Clinical, Virological, and Histologic Evolution of Hepatitis C Virus Infection in Liver Transplant Recipients


We designed a prospective study to assess the time course and evolution of hepatitis C virus (HCV) infection in 152 patients who underwent a liver transplantation (LT) in our institution. Forty-four recipients (29%) were infected by HCV after transplantation: 40 who developed recurrent infection after LT and four who acquired infection during or after LT. No differences were found in survival actuarial rates at 1, 2, and 4 years after transplantation for patients infected by HCV vs. noninfected ones. Graft hepatitis occurred in 66% of HCV-infected recipients: 18 developed chronic active hepatitis (10 of them with intense fibrosis) and 2 developed cirrhosis during the follow-up. Infection by the HCV-1b genotype was found in 79% of the infected recipients and in 100% of those in whom histologic evolution was worst. Fourteen grafts were lost in 44 HCV-infected recipients, in comparison with 12 in 108 HCV-negative patients (P < .007), mostly because of chronic rejection. HCV infection did not affect life expectancy in the midterm follow-up for LT patients. However, it was often associated with the occurrence of early and severe graft hepatitis and with a higher incidence of graft loss due to chronic rejection.

Liver transplantation (LT) is considered the best therapeutic option for the treatment of end-stage liver diseases [1]. The progressive improvement of the results of LT during the past decade has created in most institutions an unbalanced ratio between the limited number of grafts available for transplantation and the growing number of potential recipients. In this setting, some authorities have suggested careful analysis of cost/benefit ratios of LT for some liver diseases, particularly those able to recur in the graft [2]. Recurrence of primary liver diseases, especially those of viral origin, is becoming an important threat to LT patients. Evidence of the high risk of severe recurrent disease and substantial mortality associated with hepatitis B virus (HBV) reinfection in patients undergoing transplantation for chronic HBV infection has led some institutions to no longer consider patients with hepatitis B for liver transplantation [3, 4].

Hepatitis C virus (HCV)-related liver diseases have become a common indication for LT worldwide [5]. Moreover, patients noninfected with HCV prior to hepatic transplantation can also acquire this infection following LT [6, 7]. Recurrence of HCV infection has been shown to be a nearly universal complication following LT [6, 8], but the incidence of recurrent histologic hepatitis has varied widely [9, 10]. Furthermore, the clinical and histologic consequences of recurrent HCV infection on the viability of the liver grafts and their recipients remain to be adequately established.

The aim of our study was to analyze the frequency, time course, and short- and long-term consequences of HCV infection following LT. Our particular interest was in the influence of HCV infection on the survival of patients and their grafts and the evolution of liver histology in HCV-infected recipients vs. noninfected ones.

Patients and Methods

Patient Population

From July 1989 to June 1993, 175 adult patients underwent their first LT in our institution. Patients were excluded from the present study if they died in the first 72 hours after LT (n = 6), received a renal transplantation simultaneously (n = 5), did not have appropriate liver and/or serum samples obtained for microbiological and pathological analysis (n = 7), or had, before or after the transplantation, coinfection with hepatitis B virus (HBV) and HCV (n = 5). Clinical and histologic data as well as serum samples for virological analysis were prospectively collected from the remaining 152 patients, whose mean duration of follow-up was 47 months (range, 1–80 months).

From March 1990 onward, all liver and blood donors were routinely tested for antibodies to HCV and excluded if results were positive. The baseline immunosuppressive regimen was administration of a combination of cyclosporine, corticosteroids, and azathioprine (only during the first 3 months). Cyclosporine levels were routinely monitored to maintain...
blood levels of 200–300 ng/mL (measured by radioimmunoassay) in the first weeks after transplantation and 100–150 ng/mL thereafter. Rejection episodes were treated with 1 g of methylprednisolone during 3 consecutive days, and if this failed, with OKT3 monoclonal antibodies. Management of immunosuppression was not modified at the time of documented recurrence or “de novo” acquisition of HCV infection.

Antimicrobial prophylaxis consisted of administration of norfloxacin and nystatin or fluconazole during the first 4 weeks after transplantation and cotrimoxazole thrice weekly during the first 6 months. In addition, ganciclovir was administered to seronegative recipients of a graft from a seropositive donor and to seropositive recipients treated with OKT3.

