Hepatitis C virus infection in Saudi Arabian recipients of renal transplantation

AyoolaE. A. [1], Srinivas KV [2], Gadour M O EH [3]

Abstract

Background: Studies of recipients most of whom had been infected prior to transplantation, had yielded conflicting conclusions in regard to the clinical impact of hepatitis C virus [HCV] infection. We determined the frequency of new HCV infection and assessed its effect on patient – and graft – survival and occurrence of chronic hepatitis in renal transplant recipients.

Methods: We studied 54 Saudi recipients [37 males and 17 females; mean age (SD); 38.2(17.1) years] they were anti-HCV negative at the time of transplantation and followed for 3 to 19 years [mean = 8.1]. The prevalence of anti-HCV at the time of censorship was compared with the rates in 99 hemodialyzed patients, 400 healthy volunteers and 113 hospitalized patients.

Results: The period prevalence of anti-HCV in recipients was 37% [20 of 54], compared to hemodialyzed patients [17.1%], hospital patients [1.8%] and healthy volunteers [2.3%]. [$P < 0.01$]. Seroconversion to anti-HCV positivity occurring from 2 to 11 years [mean =7.8] after transplantation and was not influenced by age, gender or source of donor kidney. Cumulative frequency of HBsAg was 14.8%. Graft loss occurred in 1 HCV positive recipient. Serum aminotransferase was abnormal [>2 – fold elevation] in 2 anti-HCV positive recipients transiently. No deaths occurred among the recipients.

Conclusion: The acquisition of new HCV infections had a relatively high frequency among renal transplant recipients in the study. The course of the infection was benign in the medium term, with no discernible progression to clinically recognized chronic liver disease. Further studies are required to determine cost- benefit of antiviral therapy in such patients.

Keywords: Hepatitis B; Renal transplantation; Chronic liver disease; Saudi Arabia

Introduction

Hepatitis C virus (HCV) infection is frequent in renal transplant recipients among whom it has a variable prevalence of between 6.2% and 65.8% [1-5]. Studies of recipients, the majority of whom had been HCV- infected prior to transplantation, produced conflicting conclusions in regard to the incidence of graft loss, patient survival and occurrence of liver diseases [1-2]. In some reports, HCV infection was associated with deleterious effects that included higher frequency of graft loss and patient mortality [6-11]. Others reported low frequencies of HCV-induced chronic hepatitis [12] and insignificant impact on the survival of patients or grafts [13]

Information is scant on the natural history and clinical significance of HCV infection that was acquired after transplantation [14]. We analyzed renal transplant recipients that were followed in a tertiary hospital in Saudi Arabia in order to determine the incidence of HCV infection after transplantation and its relationship to graft survival, the development of chronic liver disease and patient- survival. We report the period - prevalence and, the cumulative incidence of anti-HCV in a cohort of renal transplant recipients who were followed in a tertiary regional hospital in Saudi Arabia. The effects of newly acquired HCV infection on graft survival, patient mortality and occurrence of chronic liver disease were evaluated.

Materials and Methods

The subjects were 54 renal transplant recipients [37 males and 17 females] who were HCV negative at the time of transplantation and were followed for 3 to 19 years [up to June 2002] in the Nephrology unit [Table 1]. The transplantation was carried out in special centers located in India [36 cases], the USA [10 cases] and Riyadh, Saudi Arabia [8 cases] The recipients were evaluated clinically and by laboratory tests at regular intervals [3 – 4 months] in the clinics and were maintained on immunosuppressive drugs [cyclosporine, azathioprine and prednisolone] in doses adjusted as indicated [Table 2].

