A comparison of genotype and markers of disease severity of chronic hepatitis C in patients with and without end-stage renal disease


ABSTRACT

Introduction: This study was conducted to compare the genotype and markers of disease severity of chronic hepatitis C (CHC), namely viral load, alanine transaminase (ALT) levels and histopathological findings on liver biopsy, in patients with and without end-stage renal disease (ESRD).

Methods: This was a cross-sectional retrospective comparative study that included ESRD patients on haemodialysis and non-ESRD patients with CHC who underwent liver biopsy between January 2004 and December 2006. Blood tests for viral load (VL) (hepatitis C virus, ribonucleic acid, polymerase chain reaction), genotyping and ALT were administered. VL was grouped into low (less than 5 log_{10}) and high (more than or equal to 5 log_{10}) VL, genotype into GI and 2, 3, 4, and ALT into normal and elevated ALT. Necroinflammatory activity was grouped into mild (G0-6) and moderate/severe (G7-18) activity, and fibrosis into mild (S0-2) and moderate/severe (S3-6) fibrosis. These variables were compared between the two groups.

Results: Genotype 1 was significantly higher in ESRD patients than in non-ESRD patients, in whom genotypes 2, 3 and 4 were higher. Although the proportion of patients with high VL was greater and the duration of CHC was longer in the ESRD group, the ALT levels were lower and the histopathological grading of necroinflammatory activity and stages of fibrosis were less severe in ESRD compared to non-ESRD patients.

Conclusion: The lower levels of ALT observed in CHC patients with ESRD translate to histopathological benefits.

Keywords: dialysis, end-stage renal disease, genotype, hepatitis C, liver fibrosis

INTRODUCTION

Patients on haemodialysis are at a high risk of acquiring chronic hepatitis C (CHC). The incidence of seroconversion is dependent on many factors, including failure in patient isolation (by dedicated equipment, personnel and days for hepatitis C virus [HCV]-positive patients), a break in the use of cross infection prevention measures (such as the use of disposable gloves), the duration of haemodialysis and the number of blood transfusions.12 The use of dedicated equipment, personnel and days for HCV-positive patients and the retraining of dialysis personnel in the use of cross-infection prevention measures have been shown to reduce the incidence of transmission.12 Furthermore, the growing use of erythropoietin has significantly reduced the requirement for blood transfusions. Still, iatrogenic transmission of HPV among haemodialysis patients remains a challenge worldwide. The risk of death, morbidity, genotyping and the cost of dialysis treatment of CHC patients are much higher than those of non-CHC patients.5-6

Although iatrogenic factors for transmission have been recorded in many studies, few studies have reported viral and patient factors (such as viral genotype, viral titre, liver enzyme and histological changes) in these patients compared to CHC patients with normal renal function. Earlier studies have reported a higher incidence of genotype 1 among patients with end-stage renal disease (ESRD).6-7 In this study, we compared the genotype, viral load, alanine transaminase (ALT) and liver histology (necroinflammatory activity and fibrosis) of ESRD with non-ESRD patients with CHC.

METHODS

This was a cross-sectional, retrospective comparative study conducted at the Hospital Sultanah Bahiyah, Alor

Correspondence to: Dato' Dr Muhammad Radzi bin Abu Hassan Tel: (60) 044131565 Fax: (60) 4740 7373 Email: radzi@erc.gov.my
Star, Kedah, Malaysia. The inclusion criteria were ESRD and non-ESRD patients on dialysis with CHC, who underwent ultrasonography-guided liver biopsy from January 2004 to December 2006. HCV seropositivity was identified using enzyme-linked immunosorbent assay, which was conducted periodically for ESRD patients on follow-up as part of the unit protocol and for non-ESRD patients attending the hospital. All patients who did not undergo a blood test for viral load (VL) (HCV, ribonucleic acid, polymerase chain reaction, iu/mL) in 2006, HCV and ALT levels were higher in ESRD patients as compared to non-ESRD patients. The proportion of patients with ALT > 1 upper limit of normal (ULN) and ALT > 2 ULN were higher in the non-ESRD group (Fig. 1). ALT levels were lower in ESRD patients compared to non-ESRD patients. The proportions of patients with ALT > 1 ULN and ALT > 2 ULN were higher in the non-ESRD group (Fig. 1). ALT levels were lower in ESRD patients compared to non-ESRD patients (Table II). The proportions of patients with moderate/severe grading of necroinflammatory activity and moderate/severe stages of fibrosis were significantly lower in the ESRD group compared to the non-ESRD group.

