Hepatitis C Virus Antibody in Patients on Chronic Hemodialysis in Fukuoka, Japan

Masakazu Washio¹,², Masato Ikeda², Seiya Okuda¹, Sadatoshi Nakamura³, Tohma Fukumitsu¹, Tetsuya Mizoue², Takesumi Yoshimura², and Masatoshi Fujishima¹

Anti-HCV was examined in 454 patients on chronic hemodialysis (HD) in Fukuoka in 1990. The anti-HCV positive rate was significantly greater in those with than in those without blood transfusion (40.5% vs 11.7% for males, p<0.01, and 29.4% vs 5.6% for females, p<0.01). The anti-HCV positive rate increased with the duration of HD treatment among all patients except for the non-transfusion female patients. Blood transfusion thus appeared to be a major route of HCV infection in HD patients as had been reported previously. The anti-HCV positive rate was 2.6 times higher in those who had less than 5 years HD treatment but had never received a blood transfusion than found in the blood donors of Kitakyushu Red Cross Blood Center, adjusted by age. These results suggest that HD treatment might increase the exposure to HCV infection apart from blood transfusion. J Epidemiol, 1991; 1: 31-36.

case chronical hemodialysis, hepatitis C virus, blood transfusion, renal failure

There have been many patients on chronic hemodialysis (HD) who used to suffer from anemia until recombinant erythropoietin became clinically available. They were often at a high risk of posttransfusion hepatitis due to frequent blood transfusions for anemia¹.²

Although more than 90% of posttransfusion hepatitis are non-A non-B hepatitis³, infections due to non-A non-B hepatitis virus have only been suggested by epidemiologic arguments⁴. Recently, Choo et al.⁵ and Kuo et al.⁶ isolated the gene products of the hepatitis C virus (HCV) and a test for antibodies to HCV has become available.

Very recently, Yamaguchi et al.⁷ reported that the anti-HCV positive rate was high in HD patients even in those without undergoing blood transfusions and the positive rate of HCV infection increased with the duration of HD in Kumamoto prefecture, Japan. However no detailed analysis by sex and age group was given in this paper.

The present study intends to evaluate the effect of blood transfusion and conditions of renal failure with HD treatment on the anti-HCV positive rate.

STUDY SUBJECTS AND METHODS

Two hundred and eighty three HD patients from a hospital in Kitakyushu city and 171 HD patients from a hospital in Fukuoka city were investigated. They consisted of 280 males and 174 females, with a mean age of 54.7 years old, ranging from 14 to 87 years old. The mean duration for hemodialysis was 7.2±5.9 (±SD) years. Of these 454 patients, 228 had a history of blood transfusion and 175 had a habit of drinking. Hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs) were tested by the enzyme immunoassay (Dainabot Co., Tokyo), and anti-HCV antibody was also tested by the enzyme immunoassay (Ortho Co., Tokyo).

A statistical analysis was performed using the statistical package of the Statistical Analysis System (SAS Institute Inc). A statistical significance test was made...
by the chi-square test and by the trend test using a logistic regression model and the Mantel Haenszel test. The ratio of the observed number of cases to the expected number (O/E ratio) was calculated to see the effect of blood transfusion and conditions of renal failure with HD treatment on the anti-HCV positive rate. The expected number was calculated based on the anti-HCV positive rate among blood donors at the Kitakyushu Red Cross Blood Center.7

RESULTS

As shown in Table 1, the anti-HCV positive rate in patients with a history of blood transfusions was greater than in those without (male p<0.01, and female p<0.01). Similarly, the rate was also greater in patients with anti-HBs positive (male p<0.01, and female p<0.01) than those without regardless of sex. Among females, the anti-HCV positive rate was significantly greater in those with a habit of drinking (p<0.05) than those without such a habit.

The anti-HCV positive rate increased with the duration of HD treatment in both males who had blood transfusions (p<0.001) as well as in those who did not (p<0.05). Among females, however, the rate increased only in those with blood transfusions (p<0.001) but not in those without transfusions (Table 2). As shown in Table 3, the anti-HCV positive rate did not increase with age for patients either with or without blood transfusions regardless of sex.

