Original Research Article

Clinical Outcomes of Renal Transplantation in Hepatitis C Virus Positive Recipients

Surendran Sujit[1*], N. Gopalakrishnan[2]

[1]Assistant Professor, [2]Professor and Head
Department of Nephrology, Madras Medical College, Chennai, Tamil Nadu, India
[*]Corresponding author email: **nephrosuji@yahoo.in**

International Archives of Integrated Medicine, Vol. 3, Issue 8, August, 2016.

Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 13-07-2016 **Accepted on:** 23-07-2016
Source of support: Nil **Conflict of interest:** None declared.
How to cite this article: Surendran Sujit, N. Gopalakrishnan. Clinical Outcomes of Renal Transplantation in Hepatitis C Virus Positive Recipients. IAIM, 2016; 3(8): 45-52.

Abstract

Background: Hepatitis C virus infection confers 1.62-2.39 fold increase in risk of death for hemodialysis patients. The quality of life, morbidity and mortality of chronic kidney disease patients on maintenance hemodialysis is worse when compared to the quality of life, morbidity and mortality of patients undergoing renal transplantation. For these reasons, renal transplantation is better therapeutic option for hepatitis C virus infected patients on maintenance hemodialysis.

Aim: To study of clinical outcomes of renal transplantation in hepatitis C virus positive renal transplantation recipients.

Materials and methods: Single arm prospective observational study done on 28 hepatitis C virus positive patients who underwent either live related or deceased donor transplantation in our department during 2010 -2013 were followed in our ward and outpatient department.

Results: Delayed graft function was present in 11 (39%) patients. Acute cellular rejection was present in 8 patients (26%). New onset of diabetes mellitus after transplant (NODAT)/ Post Transplant Diabetes Mellitus (PTDM) was present in 16 patients (57%). Sepsis occurred in 17 recipients (61%). Cytomegalovirus infection was present in 11 recipients (39%). Invasive fungal infection was present in 7 recipients (25%).

Conclusion: The short term patient and graft survival of HCV positive recipients was better. There was high incidence of NODAT in HCV positive recipients, and occurrence of NODAT was within 3 months after transplant. The incidence of sepsis and cytomegalovirus in HCV positive recipients was higher, it is better to keep minimal level of immunosuppression. The incidence of acute rejection, interstitial fibrosis, fungal infection and graft survival in HCV positive recipients was not statistically

significant from HCV negative recipients. The short duration of follow up is a main limitation of the study.

Key words

Hepatitis c virus recipients, Renal transplantation, Patient and graft survival.

Introduction

Hepatitis C virus (HCV) infects 20-50% of chronic kidney disease patients [1]. The number of chronic kidney disease patients is on increasing trend. The number of chronic kidney disease patients undergoing dialysis is also increasing. Various studies have shown that 3.4-43% of chronic kidney disease patients undergoing maintenance hemodialysis test positive for anti HCV antibodies [2]. Hepatitis C virus infection confers 1.62-2.39 fold increase in risk of death for hemodialysis patients [3]. Various studies have shown that quality of life, morbidity and mortality of chronic kidney disease patients on maintenance hemodialysis is worse when compared to the quality of life, morbidity and mortality of patients undergoing renal transplantation. For these reasons, renal transplantation is better therapeutic option for hepatitis C virus infected patients on maintenance hemodialysis. Anti viral therapy for hepatitis C virus should be given before transplantation. The recommendation is to screen for hepatitis C virus infected patients on transplant programme by testing antibodies for hepatitis C virus. If antibodies to hepatitis C virus are detected, we should proceed testing hepatitis C virus RNA. If hepatitis C Virus RNA is detected, genotyping should be done. Based on the genotype, interferon should be given before transplant. Patients attaining sustained viral response after interferon therapy should be taken for renal transplant, after ruling out clinical and biochemical evidence of liver cirrhosis.

Most of the available studies have shown that the patient and graft survival is worse in hepatitis C virus infected recipients when compared with hepatitis C uninfected recipients. The incidence of acute rejection, new onset of diabetes mellitus after transplant (NODAT), sepsis, interstitial fibrosis and tubular atrophy, progression of liver disease is higher in hepatitis C virus infected recipients when compared with hepatitis C uninfected recipients. Hepatitis C virus infected recipients are also at risk of developing glomerular diseases like membrano proliferative glomerulonephritis with or without cryoglobulinemia, membranous glomerulonephritis, and thrombotic microangiopathy. After transplant, interferon given increases the immunogenicity of the graft leading to graft loss. The only indications for giving interferon post transplant are fibrosing cholestasis and life threatening vasculitis.

