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BRIEF ARTICLE

Efficacy and safety of treatment of hepatitis C virus infection in renal transplant recipients

Abdulrahman A Aljumah, Mohamed A Saeed, Ahmed I Al Flaiw, Ibrahim H Al Traif, Abduljaleel M Al Alwan, Salem H Al Qurashi, Ghormallah A Al Ghamdi, Fayez F Al Hejaili, Mohammed A Al Balwi, Abdulla A Al Sayyari

Abdulrahman A Aljumah, Mohamed A Saeed, Ibrahim H Al Traif, Abduljaleel M Al Alwan, Division of Hepatology, Department of Hepatobiliary Sciences and Liver Transplantation, King Abdulaziz Medical City and King Saud bin Abdulaziz University for Health Sciences, National Guard Health Affairs, Riyadh 11324, Saudi Arabia
Ahmed I Al Flaiw, Salem H Al Qurashi, Ghormallah A Al Ghamdi, Fayez F Al Hejaili, Abdulla A Al Sayyari Division of Nephrology and Renal Transplantation, Department of Medicine, King Abdulaziz Medical City and King Saud bin Abdulaziz University for Health Sciences, National Guard Health Affairs, Riyadh 11324, Saudi Arabia
Mohammed A Al Balwi, Division of Molecular Pathology and Genetics, King Abdulaziz Medical City and King Saud bin Abdulaziz University for Health Sciences, National Guard Health Affairs, Riyadh 11324, Saudi Arabia
Author contributions: Aljumah AA designed the study, drafted the manuscript, analyzed data, wrote the paper and gave final approval of the version for publication; Saeed MA, Al Flaiw AI, Al Traif IH, Al Alwan AM, Al Qurashi SH, Al Ghamdi GA and Al Hejaili FF collected data, critically revised the manuscript and gave final approval of the version for publication; Al Balwi MA analyzed and revised virological data and gave final approval of the version for publication; Al Sayyari AA analyzed data, performed statistical analysis, revised the manuscript and gave final approval of the version for publication.
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Correspondence to: Abdulrahman A Aljumah, MD, FRCPI Consultant Hepatologist and Liver Transplant Physician Head, Division of Hepatology, Department of Hepatobiliary Sciences and Liver Transplantation, King Abdulaziz Medical City and King Saud bin Abdulaziz University for Health Sciences, National Guard Health Affairs, PO Box 225264, Riyadh 11324, Saudi Arabia. draljumah@hotmail.com
Telephone: +966-1-2520088-16786 Fax: +966-1-2520438
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Abstract

AIM: To assess the efficacy and safety of combined pegylated interferon and ribavirin therapy in hepatitis C virus (HCV) infection in renal transplant recipients.

METHODS: This is a retrospective chart review of post renal transplant patients who were positive for anti-HCV and HCV-RNA, and who have received treatment with combination of pegylated interferon and ribavirin between October 2003 and December 2008. Only patients with stable graft function and absence of evidence of cirrhosis and who received the therapy for continuous 48 wk were included. Nineteen patients (13 male and 6 female) were identified and included. The patient's complete blood count, liver and kidney profile, and calculated glomerular filtration rate (GFR) were monitored every 6-8 wk while on treatment. HCV-RNA was tested at 12 wk for early virological response, at 48 wk for end of treatment response (ETR), and then retested at 24, and 48 wk after completion of therapy for sustained virological response (SVR). Liver biopsies were obtained before treatment from all patients and graft kidney biopsies were performed as required.

RESULTS: Of the entire cohort, 9 patients (47.4%) showed an ETR and 8 had SVR (42.1%). Of the 8 patients with abnormal alanine aminotransferase (ALT) levels at baseline, 78.9% had their ALT normalized (including the virological non responders). ALT was normal in all responders at the end of therapy and at 24 wk post therapy (100%). Only one patient (5.3%) developed an increase in creatinine and decline in GFR from baseline towards the end of treatment. This patient's kidney biopsy revealed borderline rejection. There was no impact on response by HCV-genotype, initial HCV RNA load, age or sex of the patient or duration post transplant before commencement of therapy. All patients tolerated treatment in the same way as non-transplant with no unusual or increased occurrence of side effects.