The anti-HCV positive rate increased with the duration of HD treatment in both anti-HBs positive and negative patients with blood transfusions (p<0.005 and p<0.005) but did not increase in those without transfusions (Table 4). The positive rate of anti-HCV was significantly higher in blood transfusion positive patients than in blood transfusion negative patients among either anti-HBs positive (p<0.05) or anti-HBs negative patients (p<0.05). After correction by duration of HD treatment, the positive rates of anti-HCV were similar between patients with anti-HBs positive and those without regardless of blood transfusions.

As shown in Table 5, O/E ratio of anti-HCV positive patients was 15.6 (p<0.001) in HD patients with blood transfusions, 3.5 (p<0.005) in those without blood transfusions or 2.6 (p<0.05) in those without blood transfusions and with less than 5 years' HD treatment.

DISCUSSION

In the present study, 103 (23%) of the 454 HD patients were anti-HCV positive. This rate was similar to that among HD patients in both Kumamoto prefecture (22%)6 and Nagano prefecture (21%)8, while it was slightly higher than that in Ishikawa prefecture (16%)9. There was no difference in the mean age of HD patients between the present study and other studies6,8,9. The anti-HCV positive rate among HD patients was much higher than that among blood donors throughout Japan (1.3%)10 as well as among those from Fukuoka prefecture (2.1%)10. This crude rate of 23% in the present study was also similar to the rate among HD patients in Spain (20%)1, while it was much higher than that in either West Germany (10%)11 or the United Kingdom (1%)12. The far lower rate of positive anti-HCV among HD patients in United Kingdom seems due to the very low rate among blood donors.

### Table 1. Positive rate of anti-HCV in chronic hemodialysis patients

| Male | Female |
|------|--------|
| No. of subjects | Positive rate (%) | No. of subjects | Positive rate (%) |
| HBs antigen | | | |
| + | 13 | 15.4 | N.S. | 3 | 33.3 | N.S. |
| - | 267 | 25.1 | N.S. | 171 | 19.3 | N.S. |
| HBs antibody* | | | |
| + | 66 | 37.9 | ** | 35 | 31.4 | $ |
| - | 110 | 18.2 | N.S. | 72 | 16.7 | |
| Diabetic nephropathy | | | |
| + | 39 | 26.0 | N.S. | 28 | 10.7 | N.S. |
| - | 239 | 24.4 | N.S. | 146 | 21.2 | N.S. |
| A habit of drinking | | | |
| + | 133 | 26.3 | N.S. | 42 | 31.0 | $ |
| - | 147 | 23.1 | N.S. | 132 | 15.9 | |
| A history of blood transfusions | | | |
| + | 126 | 40.5 | ** | 102 | 29.4 | $ |
| - | 154 | 11.7 | N.S. | 72 | 5.6 | |
| Kitakyushu City Hospital | | | |
| 176 | 25.6 | N.S. | 87 | 21.5 | N.S. |
| Fukuoka City Hospital | | | |
| 104 | 23.1 | N.S. | 87 | 16.4 | N.S. |

* the study subjects consisted only of patients from one hospital in Kitakyushu City, because at the hospital in Fukuoka City, the HBs antibody test was done only on patients with positive HBs antigen.

* p<0.05, ** p<0.01, $ p<0.1. comparison of positive rate of anti-HCV was made between + and - for each medical condition and personal history.
Table 2. Positive rate (%) of anti-HCV antibody in chronic hemodialysis patients according to the duration of hemodialysis treatment by blood transfusion.

| Duration of HD treatment (year) | BT (+) | BT (-) | BT (+) | BT (-) |
|--------------------------------|--------|--------|--------|--------|
|                                | Male   | Female | Male   | Female |
| No. of subj. | Rate (%) | No. of subj | Rate (%) | No. of subj | Rate (%) | No. of subj | Rate (%) | No. of subj | Rate (%) |
| 0-4 | 36 | 22.2 | 97 | 6.2 | 34 | 17.7 | 37 | 5.4 |
| 5-9 | 27 | 33.3 | 36 | 19.4 | 29 | 13.8 | 25 | 8.0 |
| 10-14 | 21 | 38.1 | 12 | 25.0 | 17 | 29.4 | 8 | 0.0 |
| 15-19 | 24 | 58.8 | 9 | 22.2 | 20 | 70.0 | 2 | 0.0 |
| 20- | 8 | 75.0 | 0 | — | 2 | 50.0 | 0 | — |
| Total | 126 | 40.5 | 154 | 11.7 | 102 | 29.4 | 72 | 5.6 |