Ninety-nine patients of 146 hemodialyzed patients, who were negative on entry to the dialysis program and had been followed for 3 to 19 years during the same period as the renal transplant recipients, were enrolled and their data were analyzed. They had been re-tested for HBsAg, anti HCV at intervals ranging from 3 to 6 months. The remaining 47

1. Divisions of Gastroenterology. Department of Medicine K. F. C. H. Gizan Saudi Arabia
Current address: HEAL Medical Group PO Box 1552 Dover DE 19904
2. Divisions of Gastroenterology. Department of Nephrology. King Fahd Central Hospital Gizan Saudi Arabia
3. Current address: Department of Medicine. Omdurman Islamic University.

correspondence to: Prof. E. Ayobanji. Ayoola.
E- mail: bayoola@aol.com , bayoola@yahoo.com

Table 1: Demographic data and prevalence of anti - HCV and HBsAg in renal transplantation recipients, hemodialyzed patients and control groups

	Recipients	HD patients	Healthy controls	[a]Wards
No studied	54	99	400	113
No of male/female	37/17	41/58	244 /156	71 /42
Saudi/non – Saudi	54/1	96/3	374/26	105/8
Age in years				
Range	25 - 60	10 – 80	10 – 78	14 - 95
Mean (SD)	38.2 (17.1)	39.6 (20.7)	40.3 (18.5)	49.8 (20.2)
Anti – HCV				
No. [%] positive	20 [37.0]	9 [2.3]	17[17. 1]	2 [1.8]
{95% CI}	{24.3 – 51.3}	{1.0 – 4.2}	{10.3 – 26.1}	{0.2 – 6.2}
HCV – RNA (T/P)	8/6	7/6	5/4	2/2
HBsAg				
No. [%] positive	8 [14.8]	29 [7.3]	18 [18.2]	8 [7.1]
{95% CI}	{6.6 – 27.1}	{4.9 – 10.2}	{11.2 – 27.2}	{3.1 – 13.5}

[a] Hospitalized patients; [b] No. tested/No positive; No. , number; CI, confidence intervals

patients [32.2%] who were positive for anti–HCV before hemodialysis were excluded. Separate machines were used exclusively for those who were HBsAg – positive[15]

For comparison of prevalence rates, 2 groups served as controls [Table 1]. One group comprised 400 apparently healthy volunteers who were recruited from among the residents of the same locality as the patients[15]. None had any history or clinical evidence of hepatobiliary disease, previous blood transfusion or history of commercial blood donation. The subjects in the other group were 113 hospital patients with various chronic illnesses requiring frequent clinic visits and occasional admissions as previously described [15]. The periods of follow-up prior to the inclusion in the study varied from 3 to 10 years and the various diagnoses in these patients are summarized in table 2.

Data obtained from the subjects and the respective medical records included age, gender, history of jaundice, blood transfusions, and episodes of clinically - recognized hepatitis, jaundice or elevated serum ALT and history of travel or blood transfusions. Complete blood count (CBC), electrolytes, urea, creatinine and calcium alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, and albumin were estimated at each clinic visit. Serum ALT level higher than 2 times the upper limit of normal [2XULN; normal up to 65 iu/l] was considered abnormal. Antibodies to hepatitis C virus [anti -HCV] were detected using a third generation enzyme immunoassay [Murex III].

All positive anti – HCV antibody tests were confirmed by positive immunoblot assays [HCV Blot 3.0 Genelabs Diagnostics and Ortho Diagnostics Systems Raritan NJ]. Serum samples obtained from anti - HCV- positive recipients [n = 8], hemodialyzed patients [n=7], healthy volunteers [n=5] and hospital patients [n=2] were tested for HCV – RNA by reverse transcription - polymerase chain reaction [RT–PCR using specific primers from the 5'-UTR, [Amplicor, Roche Diagnostic systems[16] Hepatitis B surface antigen [HBsAg], total antibody to hepatitis B core antigen [anti-HBc], antibody to HBsAg [anti-HBs], total antibody to hepatitis A virus [anti-HAV], were detected by using commercial enzyme immunoassays [EIA] kits [Abbott Laboratories Chicago II.].

Protocol liver biopsies were obtained in all patients who were considered for transplantation and as part of the policy, only those who had normal histology were transplanted. Liver biopsy was done in hemodialysis patients or in the post – transplantation period only when clinical, laboratory and ultrasonographic assessment indicated the presence of liver disease.

