Assessment of hepatitis C infection and outcomes in the Scottish haemophilia population

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Abstract

Introduction: There is a paucity of accurate data in patients with bleeding disorders infected with hepatitis C virus. Aim: We identified the number of patients infected in Scotland and assessed several aspects of the outcomes of HCV infection and its treatment comparing these with cohorts infected for other reasons. Methods: We calculated the total number of individuals infected in Scotland (cohort A) by starting with the total number of patients treated in Scottish haemophilia centres registered on the UKHCDO database between 1970 and 1989. Cases were then removed or added based on additional information from centre records. A second cohort B, consisted of 255 patients from cohort A and 47 patients HCV infected outside Scotland but with follow-up data around their HCV infection. Results: We estimate 455 patients with bleeding disorders became infected by coagulation factor provided by NHS Scotland. In 302 individuals with documented HCV infection, rates of natural clearance (17.4%), genotype spread (64% genotype 1) and responses to anti-viral therapy (14.5% with monotherapy; 38.8% with combination therapy) were similar to those in other cohorts. Thirty-four liver biopsies were performed without adverse event and liver transplantation has been performed in eleven patients, seven for liver failure, four for hepatocellular carcinoma. Conclusions: Around 455 patients with bleeding disorders became HCV infected in Scotland before 1989. The natural history of HCV infection and responses to treatment are similar to those in other HCV infected cohorts. Liver transplantation has been used successfully for the treatment of end stage liver failure and hepatocellular carcinoma.

Introduction

Prior to widespread development of viral inactivation of coagulation factor concentrates in the mid 1980s, infection with hepatitis C virus (HCV) was virtually inevitable in those who received pooled plasma products as treatment for hereditary bleeding disorders [1,2]. HCV infection has been reported not only in those who received plasma-derived factor concentrate, but also in patients who received cryoprecipitate or fresh frozen plasma [3]. Approximately 15% of patients infected with HCV naturally clear the infection [4] and chronic HCV infection is a significant health problem in the remainder of individuals. Progressive fibrosis can lead to
clinically significant liver disease including cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC). In some series, up to 30% of patients with bleeding disorders have developed long term complications of chronic HCV [5]. Several features of infection in patients with bleeding disorders have prompted comparison between the outcomes of HCV infection and its treatment in this group and other groups of infected individuals. These include the early age at infection, the repeated re-exposure and re-infection with different genotypes of the virus and the background of disordered immune function secondary to heavy exposure to plasma derived products seen in heavily treated patients with bleeding disorders [6,7]. Co-infection with Human Immunodeficiency Virus (HIV), which is associated with an increased rate of progression of chronic HCV to cirrhosis, is also common in this group of patients [8]. As highly active antiretroviral therapy (HAART) has transformed the course of HIV progression, HCV-related liver disease has emerged as the leading cause of mortality in HCV/HIV co-infected individuals and indeed one of the most common causes of death in such patients with haemophilia A and B [9].

The aim of this report is to present data on the total number of patients with bleeding disorders who became infected with HCV through exposure to plasma products administered in NHS Scotland and to gather data on the outcomes of HCV in all patients whose care was provided predominantly by NHS Scotland during the period from 1978 to 2012.

Methods

Definition of “bleeding disorders”

In this study we included patients with inherited coagulation factor deficiencies, von Willebrand disease and acquired haemophilia. This included female carriers of haemophilia A and B who had received treatment with plasma derived concentrates and cryoprecipitate. We did not include patients with platelet disorders or patients who received prothrombin complex concentrate for the management of bleeding due to treatment with vitamin K antagonists.

Estimation of the total number of patients with bleeding disorders infected with HCV from plasma derived concentrates and cryoprecipitate administered by NHS Scotland (Cohort A)
The aim was to identify all patients who became, or probably became, infected with HCV due to coagulation component treatment administered by NHS Scotland (Fig 1). The baseline data received from the UKHCDO database included patient names and treatment details (within and outwith Scotland) for all patients registered or treated in Scotland from 1970 to 1989 (n=715). Due to the introduction of effective viral inactivation procedures for factor IX concentrate in late 1985 and for factor VIII concentrate between 1987 and 1989 it was assumed that treatment with factor IX concentrate, from 1985 and onward, and factor VIII, from 1989 and onwards, did not transmit HCV and that treatment with factor VIII prior to July 1987 and with factor IX prior to 1985 was uniformly associated with HCV transmission unless a recipient had a subsequent HCV antibody test which indicated otherwise. Based on previous observations it is known that patients who received treatment with cryoprecipitate also commonly became infected with HCV [10]. For the purposes of this investigation, we assumed that patients who had received cryoprecipitate prior to 1989 had contracted HCV unless they had subsequently been tested and proven negative for HCV antibody. Furthermore, we assumed that the earliest treatment with factor concentrate or cryoprecipitate or plasma (FFP) within the risk period transmitted HCV.

