Decreased prevalence and incidence of HCV markers in haemodialysis units: a multicentric French survey

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Abstract
Background. A variety of epidemiological data provide evidence for the nosocomial transmission of hepatitis C virus (HCV) infections to haemodialysis patients. We conducted a multicentric study to determine the prevalence and incidence of HCV infection in French haemodialysis units.

Methods. Patients undergoing chronic haemodialysis in 56 French units (4718 patients) were systematically screened for anti-HCV antibodies using third-generation tests. The incidence was estimated by detecting HCV RNA in seronegative patients using a standardized real-time PCR assay on pooled samples.

Results. Testing for HCV antibodies identified 361 patients with anti-HCV antibodies, giving a prevalence of 7.7%. Multivariate analysis demonstrated that anti-HCV status was linked to the time on haemodialysis, previous kidney transplantation and the presence of anti-HBc antibodies, whereas erythropoietin therapy and carrying out dialysis in dedicated spaces seem to protect against HCV infection. Only two of the 4357 patients without anti-HCV antibodies tested positive for HCV RNA, giving an estimated incidence of 0.05% new HCV infections/year. Molecular analyses indicated that the two patients probably acquired HCV outside the haemodialysis unit.

Conclusion. This decreased prevalence and incidence emphasizes the importance of adhering to the recommended universal infection-control precautions. Virological follow-up based on detecting anti-HCV antibodies with sensitive, specific new-generation serological tests could be adequate for dialysis units with few HCV infections. However, new infections in haemodialysis units should be identified by determining the HCV RNA status of seronegative patients. Standardized real-time PCR assays, plus pooling serum samples, make this a promising method for large-scale epidemiological studies.

Keywords: chronic haemodialysis; hepatitis C virus; incidence; seroprevalence

Introduction

Patients on maintenance haemodialysis are at greater risk of hepatitis C infection than the general population [1–5], with seroprevalence rates across dialysis centres in Western Europe ranging from 3% in the UK to 30% in France [6]. In France, the prevalence of hepatitis C virus (HCV) among haemodialysis patients is 15–42% [7] depending on the dialysis unit [8].

The increased prevalence of infection reflects the presence of common risk factors for HCV acquisition, including a history of drug abuse preceding kidney disease [9], transfusion and transplantation before 1994 [10] plus susceptibility to nosocomial transmission during dialysis [11–14]. External infection has been eliminated by screening blood donors for anti-HCV antibodies and using recombinant erythropoietin to treat anaemia [15,16]. Nosocomial transmission of HCV has been reported to be the major route of HCV infection and has been documented by phylogenetic analysis [11,14,17–19]. Although several studies have indicated that the incidence of HCV infection in chronic haemodialysis patients has decreased in the past [20], HCV transmission in haemodialysis units still occurs and is sometimes responsible for large outbreaks [12,21–24]. Several reports have suggested that HCV transmission is linked to breaches of standard precautions, leading to contamination of hands and the environment [25]. But the possibility of HCV transmission between patients through dialysis machines, which is still controversial, cannot be excluded when dialysers and dialysis equipment are reused among patients.
HCV infection is currently diagnosed by detecting anti-HCV antibodies by EIAs and is confirmed by the presence of HCV RNA [26]. It is important to diagnose HCV in haemodialysis patients early and accurately to prevent transmission and to ensure the appropriate management of the infection. Serum alanine aminotransferases (ALT) are not reliable markers for HCV screening as they are frequently normal [23]. Preliminary reports on selected haemodialysis patients support the use of a sensitive HCV RNA assay or the total Core Antigen assay to diagnose HCV infections in this population [27,28]. This report describes the findings of a multicentre study of 4718 patients in 56 French haemodialysis units. We have determined the prevalence of HCV antibodies, using third-generation assays, the independent factors correlated with HCV infection, and the prevalence of HCV RNA in seronegative patients.

Materials and methods

Study design

We studied a total of 4718 patients receiving chronic haemodialysis in 56 French haemodialysis units. They all satisfied the following inclusion criteria: >18 years old, had given informed consent and were undergoing regular haemodialysis for terminal chronic kidney failure. They were attending haemodialysis centres (87%) or self-care satellite units (13%). Patients on home haemodialysis or undergoing chronic peritoneal dialysis were excluded. Patients were assessed during their routine follow-ups. On the day of inclusion, blood was collected before the haemodialysis session and the serum was separated without delay. One fraction was used for transaminase determination and serum tests, and the other was divided into aliquots and stored at −80°C for HCV RNA testing. Samples from patients who tested negative for HCV antibodies were tested for HCV RNA in groups of serum from 20 patients.

