Pegylated interferon monotherapy for hepatitis C virus infection in patients on hemodialysis: A single center study

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ABSTRACT

There is no published study from India on hepatitis C virus (HCV) treatment in dialysis patients. Patients on dialysis with HCV infection treated with pegylated interferon (Peg-INF) monotherapy were studied. All patients were subjected to HCV-polymerase chain reaction, viral load, genotype, and liver biopsy. Quantitative HCV-RNA was performed monthly. Patients with genotype 1 and 4 were given 12 month therapy while those with genotypes 2 and 3 were given 6 months therapy. Response was classified as per standard criteria of rapid virological response (RVR), early virological response (EVR), end of treatment response (ETR), and sustained virological response (SVR). A total of 85 patients were treated. Mean age was 35.2 ± 10.5 (range 15–67) years, and 77.6% were males. HCV genotypes were 1 in 40.9%, 2 in 12%, 3 in 36.1%, 4 in 3.6%, and others in 7.2%. Mean viral load was 10^6 copies/mL. Mean liver biopsy grade was 4 ± 1.7 and stage 0.8 ± 0.8. Mean time from diagnosis of HCV infection and the treatment start was 10.7 ± 14.3 months. One patient died of unrelated illness, one was lost to follow-up, and three could not sustain treatment due to cost. Forty-three of the 80 (54%) patients had RVR while 49 (61%) patients had EVR and ETR. There was no difference in term of RVR related to genotype. Fifty -four percentage had SVR. Mild flu-like symptoms were seen in all patients. Sixty-four (80%) patients required increase in erythropoietin doses. Twenty-eight (35%) patients developed leukopenia (three treatment-limiting) and 16 (20%) developed thrombocytopenia (one treatment-limiting). Five patients developed tuberculosis, five bacterial pneumonia, and one bacterial knee monoarthritis. None of the patients developed depression. Our study concludes that Peg-INF monotherapy resulted in 54% RVR and SVR in dialysis patients with HCV infection. Therapy was well-tolerated with minimal side effects. There was no effect of viral genotype on response to therapy.

Key words: Hemodialysis, hepatitis C virus, India, pegylated interferon

Introduction

Hepatitis C virus (HCV) infection is the most common hepatotropic viral infection affecting the patients on maintenance hemodialysis (MHD). Its prevalence in patients on MHD ranges from 6% to 60% worldwide. In India, various studies showed prevalence of HCV in hemodialysis from 12% to 45%.[1] From our own center, we had published prevalence of HCV in MHD to be from 4.3% to 42% depending upon vintage of MHD in our unit; 42% being at the end of MHD, just before renal transplantation (RT).[2] The major factors affecting the HCV incidence during MHD are nosocomial transmission and transmission through blood and blood component.[3,4] With the development of universal screening of the blood and blood products, nosocomial transmission remains the major route of spread in these patients. We have also shown that chronic liver disease is cause of mortality in RT in the second decade in 25% of the patients at our centers.[5] HCV also increases the risk of serious infection in renal transplant patients.[6] With significant increase in spread of HCV infection

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in many dialysis units in India, we suggested to isolate HCV-infected patients in addition to universal precaution.[7] This was more relevant, once we found that hospital staff was not strictly following universal precautions.[8]

However, whatever precautions are taken to contain HCV infection during MHD, a significant proportion of patients do develop new HCV infection. KDIGO guidelines had suggested that HCV-infected kidney transplant candidates be considered for treatment with standard interferon (IFN) before transplantation, though the evidence for recommendation was weak.[9] Uncontrolled trials have demonstrated that administration of conventional IFN therapy to patients on MHD with HCV infection achieves sustained virological response (SVR) in about 40% of the cases[10-12] and this SVR achieved during MHD is sustained in 80–90% of the recipients following transplantation.[13-15] A large retrospective study of HCV infection during MHD had shown that without treatment, there is significantly increased risk for chronic allograft nephropathy.[16] Thus, large bodies of evidence suggest that HCV-infected patients during MHD should be treated before transplantation. A multicenter trial on treatment of HCV in MHD using conventional INF was prematurely terminated because of significant side effects.[17] In non-chronic kidney disease (CKD) patients, pegylated-INF (Peg-INF) with ribavirin has been standard of care. However, KDIGO guidelines suggested conventional INF for treatment of these patients. These guidelines were published in 2008 and until that time, there was limited number of studies on Peg-INF,[18-22] which might have resulted such recommendation. Our initial experience with conventional INF was not good as patients could not tolerate conventional INF (unpublished data). Following that, we started using Peg-INF monotherapy in these patients. There is no published study from India on therapy of HCV in MHD patients, and thus we thought of sharing our experience on Peg-INF monotherapy in the treatment of HCV during MHD in this part of world.