All patients whose first treatment took place outwith Scotland were then excluded (n=180). Where the earliest year of treatment included treatments both within and outwith Scotland, patients were retained as it was not possible to determine the sequence of treatments during any one year. 14 patients who received their first treatment with factor IX concentrate between 1985 and 1988 were also excluded. This left 521 patients whose first treatment was, or very probably was, in Scotland during the HCV infectivity window. Any patient known to a Scottish Haemophilia centre who had been tested for HCV and found to be negative was then excluded (n=73). These were mostly infrequently treated patients who had received small amounts of cryoprecipitate, although some had received coagulation factor concentrate. A small number had more severe disease but received their first treatments with factor VIII between 1987 and 1989 by which time the predominant product used in Scotland (Scottish National Blood Transfusion FVIII concentrate) was produced using a dry heat (80° C for 72 hrs) process for virus inactivation. Patients whose sole treatment was with non-plasma based products (e.g. synthetic haemostatic agents such as desmopressin or tranexamic acid) were also excluded (n=8). This resulted in total of 440 patients from the UKHCDO database whose first
plasma-based treatment likely to transmit HCV was certainly or probably in Scotland. A small number of patients (n=15) known by Scottish haemophilia centres to be HCV positive, most likely from treatment in Scotland, did not appear on the list from UKHCDO. These 15 patients were added giving a total of 455.

Outcomes of HCV infection and its treatment in patients managed in Scottish haemophilia centres (Cohort B)

Clinical data and outcomes were only available for 255 of the 455 patients in cohort A. The outcomes for the remaining 200 cases identified in cohort A are not known for several reasons including the death of the patients prior to the availability of anti-HCV testing and movement of patients to other centres outside Scotland. Cohort B consisted of these 255 along with 47 other patients who were presumed not infected in Scotland, as their first coagulation therapy was outwith Scotland, but who had received a significant amount of treatment and follow up in Scottish haemophilia centres between 1970 and 2012 (n=302). Each of the Comprehensive Care Centres (CCC) and Haemophilia Treatment Centres (HTC) in Scotland provided information from the centre records, case note review and laboratory data sets on patients with bleeding disorders who had received plasma derived concentrates and/or cryoprecipitate and who had ever tested positive for HCV antibodies. For each case, centres were asked to report the PCR status; predominant genotype; HIV co-infection; duration of interferon mono-therapy; duration of ribavirin/interferon combination therapy; sustained virus response to therapy which was defined as persistently negative HCV PCR 6 months after completing antiviral therapy. Data on all liver biopsies performed, as well as numbers of orthotopic liver transplants (OLT) undertaken were also collected. The date on which data were censored was the 1st of February 2012.

Statistical analysis was performed using SPSS version 19. Categorical variables were compared using the $\chi^2$ test with continuity correction. A $p$ value of less than 0.05 was considered to be significant.

Results

The care of patients with bleeding disorders in Scotland is co-ordinated by 2 CCCs (Royal Infirmary of Edinburgh and Glasgow Royal Infirmary) and 3 HTCs (Aberdeen...
Royal Infirmary, Ninewells Hospital and Raigmore Hospital. Paediatric care is provided by Yorkhill Hospital in Glasgow, Edinburgh Children’s Hospital in Edinburgh and Royal Aberdeen Children’s Hospital in Aberdeen. In these centres and at Raigmore and Ninewells the patients transfer into the adult service in teenage years.

**Estimation of the total number of patients with bleeding disorders infected with HCV from plasma derived concentrates and cryoprecipitate administered by NHS Scotland (Cohort A)**

Our estimate of the total number of patients with bleeding disorders who became infected with HCV as a result of receiving pooled plasma products administered by NHS Scotland (Cohort A) is 455. Of these, 255 had a documented positive anti-HCV antibody test and the remaining 200 were assessed as likely infected based on the assumptions made in the methodology described above. (Fig 1)

**Outcomes of HCV infection and its management in patients managed in Scottish haemophilia centres (Cohort B)**

A total of 302 patients known to be HCV antibody positive were included in the clinical cohort B. These consisted of 255 identified from cohort A and 47 patients who were not infected with HCV as a result of care provided by NHS Scotland but who were looked after in Scottish haemophilia centres between 1970 and 2012. These 47 patients acquired their HCV infection elsewhere in the UK and occasionally abroad. Table 1 shows the numbers managed at each of the centres.