Bioclinical data

The following data were collected: age, gender, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), HIV antibody status, HCV antibody status (HCV gen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), RNAs when available, recent blood transfusions or previous kidney transplants, haemodialysis vintage, the aetiology of end-stage kidney disease (ESKD), the type of dialyser, the use of erythropoiesis-stimulating agents (ESA), alcohol consumption, body mass, dedicated space for anti-HCV-positive patients and previous hepatic biopsies.

Biochemical parameters

ALT and glutamyl-gamma-transferases (γGT) activities were assayed in the laboratory attached to each haemodialysis unit using routine automated spectrophotometric methods.

Serum assays

Anti-HCV antibodies were assayed in the laboratory attached to each haemodialysis unit using routine automated second-generation assays licensed by the French Health Agency.

HCV RNA detection

Sera from patients who tested negative for anti-HCV antibodies were assayed for HCV RNA. Molecular tests were performed in the Virology Laboratory of Toulouse University Hospital, France, using the pooled serum strategy described below. Aliquots (200 μL) from each of 20 patients were pooled and centrifuged at 24 000 × g for 60 min at +4°C. The supernatant was discarded and the pellet was suspended in 900 μL of supernatant. Nucleic acids were extracted using the TN1 reagent and the COBAS Ampliprep™ Total Nucleic Acid Isolation Kit. A sample of extract (50 μL) was mixed manually with 50 μL of COBAS TaqMan™ HCV HPS test premix reagent and amplified using a real-time PCR COBAS TaqMan™ 48 instrument (COBAS Ampliprep™ analyser; Roche Diagnostics, Meylan, France). The lower detection limit of the assay was 50 IU/mL. Serial dilutions of commercially available HCV standard (Acromedrix containing 5 000 000 IU/mL HCV RNA) showed that the lower detection limit of the pooled samples protocol was 600 IU/mL.

Sequencing of HCV strains and phylogenetic analysis

The genotypes of the HCV strains from newly infected patients and those circulating in the same dialysis unit were determined by sequencing the NS5B region [29]. The genotype of each sample was determined by comparing its nucleotide sequence with those of HCV prototypes, representing different genotypes, obtained from the Los Alamos HCV sequence database (http://hcv.lanl.gov). The DNA alignments were prepared with Clustal W1.7 [30]. The genetic distances between sequences were calculated by the Kimura two-parameter method using Molecular Evolutionary Genetics Analysis software, MEGA (version 3) [31]. The reproducibility of the branching pattern was determined using bootstrap analysis (100 replicates). Subtypes were determined when sequences clustered together with a bootstrap value >70%. Finally, the phylogenetic tree was drawn using Treeview 1.66 by the neighbor-joining (NJ) method [32].

The remaining HCV RNA underwent two-strand direct sequencing on a nested PCR product in the E2 gene that encompassed the HVR-1 region [33]. The HVR-1 region of HCV isolates from newly infected patients and those with the same genotype circulating in the same dialysis unit were compared using the phylogenetic approach used to analyse the NS5B region.

Statistical analyses

The relationships between qualitative variables were tested using the χ² test. The relationships between the quantitative variables were tested using Student’s t-test. Factors that were found to be significantly linked to HCV status by univariate analysis (P < 0.05) were subjected to logistic regression analysis to determine which factors independently predicted HCV status. A P-value <0.05 was taken as statistically significant.

Results

The general characteristics of the 4718 patients from 56 French haemodialysis units are summarized in Table 1. Their median age was 72 years (range 19–103), 61% were men, and their median time on haemodialysis was 43 months (range 3–569). The prevalence of HBsAg was 2.1% and that of anti-HIV1/2 was 0.3%.