Methods

All the patients of end-stage renal disease taken for renal replacement therapy at out hospital with HCV infection and treated with Peg-INF monotherapy were included in the present study. At the time of accepting the patient for MHD, anti-HCV was tested in each patient. Any patient who was positive for HCV was taken for MHD in isolated room. During MHD, all patients were monthly tested for anti-HCV, aspartate transaminase, and alanine transaminase (ALT). Patients who had high ALT but negative for anti-HCV were also isolated unless there is satisfactory cause for high ALT.[23] Patients having positive anti-HCV were further investigated with qualitative HCV-RNA, HCV viral load, and HCV-genotype. All patients were subjected to liver biopsy except those patients who had liver cysts associated with polycystic kidney disease or those patients who were on continuous ambulatory peritoneal dialysis. Patients before starting treatment were also tested for hemoglobin (Hb), total leukocyte count (TLC), differential leukocyte count (DLC), platelets, reticulocyte counts, glucose tolerance test, T3 and T4, thyroid stimulating hormone (TSH), anti-thyroid antibodies, anti-thyroid peroxidase antibodies, anti-liver kidney microsomal type 1, anti-mitochondrial antibody, antinuclear antibodies, serum iron, ferritin, transferrin saturation, and alpha-fetoprotein using standard methods. Timing of HCV infection was taken from the time since ALT was high above normal limit or anti-HCV was positive, whichever was earlier. Time in months was also assessed from the time of HCV infection and the time when treatment was started.

HCV infection was diagnosed using the third generation ELISA test kit (J Mitra and Co., Ltd., India). HCV-RNA was determined by real-time polymerase chain reaction (PCR) and involves sequence-specific amplification. This was done on real-time PCR using TaqMan method. HCV genotyping was determined by PCR and involves sequence-specific amplification. Analysis was based on PCR of the core region with the genotype-specific primers, which allows for the determination of HCV genotypes 1a, 1b, 2a, 2b, 3a, 3b, 4, 5a, and 6a. Each test was performed with positive and negative controls. The PCR products were analyzed using electrophoresis and Gel Doc Systems. For viral load, the amplified product was detected via fluorescent dyes, which was linked to oligonucleotide probes, which bind specifically to the amplified product. Monitoring the fluorescence intensities during the PCR run allows the detection and quantification of the accumulation product, which was monitored on the desktop of computer. Nucleic acid extraction columns (QIAGEN Hamburg), and internal controls were added to lyse buffer to monitor and check for PCR. PCR Master Mix HCV RG RT-PCR reagents - QIAGEN Hamburg were used. Ten microliters of RNA and 15 μL of Master Mix were added to 0.2 mL tubes and loaded onto the real-time PCR machine, Artus 3000TM.

The first two injections of the Peg-INFα2a were given in the dose of 90 μg subcutaneously on nonvascular access forearm of the patient. Paracetamol in 500 mg dose was advised one after the injection and one after 6 h routinely. After that, paracetamol was advised as per the need of the patient. Peg-INF was given on nondialysis days. Before the next dose of injection, test

for serum bilirubin, ALT, Hb, TLC, DLC, and platelets were done. Dose of Peg-INF was decreased to 50% if TLC was between 3000/cmm and 4000/cmm, platelets between 50,000/cmm and 75,000/cmm. Dose of the drug was missed if TLC was <3000/cmm and platelets <50,000/cmm. Patients were temporarily treated with granulocyte colony stimulating factors for 1–2 doses for managing leukopenia. Dose of Peg-INF was usually not changed on the basis of Hb value alone, although Hb value was taken into account for increasing the dose of erythropoietin and/or advising blood transfusion. Quantitative HCV-RNA was done every month. If the patient completed the therapy, HCV-RNA was repeated 2 months after the last dose of Peg-INF. After the transplant, RNA was again tested after 3–4 months to classify SVR. Response to therapy was classified as rapid virological response (RVR), early virological response (EVR), end of treatment response (ETR), and SVR based on conventional criteria. After initial 50 patients experience, any patient who did not respond after 3 months of treatment, therapy was stopped. Patients with genotype-1 and 4 were given 12 months therapy while genotype-2 and 3 were given 6 months therapy.