Aim and objectives

Aim

- To study of clinical outcomes of renal transplantation in hepatitis C virus positive renal transplantation recipients.

Primary objectives

- To assessing the all cause mortality among hepatitis C virus positive recipients.

Secondary objectives

- Graft dysfunction
- Acute rejection
- New onset of diabetes mellitus
- Sepsis and associated infections.
- Proteinuria
- Interstitial fibrosis and tubular atrophy.
- Liver cell failure.

Materials and methods

Study population

Patients on live related and cadaver transplantation program were screened for Hepatitis C virus by anti HCV antibody testing and qualitative HCV RNA load, patients who were found to be positive for hepatitis C virus

and underwent either live related or cadaver transplantation in our department during 2010 - 2013 were followed in our ward and outpatient department.

Inclusion criteria

Patients who were found to have hepatitis C virus positive patients who underwent either live related or deceased donor transplantation in our department

Exclusion criteria

- Pre transplant liver cirrhosis
- Pre transplant diabetes mellitus
- Hepatitis B virus positive renal failure patients.

Study design

Single Arm Prospective Observational study.

Subjects and methods

Patients who were eligible for either live related or deceased donor renal transplant during their pre transplant work up were screened for diabetes mellitus by blood sugar testing; liver cirrhosis by liver function test, ultrasound, portal doppler, upper gastro intestinal endoscopy; hepatitis C virus by anti H C V antibody testing and qualitative hepatitis C RNA viral load, Hepatitis B virus by HBsAg.

Patients who were found to have hepatitis C virus positive and not having diabetes mellitus, clinical liver cirrhosis undergoing either live related or deceased donor renal transplantation were included in my study.

Definitions used

Sustained viral response

After treatment with interferon RNA levels should be < 50 IU/ml for six months.

Delayed graft function

Requirement of hemodialysis within seven days of transplantation.

Post transplant liver dysfunction

Depending on the degree of elevation of liver enzymes (aspartate aminotransferae and alanine aminotransferase)

Mild chronic liver dysfunction (>6 months)

Rise in liver enzymes up to two and half times the normal levels.

Moderate chronic liver dysfunction (>6 months)

Elevation in liver enzymes more than two and half times the normal levels.

Acute hepatitis (> 7 days <6 months)

Elevation in liver enzymes more than two and half times of normal.

Decompensated chronic liver disease

Occurrence of one clinical jaundice, fluid in the abdomen, encephalopathy due to liver pathology, bleeding from the varices in the gastro intestinal tract.

New onset of diabetes mellitus after transplant (NODAT)/ Post Transplant Diabetes Mellitus (PTDM)

Patients with no history of diabetes mellitus or treatment for diabetes mellitus undergoing transplantation and developing diabetes mellitus after transplant requiring treatment.

Statistical analysis

Data analysed with SPSS software version 16.0 for windows. All continuous data expressed as mean +/- standard deviation. Continuous data analysed using unpaired t test. Categorical data expressed as number (percentage). Fishers exact test were used to analyze the categorical data. A p value of <0.05 is significant statistically.

Univariate analysis done to evaluate odds ratio with confidence interval and relative risk of various parameters that increases the risk of HCV infection among recipients.

Results

A total of 266 patients underwent renal transplantation between 2010 and 2013. Three patients were detected hepatitis C virus infection after transplantation. These three patients were excluded from the study. Out of the 263 patients, 28 recipients who had hepatitis C virus infection before transplant were included in the study, the clinically significant outcomes like acute rejection,

NODAT, sepsis, cytomegalo virus infection, interstitial fibrosis and tubular atrophy (IFTA) were compared with 235 recipients whose serology were negative for hepatitis C virus.