**DISCUSSION**

In 1989, Choo et al identified the HCV genome and later proved that it was the major cause of non-A, non-B hepatitis. Aach et al and Alter et al have established that most post-transfusion non-A, non-B hepatitis cases are caused by hepatitis C. Dentico et al have described HCV in haemodialysis patients. Since then, others have reported HCV transmission that is unrelated to blood transfusion in dialysis patients. Other researchers have subsequently identified six major serotypes of hepatitis C. Genotyping of the HCV strains has shown a high prevalence of genotypes 1, 3 and 6 in Southeast Asia and has repeatedly revealed the high prevalence of genotype 1 in haemodialysis units. Likewise, our findings show that genotype 1 was the most common HCV genotype in our unit. The higher VLs associated with genotype 1 may be responsible for the higher prevalence of this genotype among haemodialysis patients. Many

---

**Table I. Baseline characteristics of ESRD and non-ESRD patients.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
<th>p-value (χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESRD (n = 28)</td>
<td>Non-ESRD (n = 50)</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>44.89</td>
<td>40.80</td>
</tr>
<tr>
<td>Mean CHC duration (yrs)</td>
<td>4.56</td>
<td>2.25</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>16 (57.14)</td>
<td>17 (34.00)</td>
</tr>
<tr>
<td>Male</td>
<td>12 (42.86)</td>
<td>33 (66.00)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>18 (64.29)</td>
<td>32 (64.00)</td>
</tr>
<tr>
<td>Chinese</td>
<td>7 (25.00)</td>
<td>15 (30.00)</td>
</tr>
<tr>
<td>Indian and others</td>
<td>3 (10.71)</td>
<td>3 (6.00)</td>
</tr>
</tbody>
</table>

* Independent t-test

ESRD: end-stage renal disease; CHC: chronic hepatitis C

---

**Fig. 1 Bar chart shows the distribution of hepatitis C virus genotypes among end-stage renal disease (ESRD) and non-ESRD patients.**
studies have indicated that genotype 1 HCV progresses more often to cirrhosis than other genotypes, and an equally large number of similar studies have indicated that cirrhosis is not more common in genotype 1 than in other genotypes. However, genotype 1 does predispose patients to the development of hepatocellular carcinoma and poor response to interferon therapy. The extent to which these findings could be extrapolated to patients with ESRD is yet to be established. The absence of genotype 6 in the current study may be attributable to the small sample size obtained from only one hospital.

Interest in the histopathology of non-A, non-B hepatitis in ESRD patients on dialysis antedates even the identification of the virus or the recognition of it being the cause of hepatitis in dialysis patients. Studies have identified steatosis, various stages of the inflammatory process from nonspecific hepatitis to chronic active hepatitis, cirrhosis and haemosiderosis. Previous studies have established that dialysis patients with a high grade of portal necroinflammatory activity had significantly higher aspartate transaminase and ALT levels. ALT levels were previously found to be lower in CHC patients with ESRD than in patients without ESRD. Our findings are similar to those of previous studies. This has invariably been ascribed to impaired immune response among ESRD patients on dialysis. The extent to which this lowered biochemical marker of hepatic necroinflammatory activity translates to histopathological benefit is not known.

