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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.

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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Table 2
Response to therapy.

RVR (in 20 patients)	95%
SVR 4 (in 20 patients)	95%
SVR 12 (in 13 patients)	76.9%
Treatment failure (in 13 patients)	23.1%

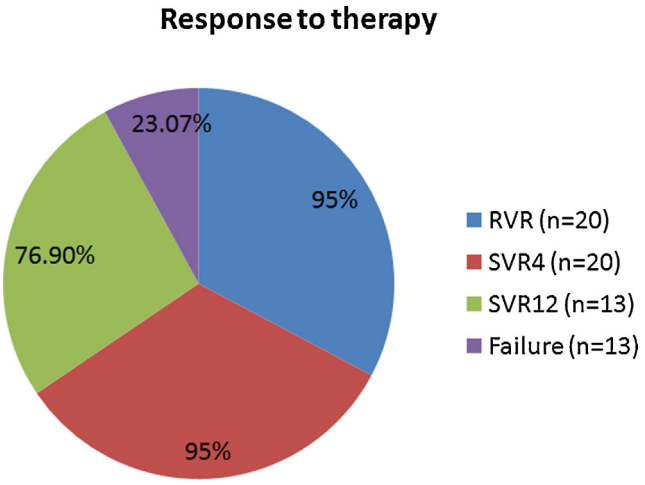

Fig. 1. Response to therapy.

showed SVR 12 (76.9%). SGOT and SGPT levels became normal in all patients after 2 weeks of treatment initiation. Mean SGOT levels 2 weeks after treatment initiation was 22.14 ± 10.3 and mean SGPT levels 2 weeks after treatment initiation was 18.6 ± 9.4. 3 out of 13 patients did not achieve SVR 12. They were considered treatment failure (Fig. 1). There was no change in the baseline creatinine 2weeks and 1 month after initiation of therapy. 13 patients were on cyclosporine and 7 patients were on tacrolimus. Routine tacrolimus or cyclosporine levels were not done after treatment initiation with sofosbuvir and ribavirin unless it was warranted clinically by graft dysfunction. All patients had stable graft function during the study treatment.

Mean haemoglobin was 13 g/dl at the baseline. There was a mild drop in haemoglobin 15 and 30 days after starting ribavirin with mean haemoglobin of 11.99 g/dl and 10.88 g/dl respectively. One patient had a significant drop of haemoglobin (>2 g% from the baseline) and erythropoietin was administered in a dose of 4000 units twice weekly. Ribavirin was withheld and restarted along with erythropoietin after haemoglobin improved to the previous baseline. There was no leucopoenia or thrombocytopenia seen in our patients.

4. Discussion

Interferon free regimens using directly acting antiviral drugs offer new perspectives for kidney transplant recipients. Apart from their efficacy, the reduced toxicity makes them an attractive therapeutic option after kidney transplantation. All our patients were known to be chronic hepatitis C positive prior to transplantation. Although HCV in post renal transplant recipients is associated with increase in mortality, interferon based therapy was not used in our patients for the inherent risk of worsening allograft function.[19] Patients were serially monitored with liver function tests and HCV viral load till sofosbuvir was made available in India. Our study suggested that a combination of sofosbuvir and ribavirin when used to treat hepatitis C infection showed a RVR of 95% and SVR 4 of 95% in all patients. SVR 12 of 76.9% was seen in 10 out 13 patients. Although SVR at 24 weeks after treatment completion was used as the standard definition, recent studies demonstrate excellent clinical correlation between SVR at 12 weeks and SVR at 24 weeks using sofosbuvir based regimens.[20] Hence, we used 12 weeks after treatment completion to define SVR in our study population. There were no new onset graft dysfunctions indicating no major drug interactions between sofosbuvir and immunosuppressants predisposing either to rejection or calcineurin toxicity. Our study demonstrates the safety and efficacy of sofosbuvir which is in concordance with other studies used in liver transplant recipients.[21] 8 kidney transplant patients showed good response to sofosbuvir and ribavirin in an early efficacy and safety study.[22] A single case of successful all oral treatment with a combination of sofosbuvir and daclatasvir after liver transplantation has been published.[23] Kamar et al. recently published the efficacy and safety of sofosbuvir based antiviral therapy. In this study sofosbuvir was combined with different anti viral agents including ribavirin, daclatasavir, ledipasvir, simpepravir. Although only 3 patients were present in the sofosbuvir and ribavirin arm, the overall SVR was 100%.[24] There is a single case report from India in which ledipasvir and sofosbuvir has been used in a post renal transplant recipient to treat hepatitis C.

There are a number of limitations to our study. We are unable to give the SVR for all the patients as 7 of them have defaulted therapy due to financial reasons. If available, the data could have thrown more light into the SVR 12 of sofosbuvir and ribavirin. The reason for the default was the cost for 12 weeks of therapy which is around Rs 50,000 to Rs 55,000, which is an overburden for the transplant patients in India. Liver biopsy was not done in any patients, thus the underlying nature of chronic active hepatitis or fibrosis was not made out. Fibroscan is a recent therapeutic armamentarium which was not available during the time of transplant to the patients at our institute. The reasons behind the low rate of SVR 12 were plenty. The constantly evolving field of direct acting antivirals in chronic hepatitis C recommends new drugs to specific genotypes as per the AASLD/IDSA guidelines. The current recommendation by the AASLD/IDSA is a fixed dose combination of ledipasvir with sofosbuvir, daclatasvir with sofusbuvir, simpepravir with sofosbuvir or fixed dose combination of paritaprevir/ritonavir/ombitsavir with twice daily dasabuvir and weight based ribavirin for genotype 1 and daclatasvir with sofosbuvir for genotype 3.[25] We could not use the above drugs as they were not available in India at that point of time. Among the treatment failures there were 2 patients with genotype 1 and 1 patient with genotype 3. The reason for the treatment failure could be due to improper selection of the drugs for these genotypes which were recommended later. The duration of treatment in our study was 12 weeks as defined by various clinical trials, where sofosbuvir and ribavirin were used. However, AASLD/IDSA recommends an extended treatment of 24 weeks duration in patients with underlying cirrhosis and this was superior to the 12 weeks of therapy to suppress the viral replication.[25] This was not possible in our study as neither liver biopsy nor fibroscan were done. The pangenotypic effect of sofosbuvir was utilised to study the virological response across all genotypes. The tolerance to oral anti-HCV therapy was excellent and no major adverse event was observed. There was no new onset graft dysfunction in all patients, indicating that there were no major drug interactions with immunosuppressant. However we did not monitor drug levels of tacrolimus or cyclosporine after treatment with sofosbuvir to demonstrate alteration in their levels. We concur with guidelines of the AASLD that serial haemoglobin needs to be monitored during ribavirin therapy and need EPO supplementation if haemoglobin falls by more than 2 g% from the baseline. We conclude that sofosbuvir combined with ribavirin is moderately effective across most of the genotypes of hepatitis C and has good efficacy and safety profile with no major drug interactions with immunosuppressive agents. Further studies are required to guide the usage of directly

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acting antiviral agents in patients who have cirrhosis and the use of these drugs in various genotypes of hepatitis C in post renal transplant recipients. Large scale prospective studies are also required to explore the pharmacokinetics and cost effectiveness of various regimens of directly acting antiviral drugs in post renal transplant recipients.

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Conflicts of interest

The authors have none to declare.

Patient consent and ethical committee clearance

Obtained.

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