Prospective study of transplant profile of 28 recipients who had hepatitis C virus before transplant were studied in detail, the results are summarised as:

- The mean duration of follow up was 23 months.
- Of the 28 recipients, 19 were males with male: female ratio of 2.1:1.
- Mean age of the study population was 34 years (14-45 years).
- Live related donor transplant was done in 23 patients (82%).
- Deceased donor transplant was done in 5 patients (18%).
- Elevation of liver enzymes was present in 4 patients (14 %).
- Hepatitis C virus RNA was detectable in 5 patients (18%).
- Out of 28 patients, only one patient (3.5%) received interferon for six months before transplant.
- All the patients were started on triple immunosuppression of prednisolone, cyclosporine and mycophenoloate mofetil.
- Out of the 5 deceased transplant recipients, 3 (60%) were given induction agents with basiliximab.
- Delayed graft function was present in 11 (39%) patients.
- Acute cellular rejection was present in 8 patients (26%) and was treated with pulse methyl prednisolone.
- New onset of diabetes mellitus after transplant (NODAT) was present in 16 patients (57%). All patients developed NODAT within 3 months.
- Sepsis (clinical evidence of sepsis and microorganism demonstrated by blood culture or urine culture) occurred in 17 recipients (61%).
- Cytomegalovirus infection was present in 11 recipients (39%).
- Invasive fungal infection was present in 7 recipients (25%).
- Biopsy done in 19 recipients (68%) revealed
- Acute tubular injury in 7 recipients, acute cellular rejection in 8 recipients, calcineurin toxicity in 7 recipients, interstitial fibrosis and tubular atrophy in 9 recipients, thrombotic microangiopathy, transplant glomerulopathy and focal segmental glomerulo sclerosis in one each recipients.

Post transplant worsening of liver function was present in 5 (18%) recipients, 4 (14%) among them had elevation in HCV RNA level.

Liver biopsy was done in 1 recipient (3.5%) findings were:

Chronic hepatitis: Ishak modified hepatitis index inflammatory scale (HAI) 4/118, fibrosis 2/6. The clinical outcome of the one recipient (3.5%) treated with interferon pretransplant was better; there was no progression of liver disease. Two recipients (7%) developed graft artery thrombosis in the post operative period and graft nephrectomy was done to both recipients and became dialysis dependent. Interferon was given to one post graft nephrectomy recipient (3.5%) who developed worsening of liver function and massive elevation of HCV RNA titers.

All recipients underwent alpha seum fetoprotein test yearly, no recipient showed clinical or biochemical evidence of hepatocellular carcinoma. Routine urine examination revealed protienuria in one patient (3.5%), for whom biopsy was done which revealed focal segmental glomerulosclerosis. One recipient (3.5%) expired due to sepsis 20 days following transplant, one year patient survival rate in HCV positive recipients was 96.43%.

On follow up, 3 recipients became dialysis dependent (10.71%). Normal graft function was

present 15 recipients (54%), with mean S. creatitine of 0.9mg/dl.

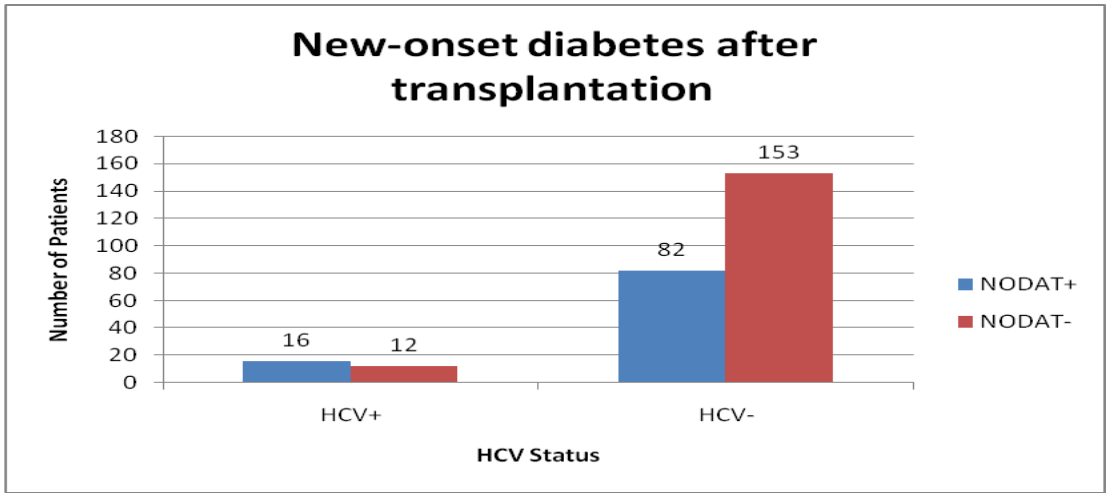
NODAT/ PTDM

The incidence of NODAT in HCV positive recipients was 57.14%, in HCV negative recipients was 34.89%. This difference was statistically significant (p = 0.0247). The HCV positive recipients have 2.24 fold increased risk of developing NODAT (Hazard ratio - H.R. 2.4878 with Confidence interval - C.I .of 1.12 to 5.5) as per **Table – 1** and **Figure - 1.**

Table - 1: The incidence of NODAT/ PTDM among HCV + and HCV - recipients.