Trend test*: p<0.001, p<0.05, p<0.01, N.S.
M.H. test#: p<0.01

BT: a history of blood transfusion.
Trend test*: trend test by logistic regression model.
M.H. test#: Mantel Haenszel test, comparison of positive rate of anti-HCV between patients with blood transfusion and those without.
N.S.: not significant.

Table 3. Positive rate (%) of anti-HCV in chronic hemodialysis patients according to the age by blood transfusion.

| Age (years old) | BT (+) | BT (-) | BT (+) | BT (-) |
|----------------|--------|--------|--------|--------|
|                | Male   | Female | Male   | Female |
| No. of subj. | Rate (%) | No. of subj | Rate (%) | No. of subj | Rate (%) | No. of subj | Rate (%) |
| 10-19 | 0 | — | 1 | 0.0 | 2 | 0.0 | 0 | — |
| 20-29 | 4 | 50.0 | 2 | 0.0 | 2 | 0.0 | 0 | — |
| 30-39 | 10 | 40.0 | 18 | 16.7 | 7 | 14.3 | 5 | 0.0 |
| 40-49 | 33 | 48.5 | 39 | 10.3 | 27 | 51.9 | 22 | 46 |
| 50-59 | 26 | 42.3 | 39 | 12.8 | 24 | 37.5 | 18 | 3.6 |
| 60-69 | 34 | 32.4 | 35 | 11.1 | 24 | 12.5 | 22 | 9.1 |
| 70- | 19 | 36.8 | 20 | 0.0 | 16 | 18.8 | 5 | 0.0 |
| Total | 126 | 40.5 | 154 | 11.7 | 102 | 29.4 | 72 | 5.6 |

Trend test*: N.S., p<0.01
M.H. test#: N.S.

BT: a history of blood transfusion.
Trend test*: trend test by logistic regression model.
M.H. test#: Mantel Haenszel test, comparison of positive rate of anti-HCV between patients with blood transfusion and those without.
N.S.: not significant.

donors (0.2%)13). In contrast, the anti-HCV positive rate among HD patients in the present study (23%) was much lower than that in Taiwan (34% or 47%)14,15 although the rate among blood donors in Japan (1.3%)10 is similar to that in Taiwan (0.8%)14. The difference in anti-HCV positive rate among HD patients may reflect the effectiveness of infectious control in HD units.

The higher positive rate of anti-HCV among HD patients compared to blood donors in Japan has been explained by HCV infection associated with blood transfusions6,8,9. Our study also demonstrated a significantly higher positive rate in patients with blood transfusion than in those without transfusion (40.5% vs. 11.7% for males, p<0.01 and 29.4% vs. 5.6% for females, p<0.01). Present result confirmed a close relationship between HCV infection and blood transfusion.

Positive rate of anti-HCV is reported to increase with the duration of HD treatment6,11,15. In our
Table 4. Prevalence rate (%) of anti-HCV antibody in chronic hemodialysis patients according to the duration of hemodialysis therapy by HBs antibody and blood transfusion.

| Duration of HD treatment (years) | Hbs antibody (+) | Hbs antibody (-) |
|---------------------------------|------------------|------------------|
|                                 | BT (+)           | BT (-)           | BT (+)           | BT (-)           |
|                                 | no. of subj.     | no. of subj.     | no. of subj.     | no. of subj.     |
| 0-4                             | 8                | 8                | 30               | 61               |
| 5-9                             | 16               | 12               | 24               | 16               |
| 10-14                           | 13               | 3                | 20               | 9                |
| 15-19                           | 30               | 3                | 17               | 3                |
| 20-                             | 8                | 0                | 2                | 0                |
| Total                           | 75               | 26               | 93               | 89               |
|                                 | 45.3             | 7.7              | 26.7             | 7.9              |

Trend test* : trend test by logistic regression model.
M.H. test#1 : Mantel Haenszel test, comparison of positive rate of anti-HCV between patients with blood transfusion and those without it.
M.H. test#2: Mantel Haenszel test, comparison of positive rate of anti-HCV between patients with HBs antibody positive and those without it.
N.S. : not significant.

