10–87)
Haemophilia type	
A	557 (87)
B	81 (13)
Severity of haemophilia	
Mild	211 (33)
Moderate	112 (18)
Severe	315 (49)
Patients treated before 1985†	523 (82)
HIV positive	28 (5)
Patients treated before 1992‡	638
Anti HCV positive	441 (68)
HCV RNA positive	344 (54)

*Information of patients treated before 1992 with a reported HCV test result. Values are medians (range) or numbers (percentage).
†At risk for HIV infection due to not adequately or non-virus-inactivated clotting factor products.
‡At risk for HCV infection due to not adequately or non-virus-inactivated clotting factor products.

197 patients (31%) had never been infected. No infections with HCV occurred in patients who were treated after 1992 only.

HCV infection was related to type of haemophilia; patients with haemophilia B had been infected more often than those with type A (84% vs. 67%, $P < 0.01$). Among patients at risk for HCV transmission, patients with severe haemophilia had the highest prevalence of hepatitis C (severe 65%, moderate 53%, mild 37%, $P < 0.001$).

The mean age of patients differed according to severity of haemophilia and HCV status; patients with severe haemophilia, who were never infected, were younger [mean age 23 years, 95% confidence interval (CI) 19–28] than both patients with severe haemophilia who cleared HCV (37 years, CI 33–41), and those currently infected (43 years, CI 41–45).

Infection rate of HCV according to treatment period

Although HCV-inactivating steps were applied since 1985, risk of HCV infection was not completely eliminated; 523 of 599 patients treated before 1985 and 95 of 136 patients treated during 1985–92 reported their HCV status. Among patients treated before 1985, 62% reported to be currently infected, while 17% cleared HCV. In contrast, the proportion of patients with chronic HCV infection was only 18%, with 7% clearing HCV and 75% never infected in those first treated between 1985 and 1992.

HIV infection

The prevalence of HIV infection among patients treated before 1985 and reporting their HIV status was 5% (28/523).

Treatment of hepatitis C

Among the 344 patients with a current HCV infection, 68% (233) had not been treated with antiviral drugs. The main reasons for refraining from therapy were shrinking from side effects (46%), normal liver function tests (45%) and expected low effectivity (35%). Other reported reasons were: doctor not convinced of benefit of treatment (19%), treatment not discussed by doctor (18%) and lack of time among patients (9%). Over the last decade, the proportion of patients having been treated, is increasing (Fig. 2).

Treatment for HCV was completed among 128 patients and successful treatment was reported in 26% (33/128). Sixteen patients were currently on combination therapy of IFN and ribavirin. Among patients who finished therapy, 57 patients were treated with IFN monotherapy, 51 patients with the combination of IFN and ribavirin, while 13 patients were first treated with monotherapy and

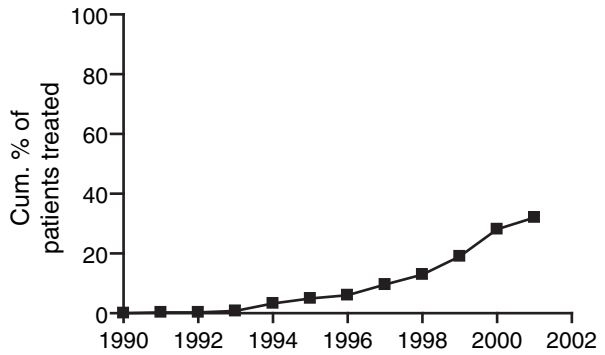

Fig. 2. Cumulative percentage of all HCV-infected patients with haemophilia treated with antiviral therapy during the last decade. Considering a spontaneous clearance of 15%, the maximum cumulative percentage would be 85%.

later retreated with combination therapy. Seven patients did not remember their treatment regimen.

Reported side effects of antiviral therapy was 84% (121/144). Fatigue (78%), flu-like symptoms (73%), and depressive symptoms (46%) were most frequently reported. In 15% of treated patients therapy was discontinued because of side effects.