Table 1. General characteristics of the 4718 patients studied

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender ratio (M/F)</td>
<td>1.5</td>
</tr>
<tr>
<td>Age, yearsa</td>
<td>68 ± 15</td>
</tr>
<tr>
<td>Aetiology of CKD</td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>700 (15%)</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>390 (8%)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>907 (19%)</td>
</tr>
<tr>
<td>Vascular nephropathy</td>
<td>1199 (26%)</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>577 (12%)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>410 (9%)</td>
</tr>
<tr>
<td>Other</td>
<td>498 (11%)</td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>95 (2.1%)</td>
</tr>
<tr>
<td>Anti-HIV1/2 positive</td>
<td>15 (0.3%)</td>
</tr>
</tbody>
</table>

aValues are means ± SD.
**Prevalence of HCV markers**

The prevalence of HCV markers is indicated in Figure 1. Anti-HCV antibodies were detected in 361 of the 4718 haemodialysis patients (7.7%; 6.9–8.5%). The prevalence of HCV serological markers varied between 0 and 18.8%. Only 17 (30%) of the 56 dialysis units had no patients with anti-HCV antibodies. Of the 361 patients who tested positive for anti-HCV antibodies, 210 were RNA positive (70%; 64.5–75.1%). HCV RNA was assayed in the anti-HCV Ab (−) patients using pooled samples from 20 patients. Two of 218 pools were HCV RNA (+). Only one serum sample in each positive pool was HCV RNA (+). A total of two of the 4357 anti-HCV Ab (−) patients (0.05%) tested were HCV RNA (+).

**Correlation between HCV markers and biochemical markers**

Patients with a positive HBsAg (n = 95) or unknown HBV status (n = 214) were excluded. Of the remainder, the HCV Ab (+) RNA (+) patients had significantly higher mean ALT (22.7 ± 0.8), aspartate aminotransferase (AST; 27.3 ± 1.3) and γGT (77.8 ± 8.7) activities than the HCV Ab (+) RNA (−) patients (ALT: 16 ± 0.8; AST: 18 ± 1.6; γGT: 41.3 ± 6.2; P < 0.001). But the mean ALT, AST and γGT activities in RNA (−) patients who were HCV Ab (−) (15.7 ± 0.1; 17.6 ± 0.2; 46.8 ± 1.1) and HCV Ab (+) (16 ± 0.8; 18 ± 1.6; 41.3 ± 6.2) were not significantly different (Figure 2).

**Correlation between HCV markers and clinical data**

The prevalences of anti-HCV antibodies in patients treated in haemodialysis centres (7.5%) and in self-care dialysis units (8.6%) were similar. Univariate analysis indicated factors associated with the presence of HCV antibodies were (i) young age, (ii) low body weight, (iii) receiving dialysis for >43 months, (iv) positive serological HBV markers, (v) previous kidney transplantation, (vi) recent blood transfusion, (vii) ESA treatment, (viii) presence of dedicated dialysis space for HCV (+) patients and (ix) vascular nephropathy as the aetiology of chronic kidney disease (Table 2). Multivariate analysis indicated that the only factors significantly associated with positive anti-HCV antibodies were age <71 years, receiving dialysis for >43 months, the presence of anti-HBc antibodies, a previous history of kidney transplantation and an absence of ESA therapy (Table 3).
Incidence of HCV infection and mechanism of transmission

Only two of the 4357 patients with no anti-HCV antibodies who were screened for HCV RNA tested positive. The incidence of HCV infection without the production of antibodies was estimated to be 5/10,000. Patient A was known to have HCV RNA without antibodies before being screened for the study and showed no antibody seroconversion 6 months later. Patient B had an unknown HCV RNA status when he was included in the study. He died after being transferred to another haemodialysis centre 18 months later. Neither of these patients had received a blood transfusion within the 6 months prior to the first HCV RNA (+) serum sample, but both had been given ESA therapy. They had not undergone any invasive procedures such as transplantation or endoscopy within the previous 6 months.

Patient A was dialysed as a consequence of diabetes mellitus-related ESKD, and patient B because of vascular kidney disease. The two patients were dialysed in the same haemodialysis unit, where patients were not isolated according to their HCV serological status.

The viral load of Patient A was 79,500 IU/mL and that of patient B was 34,960 IU/mL. Both were infected with HCV genotype 1: subtype 1i for Patient A and 1b for Patient B. Patient A had elevated ALT (49 IU/L; \( n = 37 \)), whereas Patient B had normal ALT (12 IU/L). Both had been immunized against hepatitis B virus. The 137 patients attending the haemodialysis unit where Patients A and B were treated included five who were already infected with HCV. Two had undetectable HCV RNA while two others harboured a strain of HCV that belonged to genotype 1b and 2i. The HCV genotype of the last patient could not be assessed. The HCV genotypes from the newly infected patients and those from patients infected in the past at the same unit were analysed by sequencing the NS5B region and the HVR-1 region of the E2 gene. Phylogenetic analyses with a control panel (strains from unrelated non-haemodialysed patients with hepatitis C in the same geographical area, plus strains from the EMBL data bank) did not identify the source of the new HCV infections within the unit as being the same as strains from past-infected patients (Figure 3).