NODAT	HCV+	%	HCV-	%
NODAT+	16	57.14	82	34.89
NODAT-	12	42.86	153	65.11
Total	28	100	235	100
Hazard Ratio	2.4878			
95% CI	1.1233 to 5.5097			
RR	2.2449			
P value	0.0247*			

Figure - 1: The comparison of NODAT/ PTDM among HCV+ and HCV- recipients.



Sepsis

The incidence of sepsis in HCV positive recipients was 60.71%, in HCV negative recipients was 37.45%. This difference was statistically significant (p=0.026). The HCV positive recipients were 2.32 fold higher risk of developing sepsis (2.58 with – C.I. 1.15 to 5.76) as per **Table – 2** and **Figure - 2**.

Interstitial fibrosis and tubular atrophy (IFTA)

The incidence of IFTA in HCV positive recipients were 32.14%, in HCV negative recipients were 28.94%. This incidence was not statistically significant, p=0.7247.

CMV infection

The incidence of Cytomegalovirus in HCV positive group 39.29%, in HCV negative group was 18.72%. This difference was statistically significant, p= 0.0148. The HCV positive group had 2.8 fold of developing CMV infection when compared with HCV negative group, with hazard ratio of 2.8088 with C.I. of 1.2294 to 6.4172 as per **Table – 3** and **Figure - 3.**

Fungal infection

The incidence of fungal infection in HCV positive recipients was 25%, in HCV negative recipients was 41.7%, this difference was not statistically not significant, p=0.0941.

Table - 2: The incidence of sepsis in HCV + and HCV –recipients.

SEPSIS	HCV+	%	HCV-	%
SEPSIS+	17	60.71	88	37.45
SEPSIS-	11	39.29	147	62.55
Total	28	100	235	100
Hazard Ratio	2.5816			
95% CI	1.1564 to 5.7634			
RR	2.3255			
P value	0.0206*			

Figure - 2: The comparison of sepsis among HCV+ and HCV- recipients.