CONCLUSION: The combination of pegylated interferon and ribavirin is effective in suppressing HCV-RNA,

with a low risk of graft rejection or failure in HCV infected renal transplant recipients.

Key words: Allograft rejection; Hepatitis C; Pegylated interferon; Ribavirin; Renal transplant

Peer reviewer: Sam B Ho, MD, Gastroenterology Section 111D, VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161, United States

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INTRODUCTION

Hepatitis C virus (HCV) is the major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma and is the leading indication for liver transplantation worldwide[1]. There is a marked geographic variation in seroprevalence and genotypes of HCV[2-4]. HCV infection is common among patients with end-stage renal disease. The prevalence of HCV infections in patients that undergo hemodialysis has been described in literature worldwide, reaching as high as 63%[5-8]. After implementation of regulations and routine screening in dialysis centers to prevent spread of infection, the incidence of HCV infection has declined in several countries[9-11]. A considerable number of dialysis patients will eventually undergo renal transplantation, which will ultimately increase the prevalence of HCV infection post renal transplantation. HCV has been recognized as one of the major causes of morbidity and mortality and indicates a poor prognosis of patient and graft survival in renal transplantation[12-15]. Reports on the prevalence of HCV in renal allograft recipients were variable. It has been reported to be from 10% to 49% in some centers, but may reach up to 64% in others[12,15-21]. Renal transplantation in HCV positive patients is associated with an aggressive course of liver disease[5,12,22,23]. Treatment of hepatitis C post renal transplant has been a debatable and controversial issue for a long time. Although there were some case reports of successful therapy with interferon with no serious side effects[24,25] many studies have suggested that interferon is contraindicated in such patients due to high incidence of allograft rejection, severe graft dysfunction and/or intolerance of patients to such therapy[26-33]. Most of the reported studies however, have included a small number of patients. Furthermore conventional interferon has been utilized in these studies and only limited experience with pegylated interferon (PEG-IFN) has been reported. In this retrospective study we report our experience with the largest cohort group of patients with hepatitis C post renal transplant treated with a combination of pegylated interferon and ribavirin, focusing on treatment response and allograft rejection.

MATERIALS AND METHODS

This is a retrospective, chart review study of post renal transplant recipients who were positive for anti-HCV and HCV-RNA, and who have received treatment with a combination of PEG-IFN and ribavirin, between October 2003-the time when pegylated interferon had become available as a formulary drug in our institution-and December 2008. Only patients with stable graft function, and absence of cirrhosis were included. Out of 230 renal transplant recipients followed at our institution, 40 consecutive recipients with positive hepatitis C serology were referred from nephrology to the hepatology clinic. Nineteen such patients (13 male and 6 female) were identified and included. Twenty one patients were excluded, as follows; one patient was anti-HCV positive but his HCV-RNA was negative, 4 patients refused to take therapy after they were told that they may lose their kidneys secondary to treatment, 1 patient had multiple medical problems, 3 patients had developed well established liver cirrhosis with portal hypertension, 4 patients had established rejection and had either considered or already started hemodialysis just before starting treatment, and 8 patients were recipients of double organ (liver and kidney) transplantation.

The patient's white cell count (WBC), hemoglobin, platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, bilirubin, prothrombin time, blood urea nitrogen (BUN), creatinine, and glomerular filtration rate (GFR) (calculated using Cockcroft-Gault Formula)[34] were measured before treatment and repeated every 6-8 wk while on treatment and every 12 wk after completing therapy.