Serology

Presence of antibodies to HCV was tested for with a second-generation ELISA (Ortho Diagnostics, Raritan, NJ), and positive results were confirmed by a second-generation recombinant immunoblot assay (RIBA; Ortho Diagnostics) that detects antibodies against epitopes located in the capsid (c22) and in nonstructural proteins (c33, c100-3, 5-1-1). We tested for the presence of antibodies to HCV just before the transplantation and every 3 months during the first year after surgery.

HCV-RNA Detection

Separation of serum was done within 3 hours of collection, and then the serum sample was stored at −70°C. HCV-RNA from 100 μL of serum was extracted by the guanidium thiocyanate–phenol-chloroform method and reverse-transcribed into cDNA. PCR was performed as a two-step reaction with two pairs of nested primers corresponding to a fragment of the 5′ untranslated region, as described elsewhere [6, 7]. Amplification products were electrophoresed on a 2% agarose gel (Nu-sieve, FMC, Bioproducts, Rockland, ME), stained with ethidium bromide, and photographed under ultraviolet light. PCR for HCV-RNA was performed on days 0, 7, 30, 90, 180, and 360 following LT.

HCV Genotyping

HCV genotype was determined with a line-probe genotyping assay (INNO-LiPA HCV, Innogenetics, Zwijnaarde, Belgium). This assay is based on the utilization of biotinylated primers and the hybridization to oligonucleotides directed against the variable region of 5′ untranslated region, immobilized as parallel lines on membrane strips [11].

Histology

Hepatic allograft biopsies were performed for all patients when liver test results became abnormal, and in those infected by HCV, liver biopsies were performed by protocol once a year. All liver biopsy results were reviewed by two pathologists.

Definitions

HCV infection was defined by the detection of HCV-RNA by nested PCR in serum samples. Recurrent HCV infection was diagnosed after transplantation when HCV-RNA was detected in a recipient who also tested positive for HCV-RNA before LT. On the contrary, “de novo” HCV infection was considered when HCV-RNA was detected in a posttransplantation serum sample but not before transplantation.

Graft hepatitis was defined by the presence of hepatocyte necrosis and portal or lobular infiltration by mononuclear cells. Acute and chronic rejection was defined according to internationally accepted criteria [12]. We were extremely careful in diagnosing graft hepatitis in the presence of histologic signs of acute rejection, above all if no relevant lobular infiltrate, “piecemeal necrosis,” or fibrosis existed. When both acute rejection and hepatitis were suspected, management included an increase in immunosuppression and repetition of liver biopsy within the subsequent few days to confirm the presence of graft hepatitis. Hepatitis was further classified as chronic persistent hepatitis (CPH), chronic active hepatitis (CAH), and lobular hepatitis, as previously described by Bianchi et al. [13]. Graft hepatitis was scored according to the histologic activity index described by Knodell et al. [14].

Statistical Analysis

Actuarial rates of graft hepatitis and of patient and graft survival were calculated by the Kaplan-Meier method. Comparisons between actuarial survival rates were made with the log-rank test. In the analysis of the time free of graft loss, data on patients were censored at their deaths. An unpaired Student’s t-test was used to compare quantitative values, and the χ² or Fisher’s exact test was used to analyze nominal values.

Results

Infection by HCV

Patients were categorized into two groups on the basis of the presence of HCV-RNA after LT. Forty-four recipients (29%) were infected by HCV after transplantation. In all 44 HCV-infected individuals, HCV-RNA was detected by day 90 following transplantation, and they remained positive thereafter. HCV viremia was not detected in the remaining 108 patients. As is shown in table 1, apart from the presence of HCV infection, the groups did not differ in terms of the most important variables influencing graft and patient viability following LT.