Table 2: Diagnoses in 113 patients tested as controls

Diagnosis		***No of patients***
Chronic cardiac disorders		**14**
- Ischemic heart disease	9	
- Dilated cardiomyopathy	2	
- Rheumatic heart disease	3	
Chronic obstructive lung disease		**8**
Hemoglobinopathies		**12**
- Sickle cell disease	9	
- Thalasaemias	3	
Diabetes mellitus		**15**
Hypertension		**6**
Digestive/hepatic disorders:		**25**
- Irritable bowel disease	9	
- Peptic ulcer disease	8	
- Non – cirrhotic portal hypertension	8	
Central nervous disorders		**11**
- Epilepsy	2	
- CVA	9	
Chronic renal failure		**10**
Others		**12**
- Fractures on traction	8	
- Osteoathropathy	4	

Statistical analysis

The respective numbers of patients who were positive for anti-HCV at the end of the designated study period [June 2002] were used to calculate the prevalence among renal transplant recipients and hemodialysis patients. For the apparently healthy volunteers and hospitalized patients, the prevalence rates of HCV or HBV were determined from a single blood test during the survey. Data were presented as means and standard deviations for continuous variables that are approximately normally distributed, as medians for skewed variables and as percentages for discrete or categorical variables. Comparisons of data in proportions were performed with the X^2 test or Fisher's exact test. Differences between mean values were determined using Student t-test and Mann-Whitney U-test. Where applicable, the odds ratios [OR] with the 95% confidence intervals [95% CI] were calculated. A p value of less than 0.05 was considered as significant.

Results

The recipients had been followed for an average period of 11.4 years [556 person- years]. The duration of post-transplantation follow–up was 4 years [in 1 recipient], 6-10 years [in 21 recipients], 11-15 years [in 27 recipients] and more than 16 years [in 5 recipients]. The proportion of females in the group of hemodialyzed patients was significantly higher than in other groups; [p = 0.002].

The prevalence rates of anti-HCV and markers of HBV at the time of censorship, are summarized in table 1. A statistically significant difference [OR = 2.84; 95% CI of 1.24 – 6.51; p = 0.01] was found between the prevalence of anti – HCV in the transplant recipients [37%; 95% CI, 24.3 – 51.3] and the rate [17.1%; 95% CI, 10.3 – 26.1] in hemodialysis patients The prevalence in recipients was significantly higher than the rate in the group of healthy persons [37% vs.2.3%; OR =25.56; 95% CI of 10.07 – 66.35, p = 0.000]; and the rate in hospital patients [37% vs.1.8%; OR = 32.65; 95% 6.82 –213.52; p= 0.000]

Among the 20 recipients who became positive for anti-HCV in the post transplantation period 7 of 8 serum samples tested for HCV RNA were positive. As summarized in table 3, comparison of recipients who acquired HCV and those who remained HCV-negative revealed no statistically significant differences in relation to gender, age, source of donor kidneys and follow-up period. HBsAg was positive in 1 of 20 HCV-positive and 7 of 34 HCV-negative patients.

Recipients who became positive for anti HCV or HBsAg were compared to those who remained negative for both markers during the follow-up period [Table 4]. No significant differences were found in relation to the peak ALT levels, duration of follow up, and the intervals from transplantation to sero -conversion. Most of the new HCV infections [13 of 20; 65%] occurred within 2 years of transplantation [Table 4]. The peak ALT ranged from 15 to 195 iu/l [median = 32] in the recipients. Serum ALT was abnormal [> 2 fold increase] at least once during the follow up in 2 of the 20 HCV- positive recipients [peak values of 129, and 195 iu/l] and in 2 of 34 HCV- negative recipients [peak values of 118 and156] but these abnormal levels were not sustained or persistent. Serum albumin levels were normal in all of the patients. None showed clinical features or ultrasonographic evidence of chronic liver disease, and the abnormalities of aminotransferase levels were transient.