Results

From 2005, 170 patients were screened for possible treatment, of which only 85 patients were initiated on treatment due to affordability. Table 1 shows basic details of treated and untreated patients. The only significant differences between two groups were that males were less common and ALT was significantly lower in treated group as compared to untreated group. In the treated patients, mean age was 35.2 ± 10.5 (15–67) years and males were 77.6%. Diabetes as basic disease was in 8.3% cases. Mean ALT value was 64.8 ± 42.8 (12–259) IU/dl and mean alpha-fetoprotein was 4.4 ± 7.1 (0–9) IU/dl. HCV genotypes were 1 in 40.9%, 2 in 12%, 3 in 36.1%, 4 in 3.6%, and others were in 7.2%. Mean viral load was 10^6 copies/mL. Liver biopsy grade was 4 ± 1.7 (1–10) and stage 0.8 ± 0.8 (0–3). Details of liver biopsy in our set-up of patients had been published elsewhere.[24] None of the patients had raised bilirubin and/or clinical hepatitis at presentation. Other investigations of patients done before start of treatment are shown in Table 2. Mean time duration from the time of known HCV infection and the treatment start was 10.7 ± 14.3 months (range 3–98). Flow of patient treatment is shown in Figure 1. Of 85 patients started on treatment, 1 patient died of unrelated illness, one lost to follow-up, and three could not sustain treatment due to cost involved. Eighty patients could complete at least 1 month of therapy and thus were analyzed for efficacy of treatment. Forty-three (54%) patients had RVR while 49 (61%) patients had EVR and ETR. There was no difference in term of RVR related to genotype; of the 43 patients, who had RVR, 40% were genotype-3 and 37.5% were genotype-1. None of the patients had a breakthrough infection while on therapy.

Table 1: Basic details of treated and untreated patients

Demopgraphic features	Treated patients	Untreated patients	*P*
Number of patients	85	85	
Mean age (years)	35.2±10.5 (15-67)	32.8±10.1 (15-67)	0.13
Males (%)	66 (77.6)	76 (90.5)	0.02
Diabetes as basic disease (%)	7 (8.3)	3 (3.9)	0.23
Genotype status (%)			
1	35 (40.9)	27 (31.5)	0.22
2	10 (12)	12 (14.6)	0.76
3	31 (36.1)	36 (42.1)	0.42
4	3 (3.6)	Nil	0.10
Others	6 (7.2)	10 (11.9)	0.35
ALT (IU/dl)	64.8±42.8 (12-259)	108±49.1 (22-214)	<0.001
Alpha-fetoprotein (U/L)	4.4±7.1 (0-9)	3.4±1.9 (1-6.7)	0.2
Liver biopsy grade	4±1.7 (1-10)	4.4±1.7 (1-9)	0.12
Liver biopsy stage	0.8±0.8 (0-3)	0.8±0.8 (0-3)	1.0

ALT: Alanine transaminase

Table 2: Baseline investigation in treated patients

Investigation	Mean (range)
Hb (g/dl)	10.4±2.1 (6.9-15.7)
TLC (Cells mm^3)	7374±2405 (3210-13,500)
Platelets (Cells x 100/mm^3)	188.8±58.4 (90-386)
Abnormal GTT (0, 30, 60, 90, 120 min) (%)	12.9
T3 (ng/dl)	106.9±31.3 (30-174)
T4 (µg/dl)	7.4±2.6 (0.8-11.9)
TSH (IU/dl)	5.3±9.3 (0.1-60)
High ATA (%)	10.1
High ATPA (%)	30
Positive AMA (%)	4.2
Positive ANA (%)	1.5
Positive LKM-1 antibody (%)	0
Serum iron (µg/dl)	128.6±72.8 (19-309)
Ferritin (ng/dl)	925.8±919 (56-4840)
Iron saturation (%)	44.3±26.3 (7-100)