Discussion

We report on a nationwide survey on the current prevalence of hepatitis C in haemophilia patients. Of 771 patients at risk for HCV infection, 638 reported their hepatitis C status. Fifty-four per cent of tested patients reported to be currently infected with HCV, of whom 32% had been treated with antiviral therapy.

We performed a cross-sectional study to assess the prevalence of hepatitis C infection among patients with haemophilia in the Netherlands and to examine the use of antiviral treatment. To appreciate our findings some limitations need to be discussed. First, the response rate to the questionnaire was 70%, and selection bias cannot be ruled out. Non-responders to the questionnaire may have been less severely affected, therefore failing to see the need for a survey in this population. This may have led to an overestimation of the prevalence of hepatitis C. However, percentages of type and severity were similar in responders and non-responders, rendering bias less likely.

Secondly, self-reported data may be unreliable. We therefore performed a validation study and found that these self-reported data were highly reliable, confirming previous observations that most patients with haemophilia are well informed about their disease and its complications [21].

In this study, 68% of all tested patients potentially exposed to insufficiently viral-inactivated clotting factor products had ever been infected with HCV and 54% of them reported a current HCV infection. The prevalence of hepatitis C in this population is similar to that reported by others [4,9,25]. As expected, the prevalence was highest among patients with severe haemophilia due to a higher number of exposures to clotting products than patients with mild or moderate disease. Haemophilia B was associated with a higher HCV infection rate (84% vs. 67%) due to exclusive treatment with large pool plasma products, whereas patients with haemophilia A were in many cases exclusively treated with small pool cryoprecipitate [26]. Confirming data in a Dutch study on 316 patients, reported HCV infection rates of 66% and 98% in patients exclusively treated with small pool cryoprecipitate and patients treated with large pool products, respectively [4]. In addition, the proportion of patients with severe haemophilia was higher among patients with haemophilia B than in those with haemophilia A (58% vs. 48%), with concomitant higher exposure rates to potentially unsafe clotting factor products.

In our study, we found that the risk of HCV transmission was lower among younger patients. This may be explained by the lower number of exposures and the introduction of dry heat treatment (up to 68 °C) in 1985. Although completely effective for HIV, this method of viral inactivation did not eliminate HCV infection risk, but resulted in a reduction of HCV load only [27]. This is also shown in our study, in which patients exclusively treated with clotting products between 1985 and 1992 had a lower risk of HCV infection than patients treated before 1985. Although this risk was decreased, HCV transmission was not eliminated. Finally, donor screening, pasteurization, steam heat treatment and chemical viral inactivation through the combination of solvent and detergent methods were introduced on a large scale, eliminating transmission of HCV completely in 1992 [6,28,29].

Although there has been a trend towards starting treatment of HCV infection, only 32% of the HCV-infected patients reported use of antiviral therapy, with a success rate of 26%. The main reasons for refraining from antiviral therapy were expected low effectivity of therapy, normal liver function tests and expected side effects. The argument of low expected effectivity loses its strength as treatment with PegIFN and ribavirin results in a sustained response in 50–90% in treatment-naive patients dependent on viral genotype [18]. It has been suggested that refraining from therapy in case of normal liver function tests

may be appropriate in patients with genotype 1 and 4 with normal histology at liver biopsy [30]. But this is inappropriate in patients with HCV genotype 2, 3 and 5, of whom 90% will achieve a sustained response.

Fatigue, flu-like symptoms and depression were the most frequently reported adverse events of antiviral therapy; this is in accordance with other reports [17]. Depression has been a common indication for dose reduction or even discontinuation of therapy [17,31]. Discontinuation of therapy due to adverse effects was reported in 15% in this study and was similar to that reported by others [18,19,32,33].

The reported reasons for refraining from antiviral therapy indicate that there are still uncertainties about long-term complications of hepatitis C and effectivity of antiviral therapy. Therefore, patients need to be fully informed about HCV infection, its consequences, possibilities of treatment and its effectivity.

In summary, this study shows that hepatitis C is still a major comorbidity in the Dutch population of haemophilia patients and only a minority of patients with an HCV infection has been treated.

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