All patients were screened for hepatitis B virus (HBV), human immune deficiency virus (HIV) and autoimmune markers pre and post transplantation. Anti-HCV was tested using either the 3rd generation enzyme immunoassay (AxSYM HCV Version 3.0, Abbott laboratories, Diagnostics Division, Abbott Park, IL 60064, United States) or more recently with ARCHITECT Anti-HCV (Abbott GmbH and Co. KG, Max-Planck-Ring 2, 65205 Wiesbaden, Germany). Quantitative HCV-RNA was performed using Roche COBAS Ampliprep/ COBAS TaqMan System (Roche Molecular Systems, Pleasanton, United States). Qualitative HCV-RNA was performed using Roche Automated COBAS Amplicor Analyzer (Roche Molecular Systems, Pleasanton, United States). The HCV genotype detection assay was performed using m2000 real-time system (Abbott Molecular Diagnostics, Abbott Park, IL, United States). HCV genotype was determined in 14 of the patients. Quantitative HCV-RNA test was carried out in all patients prior to treatment, at 12 wk after starting treatment for early virological response (EVR), at 48 wk for end of treatment response (ETR), and then qualitative

and quantitative assays for HCV-RNA were performed at 24 and 48 wk after completion of therapy for sustained virological response (SVR). All patients had under gone liver biopsy prior to treatment. We used modified Ishak histological grading and staging of chronic hepatitis using the histological activity index (HAI) scoring system for the degree of necroinflammatory activity and a staging system for degree of fibrosis[35]. For simplification purposes, we classified necroinflammatory grading on liver histology into; minimal/mild chronic hepatitis if score is 0-6, moderate chronic hepatitis if score is 7-9, and marked chronic hepatitis, with or without bridging necrosis, if score is 10-18. Fibrosis staging was classified into minimal/mild fibrosis for score 0-3, and moderate/marked fibrosis for score 4-6.

Kidney biopsies were performed on patients who developed abnormal renal function or reduction of GFR, either before or during therapy according to the normal unit indications.

HCV treatment protocol used

This was based on the standard international guidelines for therapy of hepatitis C. However because these are a special group of patients and since there is no agreed-on defined protocol to treat such patients and as our study is a retrospective, the individual treatment protocol was left to the discretion of the treating hepatologist. Pegylated interferon α-2a (Pegasys, F. Hoffmann-la Roche Ltd., Basel, Switzerland) at a dosage of 135-180 μg (135 μg for 2 patients and 180 μg for 13 patients) every week in combination with ribavirin 400 mg (2 patients), 800 mg (11 patients), 1000 mg (1 patient), 1200 mg (1 patient) daily in two divided doses were given to 15 patients. Pegylated interferon α-2b (Peg-intron, Schering-Plough Corporation, Kenilworth, NJ, United States) at a dosage of 80-100 μg every week, in combination with ribavirin 400 mg (1 patients), 800 mg (3 patients) daily in divided doses were given to the remaining 4 patients.

All patients were treated for 48 wk. Patients whose hemoglobin dropped to below 100 mg/dL were given erythropoietin subcutaneously, and those whose absolute neutrophil count dropped to below 800/mm^3 were given granulocyte colony stimulating factor (G-CSF) subcutaneously. The dose and frequency of erythropoietin and G-CSF were given according to our center local guidelines, which are similar to the international protocols. Patients were followed up at the hepatology clinic every 2 wk for the first 6 wk and every 6-8 wk thereafter. Patients were also seen in the nephrology clinic every four to eight weeks.

Immunosuppression

All patients were on maintenance steroid therapy in the form of prednisone. Fifteen patients were on mycophenolate mofetil (CellCept), eight on cyclosporine and nine on tacrolimus. One patient received sirolimus. None of our patients received azathioprine.

Ethical and safety issues

Since there was no available international treatment protocol, the risks and benefits of therapy, including potential graft rejection were explained carefully to all patients by the nephrologists and further reinforced by the hepatologist before commencing therapy as normal precautions which were usually performed in similar conditions outside study protocols. Only those patients who consented received the therapy. The study was passed by the hospital's research committee and approved by the institutional review board.

Statistical analysis

The data was analyzed using SPSS version 17. Descriptive data was obtained for all the parameters tested (mean, median, SD). The change over time in liver profile, renal profile, and viral load were compared using ANOVA and changes between baseline and end of treatment parameters were examined using paired *t*-test. The effect of age, post transplant duration and gender on the response was tested using two-tailed independent *t* test and Pearson Chi square.