GTT: Glucose tolerance test, ATA: Anti-thyroglobulin antibodies, ATPA: Anti-thyroid peroxidase antibodies, AMA: Anti-mitochondrial antibody, ANA: Anti-nuclear antibody, Hb: Hemoglobin, TLC: Total leukocyte count, TSH: Thyroid-stimulating hormone, LKM-1: Liver kidney microsomal type 1

Mild flu-like symptoms with varying severity were seen in almost all patients. However, regular paracetamol as per our treatment protocol could control these. Some patients did require paracetamol for 2–3 days following initial injections. The majority of the patients, that is, 64 (80%) required increase in erythropoietin doses with or without injectable iron therapy. Maximum dose of erythropoietin given was 14,000 units/week in 3 patients. Twenty-eight (35%) patients developed leukopenia, of which three had treatment-limiting leukopenia. Sixteen (20%) patients developed thrombocytopenia, of which one had treatment-limiting thrombocytopenia. One patient developed optic atrophy during treatment and

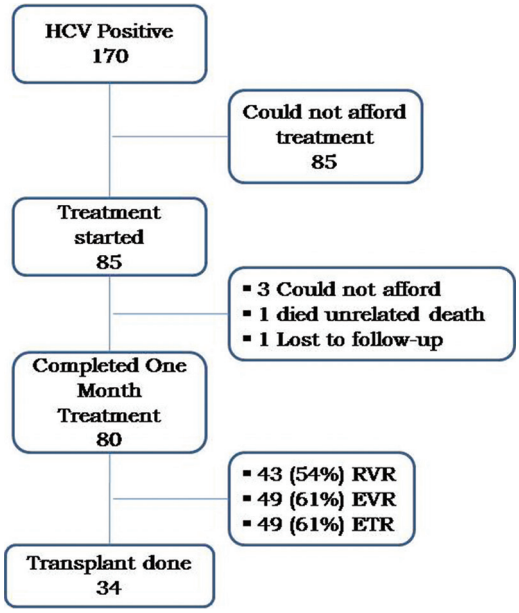

Figure 1: Flow of patients in the study

1 patient developed lupus activation with cerebritis while on therapy.[25] Six patients who had high TSH required concomitant thyroxin while on Peg-INF. None of the patients who had isolated high anti-thyroid antibodies, anti-thyroid peroxidase antibodies without increased TSH required thyroxin while on Peg-INF. One patient, who had positive ANA, did not have any symptoms of lupus clinically while on therapy. Five patients developed tuberculosis, five bacterial pneumonia, and 1 patient developed bacterial knee monoarthritis. None of the patients developed depression and no patient had treatment-limiting asthenia. Of the treated patients, 34 could be transplanted. Immunosuppressive therapy was decided on patient own immunological risk profile rather than HCV infection and or response to treatment. HCV-RNA just before renal transplant and 3–4 months following transplantation did show relapse in 6 patients, thus keeping SVR of 54%.

Discussion

Therapy of HCV is expected to change significantly in time to come and we may look forward to non INF-based therapy even in patients on MHD and renal transplant also. However, until it is applicable, it will be worthwhile to review the current status of INF-based treatment of HCV in MHD patients. The present study is the first single center study from India in sizeable number of patients showing SVR in 54% of the patients with minimal dropout rate. Previously published studies of Peg-INF monotherapy in these patients are shown in Table 3 for comparative analysis.[24-49] The goal of the treatment of HCV-infected patient is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by achieving virological cure as evidenced by an SVR. Although patients treated with either conventional or Peg-IFN-a have similar efficacy and safety results on the basis of meta-analysis studies, one head-to-head randomized trial showed that the overall efficacy and safety in patients treated with Peg-IFN-a were superior to those treated with conventional IFN-α.[36] In published studies with Peg-INF in these patients, SVR had ranged from 0% to 92%. One of the major variables affecting these results has been number of patients included in the studies, which has ranged from 3 to 102. Obviously, results in percentage in studies with small numbers of patients are misleading. If we only include studies with at least 50 patients, there are only five studies including present study with SVR ranging between 14% and 50%.[20,42,45,48] There is no study that has compared Peg-INF α2A and Peg-INF α2b in these patients.

