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Original Article

Treatment efficacy and tolerability of Sofosbuvir and Ribavirin for chronic hepatitis C infection in post renal transplant patients – A retrospective single centre study

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ABSTRACT

Aim: To study the efficacy and tolerability of sofosbuvir and ribavirin in post renal transplant patients with chronic hepatitis C infection.
Methods: Data of 20 hepatitis C positive patients who had a negative viral load prior to renal transplant were analysed. They were given treatment with sofosbuvir 400 mg/day and dose adjusted ribavirin for 12 weeks, when they were found to have viraemia after transplant. Viral load was monitored at 4 weeks, 16 weeks and 24 weeks after initiation of therapy.
Results: 12 patients had genotype 1, 6 patients had genotype 3 and only 1 patient had genotype 4. 1 patient had mixed genotype infection. The median viral load was 3,394,705 IU/ml. Virological response was assessed at 4 weeks, 16 weeks and 24 weeks after treatment initiation. Rapid virological response (RVR) was seen in 19 patients (95%). Virological response at 4 weeks after treatment completion (SVR 4) was seen in 19 (95%) patients. Data were available for 13 patients who completed follow-up for 12 weeks after treatment completion. The remaining patients discontinued the drugs due to financial reasons. Sustained virological response at 12 weeks after treatment completion (SVR 12) was seen in 10 out of the 13 patients (76.9%). 3 patients did not attain SVR 12 and were regarded as treatment failure. The drugs were well tolerated in the majority. 1 patient required erythropoietin temporarily after ribavirin therapy.
Conclusion: Sofosbuvir and ribavirin showed a good efficacy and tolerability when used in renal transplant recipients. However, the genotype, nature of underlying liver disease, duration of therapy play an important factor in deciding the response to therapy.

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1. Introduction

Chronic hepatitis C remains an important health problem in chronic kidney disease and is associated with reduced graft survival after renal transplantation.[1] Besides this, hepatitis C is also associated with increased rates of rejection,[2] new onset diabetes mellitus[3] and occurrence of de-novo glomerulonephritis after renal transplant.[4] It is associated with fibrosing cholestatic hepatitis and extra hepatic complications like vasculitis.[5] The recommended treatment in the post-transplant setting with interferon is only when the benefits of the treatment outweigh the risks.[6] Conventional interferon therapy in the post renal transplant scenario has been associated with increased rates of allograft rejection.[7] Directly acting antivirals (DAA) could offer a new therapeutic armamentarium in post renal transplant recipients without precipitating rejection.

Directly acting antiviral agents (DAA) target different non-structural proteins of hepatitis C virus and inhibit its replication.[8] 4 classes of DAAs are present, which are defined by their mechanism of action and therapeutic target. The four classes are non-structural proteins 3/4A (NS3/4A) protease inhibitors (PIs),

Abbreviations: DAA, directly acting antivirals; PI, protease inhibitor; NPI, nucleoside protease inhibitors; NNPI, non nucleoside protease inhibitors; HCV, hepatitis C virus; MMF, Mycophenolate mofetil; FDA, Food and Drug Administration; IFN, interferon; RBV, ribavirin; SVR, sustained virological response; RVR, rapid virological response; CKD, chronic kidney disease; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; AASLD, American Association of Study of Liver Disease; EPO, erythropoietin; IDSA, Infectious Disease Society of America.

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NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors.

Telepravir and Bocepravir were the first generation NS3/4A inhibitors. They were used along with ribavirin and pegylated interferon for treatment of hepatitis C genotype 1 infection. Following the introduction of other potent and better tolerated DAA, the clinical importance of these agents diminished substantially because of their cumbersome administration, substantial adverse effects, drug-drug interactions, and low barrier to resistance.[9,10] Simeprevir and paritaprevir are second generation protease inhibitors which are known to have less side effect profile and drug interactions.[11] In post-liver transplant patients with HCV infection, significant interaction has been described when simeprevir and cyclosporine were coadministered and it resulted in significantly elevated simeprevir levels.[12]

NS5A inhibitors, ledipasvir and daclatasvir are potent drugs across all genotypes with less side effects, and have been shown to have no major clinical drug interactions with CYP3A inducers and inhibitors. Hence no major dose adjustments need to be made with tacrolimus, cyclosporine or MMF. Increase in the drug levels of daclatasvir has been found when administered with cyclosporine, but it has no clinical relevance.[13] The current recommendations for hepatitis C infection are based on genotype, subtype and the presence of cirrhosis. Ledipasvir is used in the treatment of genotype 1a,1b, 5 and 6. Daclatasvir is being used extensively across all genotypes. Both the drugs were not available in India at the time of the study.