RESULTS

Of the nineteen recipients included in the study there were 13 males and 6 females. Age ranged from 20 years to 66 years, with a mean age of 39.9 (± 12.6) years. The time from transplant to initiation of treatment ranged from 14 mo to 156 mo with a mean of 66.3 (± 45.7) mo. All patients had undergone hemodialysis in more than one dialysis unit before renal transplant. Our patients tolerated the treatment fairly well. There were no unusual side effects to therapy. None of our patients were intolerant to therapy requiring discontinuation. None of our patients experienced a serious infection or sepsis during the course of therapy.

Liver biochemical profile

ALT was high in 9 patients at baseline, 15 patients (78.9%) had normal ALT at the end of therapy (including non responders). Nine patients had high AST at baseline, 13 (68.4%) of them had normal AST at end of therapy. ALT and AST were normal in all responders at the end of therapy and at 24 wk follow up post therapy (100%). There was a drop in AST between baseline and 48 wk of therapy but this was not statistically significant. The drop in ALT however was significant ($P = 0.01$) (Tables 1 and 2).

Liver histology profile

The histological activity index (HAI) scoring system revealed minimal/mild hepatitis in 14 patients (73.7%), and moderate hepatitis in 5 patients (26.3%). None of our patients was in the marked grade. The staging system for degree of fibrosis revealed 16 patients (84%) had minimal/mild fibrosis, and 3 patients (16%) had moderate/marked fibrosis.

Virological profile and genotype

All 19 patients had a high HCV-RNA load before treatment with values ranging from 5.1 log10 IU/mL to 7.4

Table 1 Mean ± SD of parameters measured at different stages of therapy (n = 19)

Parameters	Baseline	12 wk	24 wk	48 wk	*P* value (baseline *vs* 48 wk)
AST (U/L)	43.7 (30.4)	32.4 (29.6)	36.8 (35.4)	32.9 (34.3)	0.18
ALT (U/L)	65.4 (56.3)	34.0 (33.7)	34.9 (25.9)	30.8 (21.3)	0.01
HCV-RNA (log10 IU/mL)	6.3 (0.69)	3.0 (2.9)	2.6 (3.0)	1.1 (2.1)	0.0001
WBC (10^9/L)	5.5 (2.7)	4.5 (2.7)	5.1 (4.8)	6.6 (1.0)	0.698
Hemoglobin (G/L)	116.7 (43.6)	100.1 (33.8)	101.2 (24.7)	107.7 (25.8)	0.238
Platelets (10^9/L)	195 (101)	154 (76)	175 (83)	188 (98)	0.752
Creatinine (Umol/L)	122 (41)	122 (41)	138 (75)	130 (52)	0.183
GFR (mL/min)	70.4 (24.5)	69.0 (22.7)	68.2 (27.2)	69.7 (25.2)	0.772

AST: Aspartate aminotransferase; ALT: Abnormal alanine aminotransferase; HCV: Hepatitis C virus; WBC: White cell count; GFR: Glomerular filtration rate.

Table 2 Hepatitis C virus-RNA, alanine aminotransferase, and aspartate aminotransferase at different times of treatment and follow up

	0 (before treatment)	24 wk	48 wk	24 wk post treatment
No. of patients with 2 log drop in HCV-RNA	0	1 (0.05%)	2 (0.1%)	NA
No. of patients with undetected HCV-RNA	0	9 (47.4%)	9 (47.4%)	8 (42.1%)
Normal ALT	10	14 (73.6%)	Out of all patients 15/19 (78.9%) Out of responders 9/9 (100%)	Out of all patients15/19 (78.9%) Out of responders 8/8 (100%)
Normal AST	10	13 (68.4%)	Out of all patients13/19 (68.4%) Out of responders 9/9 (100%)	Out of all patients13/19 (68.4%) Out of responders 9/9 (100%)

AST: Aspartate aminotransferase; ALT: Abnormal alanine aminotransferase; HCV: Hepatitis C virus; NA: Not applicable.