The 108 HCV-negative recipients were given transplants because of alcoholic cirrhosis (n = 51), primary biliary cirrho-
Table 1. Major variables influencing patient and graft viability in liver transplant recipients who were infected (+) or uninfected (−) by HCV.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HCV+ (n = 44)</th>
<th>HCV− (n = 108)</th>
</tr>
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<tbody>
<tr>
<td>Age, y (mean ± SD)</td>
<td>47 ± 10</td>
<td>46 ± 10</td>
</tr>
<tr>
<td>Sex (no. of male/female patients)</td>
<td>33/11</td>
<td>65/43</td>
</tr>
<tr>
<td>Weight in kg (mean ± SD)</td>
<td>67.8 ± 16</td>
<td>65.9 ± 15</td>
</tr>
<tr>
<td>Mean follow-up, mo (range)</td>
<td>41 (1—71)</td>
<td>37 (1—71)</td>
</tr>
<tr>
<td>Child ‘C’ liver disease</td>
<td>31 (70)</td>
<td>72 (66)</td>
</tr>
<tr>
<td>Emergency transplantation</td>
<td>0</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Rejection episodes (mean ± SD)</td>
<td>0.61 ± 0.63</td>
<td>0.62 ± 0.64</td>
</tr>
<tr>
<td>Cytomegalovirus infection</td>
<td>35 (79)</td>
<td>81 (75)</td>
</tr>
<tr>
<td>Cytomegalovirus disease</td>
<td>8 (18)</td>
<td>19 (17)</td>
</tr>
<tr>
<td>OKT3 use</td>
<td>11 (25)</td>
<td>24 (22)</td>
</tr>
<tr>
<td>Blood administered during surgery, U (mean ± SD)</td>
<td>12 ± 4</td>
<td>13 ± 5</td>
</tr>
</tbody>
</table>

NOTE. P values were not significant for any comparisons between groups. Data shown are numbers (%) of patients, except as otherwise indicated.

Recurrent vs. “De Novo” HCV Infection

HCV viremia was detected by PCR in 40 recipients before transplantation. Recurrent infection, defined by the detection of HCV-RNA in a posttransplantation serum sample, appeared in all these 40 patients. Twenty-five recipients with recurrent infection were HCV-PCR-positive as early as 1 week after transplantation, and the remaining 15 became PCR-positive during the first 3 posttransplantation months. Four patients developed “de novo” HCV infection, as demonstrated by the absence of detectable viremia in the sample obtained before transplantation. Viral infection in this particular population could be the consequence of HCV transmission through the liver graft or blood products administered during the surgical procedure.

Actually, three of these four recipients received a transplant in the period (July 1989 to March 1990) in which serological tests for the diagnosis of HCV infection were not available. Overall, 19 patients underwent LT in our center during this period; the incidence of “de novo” HCV infection from unscreened liver grafts and blood was then 15% (three cases). In contrast, of the 105 HCV-RNA-negative recipients who underwent LT after screening began for the presence of HCV antibodies in all organ and blood donors, only one (1%) became infected by HCV after transplantation. Detection of HCV-RNA by PCR was not attempted in donors.

Serological Evaluation

Thirty-seven of the 40 recipients infected by HCV before LT were seropositive by both second-generation ELISA and RIBA, and they remained seropositive in all posttransplantation serum tests. Only one of the four patients who developed “de novo” HCV infection following LT became seropositive (confirmed by both ELISA and RIBA) on day 180 after surgery. The remaining three patients who presumably acquired HCV infection after LT did not seroconvert during the follow-up.

Six recipients had antibodies to HCV detected by the second-generation ELISA before LT, but in five of them seropositivity was not confirmed by RIBA. All of them tested negative by second-generation ELISA from the third month after transplantation onward. None of the 108 posttransplantation PCR-negative individuals had detectable antibodies beyond day 90 after transplantation.

Mortality

Forty-seven of the 152 patients (31%) died during the follow-up, including 11 of the 44 (25%) infected by HCV. As shown in figure 1, the overall actuarial survival rates among HCV-infected individuals were 84%, 81%, and 74% at 1, 2, and 4 years after liver transplantation and were not significantly different from those among noninfected recipients (70%, 69%, and 65%, respectively).

Causes of death are shown in table 2. In only one case was recurrent HCV infection with the development of severe cholestatic hepatitis and subacute hepatic failure directly associated with death. Infectious complications accounted for 45% of mortality in HCV-infected recipients and 30% in noninfected individuals (P = .18).

Histologic Evolution

Graft hepatitis developed in 29 patients (66%) infected by HCV but in only 12 (including 6 HBV-infected recipients) of the 108 (11%) of those not infected by the virus (P < .001). Moreover, when only patients with a follow-up longer than 1 year were analyzed, hepatitis appeared in 76% of HCV-infected individuals (28 of 37). Actuarial rates of occurrence of graft hepatitis in this group were 48%, 70%, and 83% at 1, 2, and 4 years after transplantation, respectively (figure 2). The mean (±SD) time from LT to the first evidence of graft hepatitis in HCV-infected recipients was 316 ± 242 days (range, 57–814 days).