Sofosbuvir is an NS5B nucleotide polymerase inhibitor available in India since March 2015. It is has to be administered along with other anti viral agents as a combination therapy. It's ease of administration, safety profile, least drug interaction potential among all DAA, availability and subsidised cost in India has made it the drug of choice for treatment for hepatitis C infection across all genotypes.[14] Renal elimination is the main form of excretion. It is not recommended in those patients with eGFR <30 ml/min.[15] Sofosbuvir was approved by the FDA as IFN-free therapy in combination with RBV for genotypes 2 and 3.[16] For patients with genotype 1 infection the combination of sofosbuvir and simeprevir might be an option, as good results have been obtained.[17] Other interferon-free options for chronic hepatitis C might include the combination of sofosbuvir and daclatasvir for genotypes 1–3.[18] Clearly, randomised clinical trials will be required to closely evaluate IFN free regimens in kidney transplant recipients.

2. Methodology

All our patients were known to be hepatitis C positive prior to transplantation. HCV viral load was negative at the time of transplantation. None of the donors (both live and deceased) were hepatitis C positive. Only one patient had evidence of cirrhosis by ultrasound. Liver biopsy was not done in any patient and fibroscan is not available at our institution. Patients were serially monitored with liver function tests once in 6 months and HCV viral load annually after their transplant. Treatment was commenced when sofosbuvir was available in India. Data was analyzed in 20 patients. The details of the pre-transplant evidence of cirrhosis (clinical and ultrasound), previous treatment with interferon, date of transplant, induction regimen use, pre-treatment viral load and genotype, creatinine and liver enzymes before and after starting treatment were included. Virological response after 4 weeks of treatment initiation (RVR) was monitored. Virological responses after 4 weeks of treatment completion (SVR 4) and after 12 weeks of treatment completion (SVR 12) were observed. Sofosbovir in the standard dose of 400 mg per day was used in all patients. Dose of ribavirin was adjusted based on the eGFR and serial haemoglobin values. The treatment was given for a period of 12 week. Erythropoietin was given if there was a significant drop in haemoglobin by more than 2 g/dl from the baseline. Haemoglobin was checked every week for 1 month. Liver function test were done every 2 weeks after treatment initiation till liver enzymes reached normal levels. Renal function test were monitored every month. HCV viral load was done by Roche COBAS® Ampliprep TNAI/TaqMan® 48 RUO Assay.

3. Results

20 patients were studied. 14 were men (70%) and 6 (30%) were women. Mean age of the patients was 43.4 ± 10.57 years (95% confidence interval). Hypertension was present in all the patients. 12 had genotype 1, 6 patients had genotype 3 and only 1 patient had genotype 4. 1 patient had a mixed genotype infection with 1a and 2. 19 patients were treatment naïve, while only1 patient had previous exposure to interferon for 48 weeks for which he had responded to treatment prior to transplant. The median viral load was 33,94,705 IU/ml.

The main cause of CKD was Chronic glomerulonephritis (50%), followed by Chronic interstitial nephritis (30%), autosomal dominant polycystic kidney disease (10%), diabetic nephropathy (5%) and hypertensive nephrosclerosis (5%). 5 patients underwent deceased donor renal transplantation and the remaining underwent living donor renal transplantation. 6 patients received induction regimen with thymoglobulin and the remaining patients received basiliximab as induction agent. 3 patients had previous evidence of hepatitis B infection and were treated during haemodialysis. Hepatitis B viral load was negative prior to transplantation and prior to initiation of hepatitis C treatment. None of the patients had clinical evidence of decompensated liver cirrhosis. HCV viral load was tested annually in the post transplant period and when patients had elevated liver enzymes. Liver function tests were monitored once in 6 months after transplant. Mean SGOT levels prior to treatment initiation were 64.4 ± 54.22 and mean SGPT levels prior to treatment initiation were 65.15 ± 60.0. 12 out of 20 patients had elevated SGOT and 13 of 20 patients had elevated SGPT (Table 1). Median time to initiation of therapy for Hepatitis C treatment was 12.5 years after their renal transplantation.

RVR was 95%. Only one patient did not attain RVR, but was continued on treatment and achieved SVR 4. SVR 4 was 95%. Data is available for only 13 patients who completed 12 weeks follow up after 3 months of treatment (Table 2). 10 out of the 13 patients

Table 1
Baseline characteristics of the patient.

Age (mean in years)	43.4 ± 10.57
Male:female ratio	2.33:1
Basic disease	
Chronic glomerulonephritis	10
Chronic interstitial nephritis	6
Polycystic kidney disease	2
Diabetic nephropathy	1
Hypertensive nephrosclerosis	1
Pre treatment median HCV viral load (IU/ml)	3,394,705
HCV genotype	
1	12
2	0
3	6
4	1
1a and 2	1
Live renal transplant	12
Deceased donor renal transplant	6
Prior transplant	7
Prior treatment with interferon	1
Baseline mean S. creatinine (mg %)	1.41 ± 0.54
Baseline mean SGOT, IU/ml	64.4 ± 54.22
Baseline mean SGPT, IU/ml	65.15 ± 60.0

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