Many previous studies have attempted to compare liver biopsy findings among CHC patients on dialysis with those of CHC patients without ESRD. These studies have also found that necroinflammatory activity and fibrosis were much lower in ESRD patients with CHC than in CHC patients without ESRD. A study by Akpolat et al, which compared nine CHC patients with ESRD and 37 patients without ESRD, showed that haemodialysis patients may have less active and progressive CHC than patients with normal renal function. As the number of patients studied was small, it was suggested that further studies be conducted. Luzar et al compared 13 CHC patients with ESRD and 154 patients without ESRD and observed that non-uremic patients had more hepatic inflammatory activity and progression of fibrosis compared to uremic patients who were treated with haemodialysis.

The current study compared 28 CHC patients with ESRD and 50 patients without ESRD. The predominant HCV genotype in ESRD patients was type 1. Significant differences were observed between HCV-infected uremic and non-uremic patients in terms of their genotype, ALT levels, extent of necroinflammatory activity and fibrosis, revealing less severe disease activity in the ESRD group. Some studies have compared liver biopsy findings in

Table II. Study characteristics of patients with ESRD and non-ESRD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ESRD</th>
<th>Non-ESRD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>Geno 1: 22 (81.5)</td>
<td>13 (32.5)</td>
<td>0.0002a</td>
</tr>
<tr>
<td>Grade of necroinflammatory activity</td>
<td>Mild (0–6): 26 (92.9)</td>
<td>30 (60.0)</td>
<td>0.0017b</td>
</tr>
<tr>
<td>Stage of fibrosis</td>
<td>Mild (0–2): 24 (85.7)</td>
<td>29 (58.0)</td>
<td>0.0128b</td>
</tr>
<tr>
<td>Viral load</td>
<td>&lt; 5 log10: 5 (18.5)</td>
<td>18 (43.9)</td>
<td>0.0571a</td>
</tr>
<tr>
<td>No. (%)</td>
<td>p-value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Of the 28 ESRD cases, 1 sample could not be tested for Geno class and 1 for viral load, as the samples were inadequate or unsuitable.

b Of the 50 non-ESRD cases, 10 samples could not be tested for Geno class, 2 for ALT and 9 for viral load, as the samples were inadequate or unsuitable.

*Percentages are calculated based on the total number of patients tested for each variable.

a chi-square test b Fisher's exact test

ESRD: end-stage renal disease; ULN: upper limit of normal
CHC patients on dialysis with those of CHC patients who had undergone renal transplant.15-20 There was a larger proportion of renal transplant cases with higher degrees of hepatic fibrosis and liver cell necrosis than ESRD patients on dialysis, suggesting that renal transplantation may lead to more aggressive liver disease. These findings also correlate well with our conclusion that dialysis influences the natural history of CHC in ESRD patients and makes it less aggressive.

One possible explanation for the observed phenomenon is the elevation of the hepatocyte growth factor during dialysis in patients with ESRD.21-25 However, we cannot rule out the possibility that asymptomatic CHC in ESRD patients might have been detected earlier due to better screening, as the two groups were not precisely matched. One group consisted of ESRD patients who were screened periodically for HCV and liver disease, while the other consisted of patients with symptomatic liver disease. The fact that the duration of disease in ESRD patients was twice as long as in those without ESRD may at least partially offset this. Although the difference in the duration of disease was highly significant statistically, this should be interpreted with caution, considering the slow progression of CHC, often over the course of decades. Moreover, since our sample size was small, these findings need to be confirmed with larger studies. In conclusion, this study has shown that necroinflammatory activity and fibrosis are much less prevalent among ESRD patients with CHC than among CHC patients without ESRD despite the longer duration of illness and a higher VL in the ESRD group.

ACKNOWLEDGEMENT

The authors acknowledge the technical assistance rendered by the Malaysian Liver Foundation, Petaling Jaya, Selangor Darul Ehsan, Malaysia.

REFERENCES