Of the 302 patients in cohort B, 232 (76.8%) were still alive and 67 (22.2%) were deceased on the 1st of February 2012. Data were missing on 3 patients (1.0%) who had moved away and were lost to follow up. 36 (11.9%) patients were HIV co-infected of which 23 (63.9%) were still alive at the end of the study period.

**PCR and Genotypes**

293 of 302 patients had had PCR testing performed. Of these 243 (83 %) have been PCR positive at some point. Natural clearance of HCV was documented in 51 (17.4%) which is similar to the rate observed in cohorts of HCV infected individuals who acquired the infection in other ways [4]. Of the 243 patients who were PCR
positive at some point, one patient was documented as being positive on one occasion and negative thereafter without treatment, giving a total of 51 patients with natural clearance. The PCR status of 9/302 (2.9%) cases was unknown. Of 243 PCR positive individuals 57 have become persistently negative following anti-viral treatment for HCV which was administered to 169 of the 243 patients. This represents 23.5% of the total number of patients who had evidence of persistent viral replication. Further details of response rates to antiviral therapy are given below. The genotype was unknown in over a third of patients (34.4%). Reasons for this include the lack of availability of testing before patients died, patients being deemed unsuitable for treatment and therefore not tested and the personal preference of patients not to have testing. Amongst patients with a known genotype, 67.4 % were genotype 1, 5.7% genotype 2, 25.4% genotype 3 and 1.5 % other genotypes.

Liver Biopsy

34 liver biopsies have been performed in 34 (11.3%) patients. None of the biopsies was associated with significant bleeding complications.

Hepatocellular Carcinoma and liver transplantation

Hepatocellular carcinoma has been diagnosed in 14 (4.6%) patients of whom only 4 were still alive at the date the data collection was censored.

From cohort B, 11 patients have undergone OLT and 1 patient was on the transplant list on February 1st 2012. Seven transplants were undertaken because of the development of liver failure and 4 were performed for the management of HCC. In one patient transplanted for liver failure there was a chance finding of a HCC in the explant. Two transplants have been performed in HIV co-infected patients. Of the patients who have had liver transplantation, 7 were alive at the end of the study period. The causes of death post-transplant included recurrent and metastatic HCC.

Interferon-alpha monotherapy

Seventy four of the 243 PCR positive patients have yet to receive any anti-viral therapy. The reasons for not receiving antiviral treatment included contraindications to treatment, evidence of non-progressive disease, patient preference and death prior to the availability of treatment. 117 patients have received interferon-alpha
monotherapy with median duration of treatment of 24 weeks (range 1-96). The overall SVR rate for interferon-alpha monotherapy therapy was 14.5%. The response rates based on genotype are shown in table 2. The SVR rate for genotype 1 was not significantly different from non-genotype 1 cases (8.7% v 14.7%, p=0.498).

Combination anti-viral therapy

Combination anti-viral therapy consisted of ribavirin with either interferon-alpha or pegylated interferon-alpha. 103 patients received combination therapy including 52 interferon naive patients. The median duration of treatment was 36 weeks (range 1-80). The overall SVR rate for combination therapy was 38.8% which was significantly higher than for monotherapy (38.8 % versus 14.5%, p< 0.001). Table 3 shows response rates to combination anti-viral therapy by genotype. The response rate for non-genotype 1 cases was higher than for genotype 1 (51.5% v 29.0% p=0.052). 51 patients who had previously failed to achieve SVR with interferon-alpha monotherapy received subsequent combination therapy with a response rate of 29.4%. The difference in response rates with combination therapy between interferon treated and interferon naive patients failed to reach statistical significance (29.4% versus 48.1%, p=0.082).

Discussion

Chronic HCV infection remains a major burden on the haemophilia population. The natural history of chronic HCV in the non-haemophilic population is well documented [11,12]. There is, however, a relative paucity of long-term outcome data in haemophilia patients. In addition, because many patients died before testing for HCV became available, the total number of infected individuals has been difficult to assess accurately. We present a retrospective analysis of data on all patients with bleeding disorders who probably acquired HCV infection as a result of treatment administered by NHS Scotland and on a separate but overlapping cohort of patients cared for predominantly in Scottish haemophilia centres who were infected with HCV mostly in Scotland but also at other sites mostly in the UK.