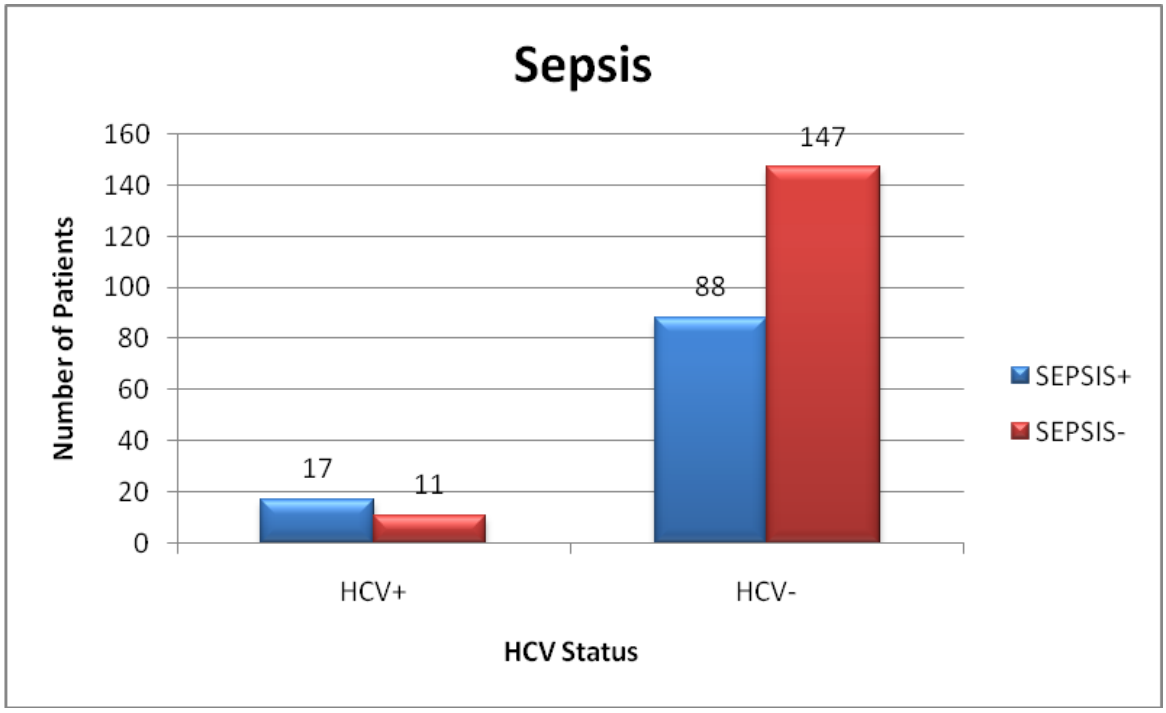
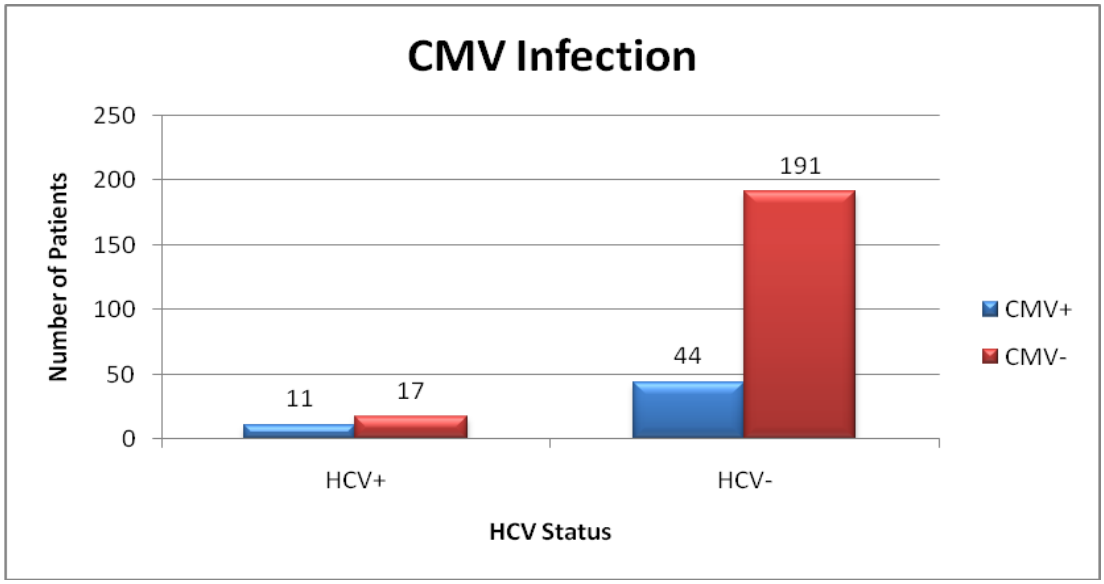


Table - 3: The incidence of CMV infection in HCV + and HCV – recipients.

CMV	HCV+	%	HCV-	%
CMV+	11	39.29	44	18.72
CMV-	17	60.71	191	81.28
Total	28	100	235	100
Hazard Ratio	2.8088			
95% CI	1.2294 to 6.4172			
RR	2.7723			
P value	0.0143*			

Figure - 3: The comparison of CMV infection among HCV+ and HCV- recipients.



Acute rejection

The incidence of acute rejection in HCV positive recipients was 28.57%, in HCV negative recipients was 28.575, this difference was statistically insignificant, p=0.9679.

Mortality

The incidence of mortality in HCV positive group was 3.57%, in HCV negative recipients was 13.62%, this difference was statistically insignificant, p=0.1621.

Graft loss

The incidence of graft loss in HCV positive recipients was 7.14%, in HCV negative recipients was 3.83 %, this comparison was statistically insignificant, p=0.4156.

Dialysis dependency

The incidence of dialysis dependency in HCV positive recipients was 10.7%, in HCV negative recipients was 7.665, this comparison was statistically insignificant, p= 0.5749.