log10 IU/mL and a mean of 6.25 log10 IU/mL. Seven patients developed EVR (36.8%) at 12 wk of therapy, while two patients had a low target level at 12 wk of therapy. Nine patients had negative HCV-RNA at 24 wk and at the end of 48 wk of therapy (ETR) (47.4%). HCV-RNA utilizing qualitative and quantitative assays was performed at 24 wk and 48 wk after completion of therapy for SVR. This revealed negative HCV-RNA (SVR) in 8 of the 9 responders (42.1% of total treated patients and 88.9% of responders) and only one patient had relapsed at 24 wk. There was no impact of response by the initial HCV-RNA load. Several genotypes were identified: genotype 1 is the most common and found either alone or in combination with other genotypes (genotype 1 alone in 6 patients; 1 and 2 together in 3 patients; 1 and 3 together in 1 patient; 3 alone in 2 patients; 3 and 4 together in 1 patient; 1, 4, and 5 together in 1 patient). The multiple genotypes in one patient could have been acquired from using multiple dialysis units before transplant. Five patients did not have their genotype tested. Using ANOVA, we found that the genotype did not influence the 24 wk or the end of treatment HCV-RNA load (P = 0.084 and 0.059 respectively). There was a significant fall in the load from 6.3 log10 IU/mL (± 0.69) at baseline to 2.6 log10 IU/mL (± 3.05) at 24 wk, and a further fall at 48 wk to 1.1 log10 IU/mL (± 2.1), (P = 0.0001) (Tables 1 and 2).

Hematological profile

All patients had normal leukocyte count before treatment. One patient developed leucopenia, with an absolute neutrophil count of less than 800/mm³. This patient was given G-CSF and maintained a normal count throughout the course of treatment. Hemoglobin (Hb) level was above 100 mg/dL in all patients except for three who had their Hb between 92-95 mg/dL before treatment. Those patients were given erythropoietin injections to maintain their Hb above 100 mg/dL throughout the treatment course. Platelet count ranged from 108 000/m³ to 403 000/m³. There was no significant drop in platelet count in any of the patients. None of the changes in WBC, hemoglobin or platelets during the treatment period was statistically significant (Table 1).

Renal profile

Six patients had high serum creatinine before treatment. These patients underwent renal biopsies prior to treatment which revealed chronic allograft nephropathy (CAN) in 2 patients, membrano-proliferatve glomurulonephritis (MPGN) probably related to HCV in 2 patients, and calcineurin inhibitors toxicity in 2 patients. Three patients developed renal dysfunction while on treatment; one patient developed an increase in serum creatinine and decline in GFR from baseline towards 24 wk of treatment. This patient's serum creatinine rose from 109 μmol/L before treatment to 153 μmol/L after 24 wk of treatment. Kidney biopsy showed a borderline acute cellular rejection, probably related to interferon. However since he was showing an excellent response and only a mild change in

Table 3 Impact of patient gender on the parameters at the end of therapy

Parameters	Males (n = 13)	Females (n = 6)	P value
AST (U/L)	33.69	27.67	0.56
ALT (U/L)	32.23	28.33	0.62
HCV-RNA (log10 IU/mL)	2.3	3.27	0.54
WBC (10^9/L)	4.08	7.05	0.43
Hemoglobin (G/L)	99.77	102.33	0.88
Creatinine (Umol/L)	145.62	123.33	0.53
GFR (mL/min)	66.15	72.67	0.71

AST: Aspartate aminotransferase; ALT: Abnormal alanine aminotransferase; HCV: Hepatitis C virus; WBC: White cell count; GFR: Glomerular filtration rate.

Table 4 Impact of duration post transplant on the parameters at the end of therapy

Parameters	Duration post transplant		P value
	> 49 mo (n = 10)	< 49 mo (n = 9)	
AST (U/L)	27.6	36.44	0.63
ALT (U/L)	33.4	28.33	0.59
HCV-RNA (log10 IU/mL)	2.38	2.94	0.72
WBC (10^9/L)	4.38	5.73	0.59
Hemoglobin (G/L)	107	93.44	0.28
Creatinine (Umol/L)	161.80	112.78	0.15
GFR (mL/min)	61.90	75.22	0.37

AST: Aspartate aminotransferase; ALT: Abnormal alanine aminotransferase; HCV: Hepatitis C virus; WBC: White cell count; GFR: Glomerular filtration rate.