Response rate to Peg-IFN in HCV infection also varies as per the genotype of the virus. Though genotype in dialysis unit is primarily affected by the frequency of genotype infection in population, due to nosocomial mode of spread, it is possible that frequency of genotype in patients on dialysis may differ from general population due to accumulation of patients of one particular genotype. In the present study, genotype-1 was present in 41% patients followed by genotype-3. There has been variable frequency of genotype-1 in different studies. While five studies had not mentioned genotype status, in rest of the studies, frequency of genotype-1 has ranged from 20% to 100%. In five studies with sizeable number of patients, genotype-1 had ranged between 41% and 100%. There are seven studies in dialysis patients with all patients having genotype-1 infection but still SVR had been 33–75%. Almost all of these studies had not reported duration of HCV infection before treatment started except one study,[29] where mean duration of infection was 41 months before start of treatment. Viral load in all the studies was between 10^5 and 10^7 and, therefore, it was difficult to separate out impact of viral load on response to therapy in these patients. In our study also mean viral load was 10^6 copies.

SVR in HCV has been reported to be more likely in patients who had taken at least 80% of all scheduled IFN injections for at least 80% of the anticipated duration of treatment.[50] The two most important factors affecting dose and duration are cost of therapy and drug side effects. We have started therapy in patients after explaining cost and duration in great detail. Still, we had 3 of 85 stopping treatment very early because of cost. In previous studies, cost had not been discussed, may

Table 3: Peg-INF monotherapy therapy in dialysis patients with HCV infection

Author	Year	Number of cases	DOI (month)	Genotype-1 (%)	Mean viral load	DIM	Dose (µg)	RVR (%)	EVR (%)	ETR (%)	SVR (%)	Drop out	Comments and side effect
Annicchiarico and Siciliano[26]	2004	6	NA	100	106	6	0.6-1.1 µg/kg	NA	60	NA	33	33	Diarrhea and fatigue most common
Kokoglu *et al*.[19]	2006	12	NA	100	105	12	135	NA	75	83	75	0	Hematological side effects but no SSE
Rivera *et al*.[27]	2005	7	NA	NA	NA	48	135	NA	NA	43	NA	14	Limited information about study
Teta *et al*.[28]	2005	3	NA	66	106	12	180	NA	NA	67	67	33	Depression 33% Lung infection - 33%
Sporea *et al*.[18]	2006	10	NA	NA	105	6-12	180	NA	87	87	30	30	20% noncompliance 10% sepsis
Covic *et al*.[29]	2006	78	41	NA	106	12	135	NA	61	19	14	32	83% adverse events
Russo *et al*.[30]	2006	16	NA	89-100	106	12	0.5-1.0 µg/kg	NA	NA	NA	0-22	28-56	Two doses regimen 28-56% SSE, sepsis, hypertension, hypoglycemia, etc.
Casanovas-Taltavull *et al*.[31]	2007	12	NA	58	NA	12	135	NA	NA	83	25	25	SSE-anemia (1), sepsis (1), stroke (1)
Sikole *et al*.[32]	2007	14	53	93	106	12	135	NA	71	57	36	21	SSE-pericarditis (2), pneumonia (1), cerebral hemorrhage (1)
Chan *et al*.[33]	2007	6	NA	33	105	12	135	NA	NA	NA	33	33	1 heart failure 1 cholangitis No depression
Espinosa *et al*.[34]	2007	7	NA	NA	NA	12	135	NA	NA	NA	0	29	Various complications
Amarapurkar *et al*.[35]	2007	6				6	1.0 µg/kg				50	NA	
Espinosa *et al*.[34]	2007	9	NA	NA	NA	6	1.5 µg/kg	NA	NA	NA	57	44	
Zoppoli *et al*.[22]	2008	10	NA	60	105	6-12	135	NA	70	20	20	50	Asthenia and pancytopenia SSE
Liu *et al*.[36]	2008	25	NA	80	106	6	135	60	92	92	48	0	RCT comparing Peg-INF versus conventional INF
Ayaz *et al*.[37]	2008	22	NA	100	105	12	135	NA	82	82	65	23	SSE-anemia (2), asthenia (2) and GI bleed (1)
Akhan *et al*.[38]	2008	12	NA	100	107	12	135	NA	58	50	50	0	SSE mainly hematological
Kose *et al*.[39]	2009	33	NA	100	108	12	135		100		46.1	6	
Tan *et al*.[40]	2010	34	NA	70.6	106	6-10	1.0 µg/kg	NA	85	53	50	33	65% required transfusion SSE-anemia (6), asthenia (1), seizure (1), CAD (1)
Basic-Jukic *et al*.[41]	2011	16	NA	75	105	12	135	NA	NA	83	56	13	SSE-endocarditis (1), sepsis and vascular insufficiency (1)
Peck-Radosavljevic *et al*.[42]	2011	81	NA	75	105	12	90-135	NA	45	NA	35-40	7-13	22 center study, 6 deaths due to various causes Predictivity of SVR from EVR and viral load
Giguere *et al*.[43]	2011	5	NA	20	105	6	1.0 µg/kg	50	80	80	60	0	5 patients only Hematological side effect main side effect
Duseja *et al*.[44]	2012	13	NA	75	106			44	69	44	44	44	45% lost to follow-up
Liu *et al*.[45]	2013	102	NA	100	105	12	180	36	93	84	33	4	RCT in 8 center Taiwan, 6% breakthrough infection/RVR correlation with SVR, dose reduction in 44%
Tseng *et al*.[46]	2013	26	NA	42	105	6-12	1.0 µg/kg	55	60	80	35	23	SSE-severe anemia main cause of withdrawal
Köse *et al*.[47]	2013	38	90.1	100	107	12	135	NA	60.5	63	50	NA	Histology correlated with SVR
Kikuchi *et al*.[48]	2014	56	NA	73	106	6-12	90-135	32	54	76-100	39, 21-93	25	Multicentric study Genotype and viral load and RVR affected SVR
Wang *et al*.[49]	2014	12	NA	83	105	6-12	67.5	NA	83.3	92	92	8	SSE-leukopenia (1) Low dose therapy
Present study	2014	80	10.7	41	106	6-12	135	54	61	61	54	5	SSE-Leukopenia (3), thrombocytopenia (1)