In Table 4, the study subjects consisted only of patients from one hospital in Kitakyushu City, because at the hospital in Fukuoka City, the HBs antibody test was done only on patients with HBs antigen positive.

Table 5. O/E ratio of anti-HCV positive patients in chronic hemodialysis patients by blood transfusion.

|                        | O    | E    | O/E  | p^2  |
|------------------------|------|------|------|------|
| With blood transfusion*| 50   | 3.21 | 15.58| <0.001|
| Without blood transfusion*| 8   | 2.31 | 3.46 | <0.005|
| Without blood transfusion and with less than 5 year hemodialysis therapy*| 6   | 2.34 | 2.35 | <0.05  |

*Kitakushu, Kitakyushu and Fukuoka.
E : based on the prevalence rate of anti-HCV among blood donors in Kitakyushu.
p-value by chi-square test using (O-E)/E

study, it increases with the duration of HD treatment in patients with blood transfusion. This result may be explained by the two following possibilities. Firstly, HD patients with longer duration of HD treatment may receive more units of blood transfusion. Secondly, screening program for blood donors to avoid posttransfusion hepatitis was improved with time.

The hepatitis B virus (HBV) is horizontally transmitted by either blood transfusion or sexual contact, and vertically transmitted during child birth. HBsAg disappears after recovery from the symptoms and signs of HBV infection, followed by the appearance of anti-HBs within 1-3 months in the majority of patients with HBV infection. In infants, however, HBsAg positivity continues and anti-HBs fails to appear in the serum. In our study, the positive rate of anti-HCV was similar between HBsAg positive and negative patients, suggesting that HCV might not be transmitted vertically. After correction by duration of HD treatment, the positive rates of anti-HCV were similar between anti-HBs positive patients and negative patients, and increased with the duration of HD treatment only in patients with blood transfusion regardless of anti-HBs positivity. These results suggest that...
HCV may be transmitted horizontally, mainly by blood transfusion. Screening program of blood donors for HBsAg from 1971 may explain the reason why blood transfusion did not affect the incidence of coinfection of HCV and HBV.

Compared to blood donors, the positive rate of anti-HCV was 3.5 times higher in HD patients without blood transfusion, and 2.6 times higher even in blood transfusion negative patients with a short duration of HD treatment. These results suggested that the condition of end-stage renal failure may increase the chance of HCV infection apart from the effect of blood transfusion. The anti-HCV positive rate among HD patients is reported to be higher than that among continuous ambulatory peritoneal dialysis patients (30% vs 15%)40. In HD units, patients may have a chance of exposure to blood spills or parenteral routes of contamination. In Taiwan, where HD patients are reported to be higher than that among continuous ambulatory peritoneal dialysis patients (30% vs 15%)40. In HD units, patients may have a chance of exposure to blood spills or parenteral routes of contamination. In Taiwan, where HD patients have the very high anti-HCV positive rate of 34% or 47%14,15, the rate in patients with blood transfusion (43%) is not higher than that in those without it (51%)40. In our study, anti-HCV positive rate of male patients without blood transfusion increased with HD duration but female did not. Small number of female patients in the present study might explain the reason why their anti-HCV positive rate failed to show the relationship between the duration of HD treatment and anti-HCV positive rate. Further investigations using patients just before starting HD treatment should be carried out to clarify whether or not end-stage renal failure patients in Japan have an increased risk of HCV infection apart from any influence of HD treatment.

The positive rate of anti-HCV among blood donors is reported to increase with age7,10 but did not do so in our HD patients. The positive rate even among elderly blood donors is about 3.5%, which is half of that among HD patients without blood transfusion. The much increased positive rate during HD treatment may conceal the relationship between the positive rate and age.