Graft failure occurred in only 1 patient, a 62-year-old male who was transplanted in India 14 years before inclusion in the study became HCV-positive five years after the transplantation, and was re-grafted two years thereafter. No death occurred among the recipients during the follow-up period.

Discussion

This study showed that 37% of the recipients who were negative at the time of transplantation became positive for anti-HCV during the follow-up period, indicating a relatively high prevalence in the studied cohort. A similar survey among Korean recipients reported that 19.6% persons acquired anti-HCV after transplantation [14]. In a study from Hong Kong, the incidence of new HCV infection was 0.45% per patient-year in 185 recipients who were followed for 24 months [3].

The exact timing and mode of infection are often unknown but it is probable that the HCV infection occurring in previously negative recipients might have been transmitted through blood transfusion before or at the time of operation. However, it would be difficult to exclude acquisition of HCV from the community through unknown modes in those who became positive several years after the respective transplantation. None of the factors that were assessed [namely, gender of the recipients, the age at the time of transplantation and, source of the donor kidneys] separated those who became infected from those who remained negative for anti-HCV.

Table 3. Demographic and clinical characteristics in anti – HCV -positive or - negative recipients

	Anti - HCV		All
	Positive	**Negative**	
Number	20	34	54
Males: Females	12/8	25/9	37/17
Age: mean [SD] years.	35.3 [15.7]	39.7 [17.9]	38.2 [17.1]
Donor kidney:			
@LU/LR/CU	13/5/2	23/3/8	36/8/10
Location of transplantation			
India/USA/Saudi Arabia	13/2/5	23/8/3	36/10/8
Lab. data: median [range]+			
ALT iu/l	48.0 [15 - 195]	57.5 [11 - 156]	32 [11 - 195]
AST iu/l	35.5 [17 - 116]	30 [13 - 178]	19 [13 - 178]
Urea mmo/l	7.4 [4.5 – 10.4]	8.4 [3 – 30.4]	7.7 [3 – 30.4]
Creatinine umol/l	128 [85 - 221]	30 [81 -619]	128 [81-619]
Albumin, g/l	34 [26 - 42]	36 [31 -43]	36 [26- 43]
Drugs: mean [SD] dose (mg)			
Cyclosporin	141.7 [49.9]	130.3[44.3]	148.4[52.0]
Azathioprine	56.5 [19.3]	56.3 [23.3]	56.7[17.3]
Prednisolone	8.7 [3.7]	7.9 [2.1]	9.1[4.3]

+For each patient the highest values during the follow – up were taken for all tests except for lowest value of albumin. Lab, laboratory

@LU, Living- unrelated; LR, Living –related; CU, Cadaver- unrelated

There are conflicting data with regard to the clinical outcome of HCV infection acquired prior to transplantation and thus, the higher incidence of liver diseases and related deaths among HCV-positive recipients that was reported by some authors [7,9,11] and was not supported by other investigators [1, 2, 13]. The heterogeneity of patient characteristics in those studies, the timing of infection in individual cases and, the slow evolution of disease in HCV infection may be responsible for the discordant results. Therefore, the increased incidence of liver diseases and mortality among recipients who acquired HCV before treatment but not among those who were infected at the time of treatment is probably a consequence of a longer duration of HCV infection[17].

The natural history of HCV infection that is acquired in the post-transplantation period is not well understood, but an accelerated and sometimes aggressive course of HCV related hepatitis after renal transplantation has been reported[18]. However, our study in which abnormal levels of aminotransferases [> 2 fold elevation] occurred in only two of the anti-HCV-positive patients transiently, and in which none of the recipients developed clinical evidence of chronic liver disease is in agreement with the observations of a relatively benign clinical course in recipients infected by HCV alone [5,7, 14]. It was estimated that 30-60 % of HCV-positive recipients have persistently normal ALT serum levels[2, 9].

Liver biopsy was not performed in any recipients in the study. The consensus statements from the National Institute of Health [NIH], World Health Organization [WHO] and other countries including Saudi Arabia did not recommend liver biopsy or treatment for hepatitis C patients with normal ALT except in the context of clinical trials [23, 24, 25]. However, hepatitis C patients may have fluctuating levels of aminotransferase and 30% of hepatitis C patients with persistently normal ALT levels have histological evidence of liver disease[26].