From a histologic point of view, at the time of diagnosis of graft hepatitis, 10 of the 29 patients had lobular hepatitis, 6 had CPH, and 13 had CAH. Only three of the patients who developed histologically evident lobular hepatitis recovered completely during the follow-up. None of the patients with chronic hepatitis...
showed significant histologic improvement. Moreover, 10 patients
developed CAH with severe fibrosis (≥3 on the scale of fibrosis
in the histologic activity index of Knodell et al. [14]) or cirrhosis
(n = 2) at a mean (±SD) of 552 ± 448 days (range, 153–1603
days) after LT; remarkably, 7 cases developed before the end of
the first year after transplantation.

The histologic picture corresponding to the last available
biopsy for the 44 HCV-infected recipients is shown in table 3.
The mean histologic activity index score in the recipients with
graft hepatitis was significantly higher in the last available
biopsy (9.8 ± 3.6; range, 3–17) than when graft hepatitis was
first diagnosed (7.5 ± 3.3; range, 3–15) (P < .05). The median
time elapsed from the first biopsy showing hepatitis to the last
available biopsy was 262 ± 171 days.

Genotype 1b (HCV-1b) was the predominant type of HCV
in our recipients and was found in 34 of the 44 individuals,
followed by type 1a (9 patients) and type 3 (1 patient). Twenty-
three of 34 HCV-1b-infected patients had graft hepatitis revealed
by their last available biopsy, in comparison with only 5 of 10 non-1b-infected recipients (P = .17). Moreover, all 12
patients with CAH and severe fibrosis or cirrhosis were infected
by the 1b genotype.

Graft hepatitis was a largely asymptomatic complication in
our recipients. Seven patients developed jaundice at the time
graft hepatitis was diagnosed. In 20 patients an asymptomatic
increase in serum aminotransferase activity, with mild cholesta-
isis, was the only sign accompanying the appearance of HCV-
related hepatitis. For the remaining two patients the diagnosis
of graft hepatitis was made at autopsy (CAH) and routine liver
biopsy (CPH), respectively, without concomitant abnormalities
noted in liver function tests. Mean aspartate and alanine amin-
transferase values when graft hepatitis related to HCV infection
was diagnosed were 227 ± 135 IU and 289 ± 194 IU, respec-
tively. Overall, 3.8 biopsies per patient (range, 1–14) were
performed on HCV-infected patients, in comparison with 2.7
(1–12) in those uninfected.

### Table 2. Causes of death of recipients infected (+) vs. uninfected
(−) by HCV.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>HCV− (n = 36)</th>
<th>HCV+ (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multorgan failure</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Intraoperative bleeding</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac failure/sudden death</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Recurrence of carcinoma</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Bacterial sepsis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Severe graft hepatitis</td>
<td>1*</td>
<td>1*</td>
</tr>
<tr>
<td>Cytomegalovirus disease</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Liver failure</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous²</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

* Graft hepatitis due to HBV infection.
² Includes massive bleeding secondary to thrombopenia associated with
graft-vs-host disease (1), pulmonary embolism (1), death secondary to
unknown cause (1), and suicide (1).

### Graft Survival and Causes of Graft Loss

Fourteen grafts were lost among 44 HCV-infected recipients
after a median of 276 days (range, 5–875 days), in comparison
with 12 among 108 recipients not infected by HCV (P = .007).
Analysis of graft survival according to HCV infection status
is shown in figure 3. Causes of graft loss in the HCV-negative

#### Figure 1. Actuarial survival
rates among recipients infected (+) vs. uninfected (−) by hepatitis
C virus (HCV). (NS = not significant.)
Posttransplantation hepatitis was diagnosed before the development of chronic rejection in 9 HCV-infected grafts (lobular hepatitis in 2, mild CAH in 4, and severe CAH in 3) and simultaneously in an additional recipient with CPH. In only one HCV-infected graft, chronic rejection appeared without histologic evidence of graft hepatitis. No significant differences in the histologic score were found between those HCV-infected grafts that developed chronic rejection vs. those that did not.