Table 5 Impact of age on the parameters at the end of therapy

Parameters	Age > 39 yr (n = 11)	Age < 39 yr (n = 8)	P value
AST (U/L)	32.91	30.25	0.82
ALT (U/L)	30.09	32.25	0.81
HCV-RNA (log10 IU/mL)	2.92	2.33	0.7
WBC (10^9/L)	4.28	6.04	0.53
Hemoglobin (G/L)	109.18	88.75	0.11
Creatinine (Umol/L)	148.73	124.63	0.46
GFR (mL/min)	67.73	68.88	0.92

AST: Aspartate aminotransferase; ALT: Abnormal alanine aminotransferase; HCV: Hepatitis C virus; WBC: White cell count; GFR: Glomerular filtration rate.

his creatinine, and after careful discussion between nephrologist, hepatologist and the patient, it was decided to continue treatment for a further 24 wk. Serum creatinine was 175 μmol/L at the end of treatment. Twelve weeks after completing the treatment, his creatinine went up to 195 μmol/L and then dropped to 172 μmol/L at 24 wk follow up. Although rejection was very mild, we consider this a serious issue and it was taken as a side effect of antiviral therapy. We consider this as a case of therapy related rejection giving a rejection rate of 5.3% in our series. The second patient had attempted treatment twice; initially for 12 wk when the serum creatinine showed a mild but gradual increase. Treatment was held and a kidney biopsy was performed and showed CAN with no features of acute rejection. Her creatinine continued to rise very gradually. The patient and the nephrologist agreed with the hepatologist on retreatment. She was then retreated when her creatinine was 196 μmol/L before treatment. Creatinine went up to 215 μmol/L, 12 wk after starting therapy. The patient showed a virological response and since the nephropathy was not related to interferon it was decided to continue a full course of treatment. The third patient had only a mild elevation of serum creatinine from 168 μmol/L before treatment to 199 μmol/L at the end of treatment; however, he also underwent a kidney biopsy before starting treatment and has shown MPGN, which has no contraindication to treatment, and indeed if HCV related, may respond well to antiviral therapy. These three patients who developed abnormal renal function and underwent kidney biopsies had an excellent ETR and 2 of them had SVR at 24 wk post therapy. There was no significant change in GFR during or after therapy from baseline except in the only patient who had rejection who had a decrease in GFR from 61 mL/min to 38 mL/min at the end of therapy. Serum creatinine and GFR remained stable during the treatment period (Table 1).

Impact of type of immunosuppression

There was no relation observed between response rate and the type of immunosuppression regimen used during therapy. There was no relation between the increase of creatinine or decrease in GFR rate and the type of immunosuppression regimen used.

Impact of gender, duration post transplant and age on the parameters at the end of therapy period

Stratification by gender, duration post transplant and age had no impact on the final post transplant levels of the parameters measured (Tables 3-5).

Table 6 summarises recent reports on the efficacy and rejection rate following the use of interferon in post renal transplant HCV infection. It shows that there is a high rate of response to PEG-IFN especially when it is combined with ribavirin, compared to conventional interferon. Furthermore, the rate of rejection and graft failure with this type of therapy is much lower than that with conventional interferon (Table 6).

DISCUSSION

Several studies have shown a negative impact of HCV on patient and graft survival post renal transplantation[12-15,19,25,26]. Immunosuppressive therapy after renal transplantation usually leads to a flare up of HCV viremia[28]. In the setting of renal and other organ transplantation, HCV infected post transplant patients have an aggressive and rapidly progressive liver disease with cirrhosis, liver failure and death[12,22,23,36,37]. Therefore every effort to suppress HCV and prevent liver and renal

Table 6 Summary of some reports on the efficacy and rejection rate following the use of interferon alone or in combination with ribavirin in post renal transplant hepatitis C virus infection