Discussion

Nosocomial transmission, the second most frequent cause of HCV infection, still occurs through dialysis procedures. A prompt diagnosis is important for appropriate patient management and to prevent further transmission [11].

Current guidelines recommend that patients on haemodialysis be routinely monitored for infection by blood-borne viruses, including testing for anti-HCV antibodies.
Table 3. Factors associated with anti-HCV antibodies in multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Prior kidney transplantation (yes)</td>
<td>4.0</td>
<td>2.4–6.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HBcAb (yes)</td>
<td>2.4</td>
<td>1.5–4.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESA therapy (no)</td>
<td>2.1</td>
<td>1.2–3.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dialysis units dedicated space for HCV (+) patients (no)</td>
<td>1.9</td>
<td>1.3–2.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dialysis vintage (&gt;43 months)</td>
<td>3.7</td>
<td>2.1–6.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (&lt;72 years)</td>
<td>1.7</td>
<td>1.0–2.7</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

HB, hepatitis B; HCV, hepatitis C virus; Ab, antibody; ESA, erythropoiesis-stimulating agent; CI, confidence interval.

Fig. 3. Phylogenetic analysis of the hypervariable region 1 of strains from newly infected patients (filled stars) and already infected patients (filled triangles) treated at centre 50. Reference strains are also indicated (filled circles).
But previous studies have shown that HCV viraemia can occur in patients on haemodialysis despite the absence of detectable anti-HCV antibodies [11,34,35].

We carried out a large-scale survey using third-generation anti-HCV assays and a standardized real-time PCR assay to obtain a better estimate of the prevalence of HCV infection and assess the prevalence of Ab(−) RNA (+) HCV infection in patients undergoing haemodialysis in French haemodialysis units. In accordance with French legal requirements, each sample was assayed for anti-HCV antibodies; 7.7% of samples tested positive. The prevalence of HCV antibodies in French haemodialysis centres seems to have decreased over the past few years, but still varies from one unit to another, from 0 to 18.8% as previously reported [7]. We find, as have many others, that the time on dialysis since its initiation (dialysis vintage) is clearly associated with the risk of HCV infection, reflecting both the cumulative risk of infection over time and the immunosuppressive effects of prolonged haemodialysis [34]. Most patients with markers of HCV had probably been infected in the past either as a result of blood transfusions before the screening tests were introduced or by nosocomial transmission. Because kidney transplantation often requires blood transfusion, HCV antibodies are relatively prevalent in patients with a history of kidney transplantation. A few studies have examined the correlation between HCV and HBV status but have found conflicting results. Nevertheless, anti-HBc antibodies and the HBsAg are more frequent in anti-HCV Ab(+) dialysis patients. Haemodialysis patients have been vaccinated against HBV infection for the last few years, so that the association between these markers may also reflect past exposure to both viruses before secure haemodialysis processes were introduced. Multivariate analysis reveals that haemodialysis vintage and kidney transplantation are major independent predictive factors for positive HCV serum.

Apart from these major factors, we found that not receiving ESA therapy was an independent predictive factor of having anti-HCV antibodies [OR at 2.1 (95% CI 1.2–3.5); P < 0.01], i.e. receiving ESA therapy was protective against anti-HCV antibodies. When dialysis patients are treated with ESA, they often need/receive at the same time IV iron therapy in order to maintain adequate ferritin levels, which is required for haematopoiesis. Nascimento et al. have shown that in haemodialysis patients IV exogenous iron replacement therapy results in free iron and oxypyradoxical formation, which can damage cellular lipids and nucleic acid [36]. Hence, we can hypothesize that iterative IV iron therapy delivered to haemodialysis patients might prevent to some extent HCV infection via IV iron-induced oxypyradoxical formation.

These results suggest that blood transfusions associated with kidney transplantation have been the major source of HCV infections for many years, but the use of sensitive HCV screening tests for blood donors decreases the risk of post-transfusion HCV infection to <1/2 000 000 blood units [37,38]. This residual risk is probably linked to environmental contamination as a consequence of poor adherence to standard precautions in the haemodialysis setting [25] and may explain in Western Europe imported hepatitis C virus infection as a consequence of holiday haemodialysis when travelling and being on haemodialysis therapy in North African countries or India or Pakistan, for example [39]. This emphasizes the need to implement worldwide in the haemodialysis facilities infection control practices and aseptic techniques in order to avoid hepatitis C virus transmission [40].