Eight HCV-infected recipients were given second transplants because of thrombosis of the hepatic artery (n = 1), chronic rejection with CAH (n = 5), chronic rejection with CPH (n = 1), and HCV-related cirrhosis (n = 1). In addition, two HCV-infected individuals received a third and a fourth liver graft because of the reappearance of chronic rejection. In all cases but one, chronic rejection was accompanied by lobular or CAH graft hepatitis. The recipient who received a second transplant as a consequence of HCV-related graft cirrhosis developed CAH in the new graft after a follow-up of 213 days.

Eleven HCV-negative recipients were given new transplants for arterial thrombosis (n = 1), HBV-related hepatitis (n = 2), and chronic rejection (n = 8).

Discussion

The current study shows that HCV infection recurs in virtually all patients after transplantation. Moreover, a careful search for HCV-RNA by PCR during the first weeks after transplantation showed that recurrence of HCV infection occurred very early following transplantation. The origin of recurrent HCV infection is not fully understood. Extrahepatic sites of viral replication are well established for HBV and are implicated in the recurrence of the infection in hepatitis B surface antigen—positive liver transplant recipients [15]. Peripheral blood mononuclear cells have been shown to contain negative-stranded HCV-RNA [16], and HCV RNA has also been found in a human T-cell line infected with HCV [17]. It seems probable that extrahepatic sites of HCV replication may play an important role in the appearance of recurrent disease after transplantation.

HCV infection can also be acquired during transplantation through blood or graft donors infected by the virus. Fifteen percent of our recipients who underwent transplantation before first-generation HCV-ELISA availability developed “de novo” HCV infection. The subsequent introduction of HCV-screening tests for blood and organ donors reduced the rate of acquired HCV infection to 1%.

Although HCV-RNA detection is the most reliable marker of HCV infection, it is noteworthy that we were able to identify 37 of 40 HCV-infected candidates before LT by means of the

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**Table 3.** Liver histology corresponding to the last available biopsy findings for the 44 recipients infected with HCV: overall results and distribution according to HCV genotype.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Overall (%)</th>
<th>HCV-1b (n = 34)</th>
<th>Other HCV genotype (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>2 (4)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>10 (23)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>with severe fibrosis*</td>
<td>8 (18)</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Chronic persistent hepatitis</td>
<td>3 (8)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lobular hepatitis</td>
<td>4 (9)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Normal/minimal changes</td>
<td>17 (39)</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

* Grade 3 in the histologic activity index of Knodell et al. [14].
Figure 3. Kaplan-Meier plots of graft-loss-free proportion of patients, according to hepatitis C virus (HCV) infection status. Data were censored at death of patients.

detection of antibodies to HCV by second-generation ELISA and immunoblot assay, confirming the suggestion in our previous experience that a proper HCV serology identifies a high proportion of HCV-infected LT candidates [18]. In all recipients who tested positive for HCV before transplantation, seropositivity continued after transplantation. However, among individuals who acquired HCV infection in association with liver transplantation, only one of four developed antibodies to HCV, which is in agreement with previous reports that found a low seroconversion rate in this particular population [19].

Our data confirm most previous reports, usually of studies with shorter follow-ups, that HCV infection did not increase mortality among LT patients [6-10]. Moreover, no specific cause of death was more frequently associated with posttransplantation HCV infection. Specifically, we have not found a significant increase in mortality caused by infectious complications in recipients infected by HCV, and in only one case was HCV infection, with development of severe recurrent hepatitis in the graft, directly associated with death.

The most controversial issue involving HCV infection and liver transplantation is the frequency and severity of histologic hepatitis in the graft and the consequences of the infection in graft survival. Graft hepatitis, in our experience, was a very frequent event, developing in 76% of the individuals with a follow-up longer than 1 year. Furthermore, graft hepatitis induced by HCV infection seemed to be a severe and progressive lesion in most HCV-infected recipients, as judged by a significant increase in the histologic activity index score. In fact, only three of 29 patients with graft hepatitis caused by HCV showed significant histologic improvement during the follow-up.

On the contrary, 18 HCV-infected recipients developed CAH, 10 of them with intense fibrosis, which suggested an irreversible loss of the normal architecture of the liver, and two others had cirrhosis. Because of the small number of patients who acquired HCV infection during transplantation, we were not able to confirm previous data that suggested that LT patients with “de novo” HCV infection more frequently developed hepatitis in the graft than did patients with recurrent infection [20].