Most reports suggested a benign effect of infection on graft survival[1,3,7], while others reported increased incidence rates of graft loss in recipients with HCV infection, compared to those who were negative. The low incidence of graft rejection, occurring in only one HCV-positive recipients indicated the lack of significant impact of HCV infection on graft survival in those who were infected after transplantation. None of the studied recipients had died by the time of censorship. The impact of HCV on the mortality among recipients remains controversial. A study involving a large number of recipients concluded that recipients who are anti-HCV positive do not have an increased risk of death after transplantation compared with hepatitis C-negative recipients[1]. However, some reports have shown an increased mortality among those who acquired HCV before transplantation; but not among those who acquire the infection after transplantation, indicating a major influence of the duration of infection [4, 17]. Some reports indicated that the deaths in HCV-positive patients that are more often unrelated to liver diseases had lower rates than in recipients who are HBV-positive [2, 12].

It remains unclear whether anti-viral therapy is indicated, safe or beneficial in recipients who are infected by HCV after transplantation. Major concerns about toxicity and renal impairment have limited the use or the success of interferon treatment among patients with functioning grafts [27-29]. For example, 6 of 16 recipients with functioning grafts who were treated with interferon, developed renal impairment [28]. Theret et al[30] treated 13 post transplantation patients with interferon and therapy had to be suspended in 7 patients because of adverse effects. The decision to treat should be weighed carefully against the potential risks of therapy.

It is concluded that the incidental rate of new HCV infection after transplantation is high among recipients and is higher than the seroconversion rate in hemodialyzed patients. On the short term, post-transplantation HCV infection had a benign clinical course that was not associated with clinically recognized chronic hepatitis, increased incidence of graft loss or patient fatality in the recipients who were followed in a regional hospital in Saudi Arabia. A study with a larger number of HCV-positive recipients and a longer period of follow-up will provide firmer conclusions on the natural history of HCV infection after transplantation.

References

1. Ulf Meier-Kriesche H, Ojo AO, Hanson JA, et al. Hepatitis C antibody status and outcomes in renal transplant recipients. Transplantation 2001; 72:241-244.
2. Agarwal SK, Dash SC, Irshad M, et al Impact of hepatitis C virus infection on renal transplant outcome in India- a single centre study. J Assoc Physicians India 2000; 8:1155-1159.
3. Chan TM, Lok AS, Cheng IK et al. A prospective study of hepatitis C virus infection among renal transplant recipients. Gastroenterology 1993; 104: 862- 868.
4. Orloff SL, Stempel CA, Wright TL et al. Long-term outcome in kidney transplant patients with hepatitis C (HCV) infection. Clin Transplant 1995; 9:119-124.
5. Grotz WH, Peters TH, Schlayer HJ et al. Immunosuppressive therapy and hepatitis C virus infection: the clinical course of liver disease. J Mol Med 1996; 74:407- 412.
6. Fujimoto N, Kyo M, Ichikawa Y et al. The impact of hepatitis C virus infection on liver disease in renal transplant recipients. Transpl Int 1994; 7 Suppl 1: S346-S349.
7. Huang CC, Liaw YF, Lai MK et al. The clinical outcome of hepatitis C virus antibody-positive renal allograft recipients. Transplantation 1992; 3:763-765.
8. Mathurin P, Mouquet C, Poynard T et al. Impact of hepatitis B and C virus on kidney transplantation outcome. Hepatology 1999; 29: 257 – 263.
9. Hanafusa T, Ichikawa Y, Kishikawa H, et al. Retrospective study on the impact of hepatitis C virus infection on kidney transplant patients over 20 years. Transplantation 1998; 66: 471-476.

10.Genesca J, Vila J, Cordoba J et al. Hepatitis C virus infection in renal transplant recipients: epidemiology, clinical impact, serological confirmation and viral replication. J Hepatol 1995; 22: 272-277.