Discussion

In our study, the mortality rate in HCV positive recipients was 3.57% and adjusted relative risks for mortality was 0.235 with C.I. of 0.03 to 0.18. Hepatitis C virus positivity did not confer any increased risk of mortality and graft loss when compared to hepatitis C virus negative recipients. Meta analysis of eight clinical trials by Fabrizi, et al., comparing the outcomes of renal transplantation among hepatitis C virus positive and hepatitis c virus negative recipients, revealed that adjusted relative risk of mortality was 1.79 with a confidence interval of 1.57 -2.03 in hepatitis C virus positive recipients. There was an adjusted relative risk of graft loss of 1.56 with a confidence interval of 1.35 -1.80 [4]. Rostami, et al., reviewed 18 observational studies. They concluded that the combined hazard ratio for mortality of hepatitis C virus positive recipients compared to hepatitis C virus negative recipients was 1.69 times (1.33-1.97, p<0.0001) and graft loss was 1.56 fold (1.22-2.004) [5]. In our study, the hepatitis C virus positive recipients had 2.24 fold increased risk of developing NODAT (H.R. 2.4878 with CI of 1.12 to 5.5). The metaanalysis by Fabrizi, et al., has shown that the seropositivity of hepatitis C virus confers a 3.75 fold increased risk of NODAT in renal transplant recipients [4]. The hepatitis C virus positive recipients had 2.32 fold higher risk of developing sepsis. The hepatitis C virus positive recipients had 2.8 fold of developing cytomegalovirus infection when compared with hepatitis C virus negative recipients. Rao K, et al., analyzed the incidence of sepsis and cytomegalovirus infection among hepatitis C positive recipients and hepatitis C negative recipients. They have shown that hepatitis C

positive recipients had a 1.8 fold increase in incidence of sepsis and cytomegalovirus infection when compared to negative recipients [6]. Studies by Morales, et al. and Rao, et al. have shown that hepatitis C virus positive patients have frequent blood stream infections like cytomegalovirus and sepsis [6, 7]. According to the study by Morales, et al., the incidence of acute rejection in HCV positive recipients was 32.5% in HCV negative recipients was 27.3% [8]. In our study the incidence of acute rejection in HCV positive and negative recipients was similar.

Conclusions

The short term patient and graft survival of HCV positive recipients was better. There was high incidence of NODAT/ PTDM in HCV positive recipients, and occurrence of NODAT/ PTDM was within 3 months after transplant. The incidence of sepsis and cytomegalovirus in HCV positive recipients was higher, it is better to keep minimal level of immunosuppression. The incidence of acute rejection, interstitial fibrosis, fungal infection and graft survival in HCV positive recipients was not statistically significant from HCV negative recipients. The short duration of follow up is a main limitation of the study.

References

1. Fabrizi F, Bunnapradist S, Lunghi G, Aucella F, Martin P. Epidemiology and clinical significance of hepatotropic infections in dialysis patients. Recent evidence. Minerva Urol Nefrol., 2004; 56: 249–257.
2. Bozdayi G, Rota S, Verdi H, Derici U, Sindel S, Bali M, Basay T. The presence of hepatitis C virus (HCV) infection in hemodialysis patients and determination of HCV genotype distribution. Mikrobiyol Bul., 2002; 36(3-4): 291-300.
3. Stehman-Breen CO, Emerson S, Gretch D, Johnson RJ. Risk of death among chronic dialysis patients infected with hepatitis C virus. Am J Kidney Dis., 1998; 32: 629–634.
4. Fabrizio Fabrizia, Paul Martinb, Vivek Dixitc, Suphamai Bunnapradistd, Gareth Dulaic. Hepatitis C Virus Antibody Status and Survival. After Renal Transplantation: Meta-Analysis of Observational Studies American Journal of Transplantation, 2005; 5: 1452–1461.
5. Zohreh Rostami, et al. The impact of Hepatitis C virus infection on kidney transplantation outcomes: A systematic review of 18 observational studies. Hepat Mon., 2011; 11(4): 247-254.
6. Rao KV, Ma J. Chronic viral hepatitis enhances the risk of infection but not acute rejection in renal transplant recipients. Transplantation, 1996; 62: 1765–1769.
7. Morales JM, Campistol JM, Andres A, Rodicio JL. Hepatitis C virus and renal transplantation. Curr Opin Nephrol Hypertens., 1998; 7: 177–183.
8. Jose María Morales. Renal transplantation in patients with hepatitis C virus antibody. A long national experience NDT Plus, 2010; 3(Suppl 2): ii41–ii46.