The reported incidence of graft hepatitis in HCV-infected recipients has varied widely, from 14% to 100%. Most authors have considered graft hepatitis induced by HCV as a relatively benign and slowly progressive process. Ferrel et al. [20] reported the incidence of HCV-induced graft hepatitis among 43 HCV-infected recipients to be 41%, and only four of them developed focal bridging fibrosis and cirrhosis. Shiffman et al. [8] found a 100% incidence of graft hepatitis in 23 LT patients infected by HCV, but in all cases hepatitis was mild (mean histologic activity index score, 4.0 ± 0.3) and did not progress over a mean follow-up of 22 months.

On the contrary, Fèray et al. [10] showed that the actuarial rate of graft hepatitis in 79 recipients infected by HCV was 72% at 4 years, and progression to CAH occurred in 61% of the subjects within 3 years. More recently, Gane et al. [21] reported that only 12% of HCV-infected recipients who survived >6 months after transplantation had no evidence of chronic hepatitis in their most recent liver biopsy. These later data were similar to our findings.

These variations may arise from differences in the definition of chronic hepatitis, length of follow-up, and the frequency with which graft biopsies were performed. Besides methodological differences, viral and host factors have been implicated in the development and severity of posttransplantation hepatitis C. Viral replication was, in theory, a good explanation for the varied clinical course of recurrent HCV infection in LT patients. However, the level of viremia before as well as after transplantation has not been correlated with significant differences in the incidence and severity of graft hepatitis [22].
Rejection requiring OKT3 and high-dose intravenous methylprednisolone therapy for acute allograft rejection were associated with a higher incidence and earlier presentation of recurrent hepatitis C [23, 24]. The reported influence of donor-recipient human leukocyte antigen (HLA) matching on the rate of recurrence of histologic HCV hepatitis after liver transplantation is an example of how host factors may influence the histologic course of HCV infection in these populations [25].

As other RNA viruses, HCV exists as a variety of genotypes. Phylogenetic analysis of a specific genomic region has resulted in a classification of the virus into six major genotypes and 11 subtypes that show significant variations in their geographic distribution and appear to differ in their clinical effects [26]. HCV 1b is the predominant genotype in Mediterranean countries and is associated with more severe liver disease in patients who have not undergone transplantation [27].

With regard to the transplantation setting, two different groups in France and England have recently provided direct evidence that HCV 1b is associated with more aggressive recurrent liver disease than are other genotypes [22, 28] and that viral genotype may explain the differences in the clinical and histologic evolution of HCV infection following LT. Genotype 1b was also the predominant genotype in the current study, but the low number of patients infected by genotypes other than 1b (mostly 1a) makes it difficult to compare between genotypes. However, all the recipients who developed severe chronic hepatitis or cirrhosis in the graft were infected with HCV-1b, while with a comparable follow-up, 50% of the patients infected by other genotypes had no evidence of chronic hepatitis revealed by their last available biopsy.

Overall, graft loss was more frequent among HCV-infected individuals than among uninfected recipients. This difference was not due to the appearance of liver failure secondary to postnecrotic HCV cirrhosis, but it was related to a significantly higher incidence of chronic rejection in the grafts of HCV-infected patients. Viral diseases, mainly cytomegalovirus infection, have been related to the development of chronic rejection in organ transplantation due to an overexpression of HLA class I antigens in graft cells infected by the virus [29].

Hoffmann et al. [30] have recently linked ductopenic rejection in LT and infection by HCV, but this association has not been reported by other authors [21]. Our data seem to link HCV infection with chronic rejection. However, we cannot be sure whether the mechanism of this association is directly related with the viral infection, as suggested by the presence of graft hepatitis in nearly all cases of chronic rejection in HCV-positive individuals, or with other factors. In addition, donor-recipient HLA matching, which has been reported to be an important risk factor for the development of ductopenic rejection after LT, was not analyzed in the present study.

In summary, LT patients infected by HCV have a survival rate similar to that among other transplant recipients. However, the high incidence of recurrent infection, the severity of graft damage, especially in those infected with HCV-1b, and the association with chronic rejection seem to anticipate a poorer outcome in long-term follow-up. A better definition of the risk factors that determine which individuals are likely to develop the most severe forms of HCV-induced graft injuries should identify candidates for early therapeutic or prophylactic interventions.

References