11. Legendre C, Garrigue V, Le Bihan C et al. Harmful long-term impact of hepatitis C virus infection in kidney transplant recipients. Transplantation 1998; 65: 667-670.

12. Kazi S, Prasad S, Pollak R et al. Hepatitis C infection in potential recipients with normal liver biochemistry does not preclude renal transplantation. Dig Dis Sci 1994; 39: 961-964

13. Vafiadis I, Boletis J, Papastathi H, et al. Hepatitis C virus infection among Greek renal transplant patients. Gut 1993; 34 (2 Suppl.):S57-S58

14. Bang BK, Yang CW, Yoon SA et al. Prevalence and clinical course of hepatitis B and hepatitis C liver disease in cyclosporin-treated renal allograft recipients. Nephron 1995; 70: 397-401

15. Ayoola E A, Want M A, Gadour MOEH, et al. Hepatitis E virus infection in hemodialysis patients: A case – control study in Saudi Arabia. J Med Virol 2002; 55: 329 - 334

16. Shobokshi OA, Serebour FE, Skakni L, et al. Hepatitis C genotypes and subtypes in Saudi Arabia. J Med Virol 1999; 58: 44 – 48

17. Bouthot BA, Murthy BV, Schmid CH, et al. Long-term follow-up of hepatitis C virus infection among organ transplant recipients: implications for policies on organ procurement. Transplantation 1997; 63: 849-853

18. Fabrizi F, Lunghi G, Marai P, et al. Virological and histological features of hepatitis C virus (HCV) infection in kidney transplant recipients. Nephrol Dial Transplant 1996; 11: 159 – 164

19 Yasuda K, Okuda K, End N, et al. Hypoaminotransferasemia in patients undergoing long term hemodialysis: Clinical and biochemical appraisal. Gastroenterology 1995; 109: 1295 – 1300].

20. Durlik M, Gaciong Z, Soluch L et al. Clinical course of concomitant HBV and HCV infection in renal allograft recipients. Ann Transplant 1996; 1: 11-12

21.Allison MC, Mowat A, McCruden EAB et al. The spectrum of chronic liver disease in renal transplant recipients. Q. J Med 1992; 83: 355 - 367

22. Marcellin P, Boyer N, Behanmou JP, et al. Interferon alpha therapy for chronic hepatitis C in special patient populations. Dig Dis Sci 1996; 41 (Suppl. 1); S126 – 130S

23. National Institutes of Health Consensus development conference panel statement: Management of hepatitis C. Hepatology 1997; 26: [Suppl 1] 2S – 10S

24. Lavanchy D., Purcell R., Hollinger F.B., et al Global surveillance and control of hepatitis C Journal of viral hepatitis, 1999; 6: p. 35-47

25. Consensus guidelines for the management of hepatitis C infection in Saudi Arabia. Saudi Med J 2003; 24 [Suppl. 2:] S102 - S117

26. Healey CT , Chapmann RWG, Fleming K. Liver histology n hepatitis C infection: a comparison between patients with persistently normal and abnormal transaminase. Gut 1995; 37: 274 -278.

27.Casanovas-Taltavull T, Baliellas C, Benasco C, et al. Efficacy of interferon for chronic hepatitis C virus-related hepatitis in kidney transplant candidates on hemodialysis: results after transplantation. Amer J Gastroenterol 2001; 96:1170-1177

28. Rao KV, Anderson WR, Kasiske BL, et al. The value of liver biopsy in the diagnosis and management of chronic liver disease in renal allograft recipients. Amer J Med 1993; 94: 241 – 250.

29. Rostaing L, Modesto A, Baron E, et al. Acute renal failure in kidney transplant patients treated with interferon alpha 2b for chronic hepatitis C. Nephron 1996; 74: 512 – 516].

30. Therret E, Pol S, Legendre C et al. Low dose recombinant leukocyte interferon – alpha treatment of hepatitis C viral infection in renal transplant recipients. Transplantation 1994; 58: 625 - 628