Ref.	Yr	No. of patients treated	Anti HCV therapy used (No. of patients)	Immunosuppression used (% of patients)	ETR (%)	SVR (%)	Rate of allograft rejection/failure (%)
Ozgur *et al*[32]	1995	5	CI alone (5)	CNI (100) Aza (100) S (100)	NR	NR	40
Rosting *et al*[31]	1995[1]	14	CI alone (14)	CNI (85.7) Aza (50) S (85.7)	28.60	0	35.70
Hanafusa *et al*[14]	1998	10	CI alone (10)	CNI (NS) Aza (100) S (100)	10	0	40
Baid *et al*[27]	2003[2]	12	CI + R (11) CI alone (1)	CNI (100) Aza (17) C (67) S (100)	NS	33	17
Sharma *et al*[26]	2006[3]	6	CI + R (5) PEG-INF + R (1)	CNI (100) Aza (50) C (14) S (100)	66.60	33.30	66.60
Pageaux *et al*[67]	2009	8	PEG-INF + R (4) PEG-INF alone (4)	CNI (75) Aza (37.5) C (25) S (100)	75	50	0
Aljumah *et al*	Current study	19	PEG-INF + R (19)	CNI (89.5) C (78.9) S (100)	47.40	42.10	5.30

HCV: Hepatitis C virus; CI: Conventional interferon; PEG-IFN: Pegylated interferon; R: Ribavirin; CNI: Calcineurin inhibitors; C: Cellcept; S: Steroids; Aza: azathioprine; ETR: End of treatment response; SVR: Sustained virological response; NR: Not reported; NS: Not specified. [1]Five patients developed acute renal failure, but biopsy did not confirm rejection. [2]CI changed to PEG-IFN in 3 patients but study did not specify these patients. [3]In this study 8 patients received ribavirin alone without interferon, so they were not included. [3]Four patients developed severe renal dysfunction, only one patient biopsied and showed chronic allograft nephropathy.

diseases progression is of paramount clinical importance.

The currently accepted therapy for hepatitis C in immunocompetent patients includes a combination of conventional interferon and ribavirin, and more recently PEG-IFN and ribavirin. Several local and international studies have shown that a combination of PEG-IFN and ribavirin is superior to conventional interferon and ribavirin with a sustained virological response ranging from 41% to 82% depending on several factors including viral load, genotype, liver histology, patient age and weight[38-42].

Ribavirin alone is not recommended in dialysis patients as it is generally not tolerated due to severe hemolysis and aggravation of anemia[43]. Conventional interferon or PEG-IFN alone or in combination with ribavirin were used with varying results in hemodialysis patients with some studies suggesting prolonged durability of response after renal transplantation[44-51].

Treatment of HCV post renal transplant is even more difficult and challenging. Ribavirin alone has been used in recurrence of HCV post liver and kidney transplant but this was not associated with virological response[52-56]. Several studies and case reports have shown that the response rate to a combination of conventional interferon and ribavirin is very low. Furthermore this is associated with severe side effects including allograft rejection[26-33]. Very few studies have reported good efficacy and safety of conventional interferon in renal transplant patients[24,25]. In general, there is a major reluctance to use interferon out of fear of rejection. Fabrizi *et al*[57] have reported the meta-analysis of renal transplant patients treated with conventional interferon and ribavirin between 1994 and 2004 and have concluded that the treatment of HCV in the setting of renal transplant with interferon is contraindicated due to poor safety and efficacy. In a study one patient who was treated with PEG-IFN and ribavirin failed to achieve SVR and has developed graft dysfunction[26]. On the other hand, reports of two cases of HCV in combined liver and kidney transplant recipients treated with a combination of PEG-IFN and ribavirin revealed excellent results[58,59]. Recently eight patients were treated with PEG-IFN either alone or in combination with ribavirin and the results were encouraging, with no episodes of rejection and a SVR of 50%. However in this study there was a high incidence of side effects and intolerance to treatment[60].

The mechanism of rejection induced by interferon in renal transplant recipients is unclear. Interferon is a known strong immune modulator; hence at least theoretically it is highly possible that rejection in this setting involves an immunological reaction. Interferon may produce cell-surface expression of HLA antigens with induction of cytokine gene expression and subsequent stimulation of antibody production[61]. Baid *et al*[27] have found de novo donor-specific human leukocyte antigen

(HLA) antibodies (DSA) in serum and C4d deposits with neutrophils in peritubular capillaries in 2 renal transplanted patients with acute humoral rejection treated with interferon and ribavirin.