Persons with haemophilia (PWH) provide an important cohort for studying the natural history of HCV and associated complications. The onset of infection is known (time of first treatment with non-virus inactivated blood products) and most patients have
regular follow-up at haemophilia centres over a long period of time. Previous literature has shown that HCV has a mild, slowly progressing course in PWH [13]. Our cohort supports this with 76.8% of patients in cohort B still alive despite the majority being infected for over 25 years. These findings are commensurate with previous analyses of the natural history of chronic HCV infection in the non-haemophiliac population [14, 15].

Excluding those whose genotype was unknown, the most common genotype was 1. This is consistent with previous literature which demonstrates that the majority of infections in the UK are with genotype 1 [16]. The natural clearance rate of 17.4% for this cohort is similar to that observed in cohorts of patients with other risk factors and modes of infection [4].

For several years, monotherapy with interferon-alpha was the only anti-viral treatment available for chronic HCV infection. The SVR achieved with monotherapy is around 20% in the non-haemophilia population [16]. Previous data report a slightly lower rate of SVR for monotherapy in PWH compared with other HCV infected groups [17-19]. The SVR in this cohort (14.5%) is consistent with the previous findings of a slightly poorer response to interferon-alpha monotherapy in PWH.

Combination therapy with interferon-alpha and ribavirin has demonstrated better responses with a SVR in the non-haemophilia population of around 40%, which is further improved to around 55% by the use of pegylated interferon-alpha [20]. A meta-analysis of the outcomes of combination therapy in PWH gave an overall SVR of 61% in HIV negative patients [21]. The SVR with combination therapy in our cohort was lower than expected at 38%. This is possibly explained by the early use of interferon-alpha instead of pegylated interferon-alpha in a significant proportion of patients and the inclusion of a number of patients with HIV co-infection who typically show poorer response rates to anti-HCV therapy. In addition there is good evidence for infection with multiple genotypes in PWH and this may affect responses to anti-viral therapy compared with the non-haemophilia population [6].

In our cohort there was, as expected, a statistically significant higher response rate with combination therapy compared to monotherapy (p <0.001). The response rate for genotype 1 is generally poorer than for genotypes 2 and 3. There was no demonstrable difference between genotypes for monotherapy responses in our group. However the numbers treated are small, the selection of patients for anti-viral
therapy was not uniform across the centres and the study was not designed to assess in detail the differences in response rates between different anti-viral therapies. For combination therapy, there was a higher response rate for non-genotype 1 cases. This difference in response rates approaches statistical significance. There was a non significant trend towards inferior response rates in patients who received combination therapy after failed monotherapy compared with those who were interferon naïve.

Histological examination is still the gold standard for determining the stage and severity of liver disease. Although histological analysis has less of a role in decision making around candidates for anti-viral therapy it is very important for determining which patients might benefit from HCC surveillance. A previous study of 126 liver biopsies in 115 haemophilia patients reported significant bleeding as a complication in 12.5% of cases with 2 fatalities as a result of uncontrollable bleeding [22]. However, this was a heterogeneous group of patients who received varied coagulation factor replacement prior to biopsy. Subsequently, it has been shown that if adequate coagulation factor replacement is provided, the haemorrhagic risk for this group of patients does not appear to be higher than it is for the non-haemophilic population undergoing liver biopsy [23]. Liver biopsies were performed in 11.3% of cases in this cohort, without recorded bleeding complications. Fibroscanning is now being increasingly used as a non-invasive means of assessing fibrosis severity and the number of indications for formal liver biopsy in this group of patients will probably decrease with time.

HCC carries a poor prognosis and only 4 of the 14 patients (28.6%) in the cohort with this complication remain alive at the end of the study period. A large retrospective population based study performed in the mid-90s and including over 7000 patients showed a 5 year survival of only 5% for HCC [24]. Advances in the management of HCC over the past 15 years have however led to a decline in the mortality rate from this condition [25]. This is thought, in part, to be due to earlier detection as a result of increasing implementation of surveillance programmes for high risk patients. With more therapeutic options available and a better prognosis for HCC diagnosed at an early stage, it is important that patients with cirrhosis are identified and enrolled into appropriate surveillance
Indications for liver transplantation in PWH with HCV are the same as for other groups of HCV-infected patients, i.e., decompensated liver failure and HCC. OLT has been performed successfully in PWH with peri-operative coagulation factor replacement by various regimens such as bolus or continuous infusion [26]. The procedural complication rate and long-term survival of PWH has been reported as no different to the non-haemophilia population for OLT [27]. Eleven patients have undergone OLT successfully in this cohort. This is reassuring for the haemophilia population as it demonstrates that haemophilia doctors are referring patients for this procedure and that the Scottish Liver Transplant Unit (SLTU) is accepting patients with bleeding disorders for treatment. Of the 11 transplanted patients 2 were HIV co-infected. Seven transplanted patients were still alive at the end of the study period. Recurrent or metastatic HCC was the cause of death in 3 cases post-transplant.