The incidence of HCV in new patients beginning kidney replacement therapy ranges from 3 to 7%, and reported seroconversion rates during dialysis treatment vary from 1 to 16% per year [41].

The very few (5/10 000) patients who were anti-HCV Ab(−) RNA (+) in our study suggests that there has been a significant decrease in the annual incidence of new infections, which is in accordance with decreasing prevalence. This probably reflects better implementation of meticulous universal control measures to prevent HCV transmission in these dialysis units. We also found no phylogenetic evidence that HCV transmission occurred during dialysis procedures. The increased sensitivity of the latest generation of HCV assays has dramatically reduced the risk of HCV transmission by blood components and also the serological window between acquisition of infection and the development of anti-HCV antibodies [37,42]. But factors may reduce the antibody responses to HCV including the immunosuppressive effect of chronic uraemia, high concentrations of high pro-inflammatory cytokines and the concomitant occurrence of diabetes [34,43]. One of the two anti-HCV Ab(−) RNA(+) patients was dialysed for complications of diabetes and did not undergo seroconversion until at least 6 months after screening. Detecting of HCV RNA in the absence of antibodies may also reflect the prolonged period before seroconversion, which is characteristic of acute HCV infection. This period can be relatively long compared to the timing of infection and onset of viraemia, even with current third-generation assays.

The ability to identify patients with acute HCV infection in real time could be of great clinical benefit to these individuals because early initiation of antiviral therapy may improve virus eradication [11]. Standardized, reproducible and sensitive real-time PCR assays are now available to determine HCV RNA status [44].

The pooling strategy we used made the large-scale screening of seronegative patients economically feasible. The pooled plasma samples of 20 anti-HCV Ab(−) patients were ultracentrifuged. This did not lead to any loss of HCV RNA assay sensitivity. This strategy is cost effective with a threshold of 600 IU/mL, similar to the detection limit of commercially available assays based on conventional PCR. The exhaustive testing of anti-HCV Ab(−) dialysed patients for HCV RNA at a given time is a valid way of estimating annual incidence [7,10,11]. The test used, an enzyme immunoassay (EIA) or a nucleic acid test (NAT), should depend on the prevalence of HCV in the dialysis unit in order to minimize false-positive and false-negative results. EIA may not be suitable for screening for HCV in a dialysis unit where infection is prevalent because many patients with a negative EIA are at risk of being positive for HCV RNA. Many of the patients in these units will require additional testing with NAT. In contrast, there will be few true or false-positive EIA tests where HCV is rare, and only a few patients will require confirmation with NAT [45].
Biochemical features of anti-HCV Ab (+) RNA (+) patients that are significantly different from those of anti-HCV Ab (+) RNA (+) patients, and are very similar to those of anti-HCV Ab (−) patients, may have clinical relevance in dialysis units when an isolation policy is implemented. These patients are not protected against new HCV infection and should be considered to be anti-HCV Ab (−).

To summarize, we have found a remarkable decrease in the prevalence and incidence of HCV infection in French dialysis units. However, kidney transplantation and the time receiving dialysis remain major causes of HCV infection in haemodialysed patients. Although anti-HCV Ab (+) RNA (+) infections were rare, we believe that routine testing of dialysis patients with undetectable antibodies for HCV RNA using a pooled serum strategy could disrupt transmission chains in dialysis units and provide additional personal benefits to newly infected patients.

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Conflict of interest statement. None declared.

References
Burden on caregivers as perceived by hemodialysis patients in the Frequent Hemodialysis Network (FHN) trials

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Abstract

Background. Patients with end-stage renal disease often rely on unpaid caregivers to assist them with their daily living and medical needs. We characterized the degree to which patients enrolled in the Frequent Hemodialysis Network (FHN) trials perceived burden on their unpaid caregivers.

Methods. Participants completed the Cousineau Perceived Burden Scale, a 10-question scale previously developed in hemodialysis (HD) patients. Associations between baseline burden score and prespecified variables were evaluated using multivariable linear regression.

Results. Of 412 participants, 236 (57%) reported having unpaid caregivers. Compared to those without unpaid care-