The reason why we have less rejection than the other previously published studies is unclear. However, most published studies have a small number of patients and many did not differentiate between biopsy proven kidney rejection and renal dysfunction, unlike our study which has followed these patients carefully and performed kidney biopsies before and during treatment whenever there is decline of renal function. In addition, there are several hypotheses which may have played a role; firstly the fact that we have not used azathioprine in any patient and instead most of our patients were on mycophenolate mofetil, which has been reported to improve graft survival and decrease the incidence of rejection[62-64]; secondly, the average time frame between transplant and initiation of therapy in our patients is relatively long (66 mo). None of our patients had sepsis or severe infection during treatment course or follow up, as sepsis is a well known independent cause for morbidity and mortality in HCV positive renal transplantation[12,13]. All of our patients were on PEG-IFN and ribavirin, with 90% of them being on PEG-IFN α-2a (Pegasys, F.Hoffmann-la Roche Ltd., Basel, Switzerland) which is known for its safety in renal patients including renal failure compared with conventional interferon as its clearance is primarily by the liver[65-68]. Ribavirin has been suggested to have a protective effect against rejection in liver transplantation[69], and this could well be the case in renal transplant. We suggest that it is worth treating such patients with PEG-IFN and ribavirin. However close monitoring is essential. A weakness of our study is that it involves a small number and is retrospective in nature. Nevertheless it has shown that PEG-IFN in combination with ribavirin has a high safety profile and a very good sustained virological response. A prospective protocol involving a larger number of patients is advisable. We think that it would be much better and safer if HCV was treated before the transplant, and indeed this is the current practice at our institution; however even with this protocol there is a chance of recurrence of HCV in the post transplant period.

In conclusion, the combination of pegylated interferon and ribavirin in HCV-RNA positive renal transplant recipients was effective, with ALT normalized in 78% of patients in whom the levels were abnormal before therapy including non responders. ALT was normal in all responders at the end of therapy and at 24 wk post therapy (100%). Virological response was observed in 47.4% of all treated patients at the end of therapy and 42.1% (88.9% of responders) have a sustained virological response at 24 wk of follow up. Rejection occurred in only one patient (5.3%) during therapy. Our study, although retrospective and of small size, has shown that the combination of pegylated interferon and ribavirin has a significant role in suppressing HCV-RNA, without subjecting patients to a high risk of graft rejection or failure in HCV infected patients post renal transplantation. These findings need to be evaluated in large clinical studies. To our knowledge this is the largest reported series of HCV positive renal transplant recipients treated with pegylated interferon and ribavirin.

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COMMENTS

Background

Treatment of hepatitis C post renal transplant has been a debatable and controversial issue for a long time. Many studies have suggested that interferon is contraindicated in such patients due to high incidence of rejection, kidney failure and/or intolerance of patients to such therapy. Limited experience with pegylated interferon has been reported.

Research frontiers

This study reports on the largest group of patients with hepatitis C post renal transplant treated with a combination of pegylated interferon and ribavirin in the world, focusing on treatment response and kidney rejection.

Innovations and breakthroughs

The authors have treated 19 patients, who have hepatitis C and had kidney transplant with pegylated interferon and ribavirin for 48 wk. The virus was cleared in 42.1% and only one patient (5.3%) developed impairment of his kidney function towards the end of treatment period.

Applications

This research has clearly demonstrated the efficacy and safety of pegylated interferon and ribavirin in treating patients with hepatitis C virus (HCV) after renal transplant. This shall open doors for treating such patients, which were in the past left untreated because of a potential risk of kidney failure.

Terminology

Pegylated interferon is an antiviral therapy used for treatment of hepatitis C. Ribavirin is oral antiviral therapy that is used in combination with interferon for treatment of hepatitis C. Rejection is the process by which the human body refuses to accept the transplanted organ, and eventually leads to the organ failure.

Peer review

This is the largest reported series of HCV infected renal transplant recipients treated with pegylated interferon and ribavirin. The paper is generally well written and adds to the current experience regarding hepatitis C treatment in renal transplant patients.

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