Erythropoietin treatment for anemia may decrease the total amount of blood transfusion, and an improved screening program of blood donors for anti-HCV will decrease the incidence of HCV infection after blood transfusion. However, even blood transfusion negative HD patients had a high positive rate of anti-HCV in the present study. Since HCV plays an extremely important role in the pathogenesis of hepatocellular carcinoma and liver cirrhosis in Japan and anti-HCV positive HD patients are at a high risk of chronic liver disease19, it is important to establish the best protocol for reducing the incidence of HCV infection among HD patients.

ACKNOWLEDGEMENT

We thank B.T. Quan from Kyushu University for comments on the manuscript.

REFERENCES

1. Esteban JI, Esteban R, Viladomiu L, et al. Hepatitis C virus antibodies among risk groups in Spain. Lancet, 1989; 2: 294-296.
2. Feinman SV, Berris B and Bojarski S. Posttransfusion hepatitis in Toronto, Canada. Gastroenterology, 1988; 95: 464-469.
3. Galbraith RM, Dienstag JL, Purell RH, et al. Non-A non-B hepatitis associated with chronic liver disease in a hemodialysis unit. Lancet, 1979; 1: 951-953.
4. Choo Q-L, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A non-B viral hepatitis genome. Science, 1989; 244: 359-362.
5. Kuo G, Choo Q-L, Alter HJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A non-B viral hepatitis genome. Science, 1989; 244: 359-362.
6. Yamaguchi K, Mishimura Y, Fukunaka N, et al. Hepatitis C virus antibodies in hemodialysis patients. Lancet, 1989; 335: 1406-1410.
7. Manabe K, Tsukuba K, Asakura T, et al. The prevalence of anti-HCV among blood donors. J Fukuoka Med Tech, 1991; 1: 50. (Japanese).
8. Oguchi H, Tokunaga S, Terashima M, et al. Prevalence of hepatitis C antibody in hemodialysis patients and staff members. J Jpn Soc Dial Ther, 1990; 23: 1143-1148. (Japanese with English abstract)
9. Nomura H, Yajima M, Minamoto M, et al. Antibodies to hepatitis C virus in hemodialysis patients. J Jpn Soc Dial Ther, 1990; 23: 1307-1312. (Japanese with English abstract)
10. Watanabe H, Tanaka J, Ohishi K, et al. Prevalence of the HCV associated markers among blood donors in Japan. Jpn J Clin Med, 1991; 49: 357-365. (Japanese)
11. Schrijver U, Roggendorf M, Ernst G, et al. Hepatitis C virus antibodies in haemodialysis patients. Lancet, 1990; 335: 1469.
12. Moximer PP, Choon BJ, Litton PA, et al. Hepatitis C virus antibody. Lancet, 1989; 2: 798.
13. Bind AM, Cudd AA, Cohen BJ, et al. Low prevalence of antibody to hepatitis C virus in north east England. J Med Virol, 1990; 32: 243-248.
14. Lee SD, Chan CY, Wang YJ, et al. Seroprevalence of Hepatitis C virus infection in Taiwan. Hepatology, 1991; 13: 830-833.
15. Liu HL, Huang CC, Sheen IS, et al. Prevalence of antibodies to hepatitis C virus in the hemodialysis unit. Am J Nephrol, 1991; 11: 192-194.
16. Blumberg BS, London WT. Hepatitis B virus and the prevention of primary cancer of the liver. J Natl Cancer Inst, 1985; 74: 267-273.
17. Achard RD. Viral hepatitis. In: Feigin RD and Cherry JD, eds. Textbook of pediatric infectious diseases. 2nd ed. W.B. Saunders, Philadelphia, London, Toronto, Sydney, Tokyo and Hong Kong, 1987: 716-741.
18. Perez-Fontan M, Monealian J, Rodriguez-Carrona A, et al. Prevalence of antihepatitis C antibodies in patients
treated with continuous ambulatory peritoneal dialysis and hemodialysis. Nephron, 1991; 58: 381-382.

19. Tanaka K, Hirohata T, Koga S, et al. Hepatitis C and hepatitis B in the etiology of hepatocellular carcinoma in the Japanese population. Cancer Res. 1991; 51: 2842-2847.

20. Ponz F, Campistol JM, Barrera JM, et al. Hepatitis C virus antibodies in patients on hemodialysis and after kidney transplantation. Transplant Proc, 1991; 23: 1371-1372.