A small proportion of the patients had HIV co-infection, the majority are still alive. HAART has revolutionised HIV treatment, and the prognosis and overall survival of HIV infected patients has improved significantly since its advent [28]. However, in HCV/HIV co-infected patients, this has been overshadowed by an increase in HCV-related hepatic complications with higher levels of viraemia demonstrated, and an accelerated course of progression to cirrhosis and end-stage liver disease [29]. Therefore it is rather surprising that almost two-thirds of those co-infected in this cohort were still alive at the end of the study period. It is worth noting however that almost certainly all the HIV infected patients who died before HCV testing became available in 1991 would have been HCV positive. These patients were not included in cohort B and so the outcomes for HIV/HCV co-infected patients include only those who survived until 1991 and therefore presents a selective overestimation of the survival for this group of patients.

The method used to assess the total numbers of patients with inherited bleeding disorders and acquired haemophilia that became infected with HCV as a result of plasma based therapy is detailed in the study. It is clear however that it may be flawed for several reasons. Firstly it is clear that not all episodes of treatment had been captured by the UKHCDO database. Indeed we identified 15 patients from our own centre records who had never been included in the UKHCDO data and yet had received treatment which had transmitted HCV. Secondly, because we could not determine the order of treatments within any one year we assumed that all patients treated for the first time in the same year both in Scotland and elsewhere in the UK...
were infected in Scotland. This would be predicted to overestimate the number of patients infected in Scotland. Thirdly, although it has been previously reported that HCV infection was uniform in patients who received factor VIII concentrates produced prior to 1987 [2], in the course of this study we identified a small number of patients documented as having received concentrate who were anti-HCV antibody negative. Fourthly we assumed that all patients who had received only cryoprecipitate became HCV infected as a result and this represents a likely overestimation of the number infected. Finally, although we included only cases who received their first treatments before 1989 because this was perceived to be the latest date of infection of patients with HCV from concentrate (we are not aware of any exceptions to this), there is a very small possibility that patients may have been infected with cryoprecipitate after this date as routine donor screening for HCV did not begin until autumn 1991. By this time however it would have been unlikely that any patient would have received treatment with cryoprecipitate only and we are not aware of any such cases in Scotland. We are not aware of any patients in our cohort, treated for the first time with factor VIII concentrate in or after 1989, or with factor IX in or after 1985, that have evidence of HCV infection. Of the 14 patients who were first treated with factor IX in or after 1985 12 were documented as being HCV negative and tests were not available for the other two.

In summary, this retrospective analysis estimates the total number of patients with bleeding disorders who became infected with HCV as a result of treatment with plasma products administered by NHS Scotland as accurately as possible and shows that HCV infection in the Scottish haemophilia population has a natural history similar to HCV in other infected groups. The rate of natural clearance and the distribution of genotypes mirror the observations in non-haemophilia cohorts of infected individuals. The disease is slowly progressive and response rates to combination anti-viral therapy are better than for monotherapy. Table 4 summarises these observations. Genotype 1 is a negative predictor of response to interferon/ribavirin therapy in both PWH and the non-haemophilia population. Based on the small numbers of patients in this cohort it appears that liver biopsy and OLT can be performed successfully in PWH with no increase in complication rates when covered with appropriate factor replacement. The data from this cohort broadly support the philosophy amongst haemophilia treaters that the management of chronic HCV infection in this group of individuals should in most regards be no different to that in the non-haemophilia population.
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Authorship

All of the authors collected the data and reviewed the manuscript. Mohammed Khan developed the database and performed the statistical analyses. Ron Kerr, Campbell Tait, Christopher Ludlam, Gordon Lowe, William Murray and Henry Watson designed the study. Mohammed Khan, Campbell Tait and Henry Watson wrote the paper.
References


30. Hepatitis C in the UK. HPA report 2012
Table 1.

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<th>Centre</th>
<th>No. of HCV antibody positive patients (%)</th>
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Table 2.

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<td>1 (50%)</td>
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<td>14.5%</td>
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Figure legends.

Table 1 Numbers of HCV cases in cohort B at the individual Scottish centres

Table 2 Response rate to interferon-alpha monotherapy based on genotype

Table 3 Response rates to combination anti-HCV therapy based on genotype

Table 4 Comparison of cohort B with non-haemophiliac population

Figure 1 Flow diagram showing the derivation of the two cohorts
Figure 1. Flow diagram showing the derivation of numbers for each cohort.