DOI: Duration of infection, DIM: Duration in months, NA: Not available, SSE: Serious side effects are treatment-limiting, µg/kg dose is for Peg-INF α2b. HCV: Hepatitis C virus, RVR: Rapid virological response, EVR: Early virological response, ETR: End of treatment response, SVR: Sustained virological response, RCT: Randomized controlled trials, GI: Gastrointestinal, CAD: Coronary artery disease, Peg-INF: Pegylated-interferon

be at most places, treatment is supported by medical providers or insurance. In India, most of treatments are self-funded, so cost is an issue for sustaining prolong and costly treatment. In our cohort, there was 5% dropout rate (3 leukopenia and 1 thrombocytopenia). None of the patients had depression or severe asthenia limiting continuation of therapy. In other published studies, dropout rate due to side effects had ranged between nil to 50%. Again, if we take studies with sizeable number of patients,[20,42,45,48] treatment-limiting side effects were in 4–32%. Most common reported side effects in these patients were hematological, infection, depression, and asthenia. Although it has been reported that the rates of IFN dose reduction and discontinuation were similar among subjects receiving Peg-IFN and conventional IFN,[51] it is experience of many that tolerability of Peg-IFN is much better and also the convenience of once a week injection. Peg-IFN monotherapy has also been recommended for patients with contraindications to ribavirin, such as those with renal insufficiency, hemoglobinopathies, and ischemic cardiovascular disease.[52] However, recently ribavirin has been used in these patients with modified doses, and many consider ribavirin only a relative contraindication in patients with CKD and dialysis.

In nondialysis patients, RVR has been correlated with SVR in most clinical setting. There are six studies[36,43-46,48] who had reported RVR rate ranging between 32% and 60%. Of these, only two studies[45,48] assessed correlation between RVR and SVR and showed a positive correlation. In the present study, RVR was a major predictor of SVR and very few additional patients showed SVR if they did not achieve RVR. In fact, if patient did not respond in 3 months, we started stopping treatment as these patients were unlikely to respond. We had not seen any patient having breakthrough HCV infection while on treatment.

With the availability of direct anti-viral agents (DAA), the scenario of treatment of HCV in dialysis population is also likely to change. Though until now there is no published randomized trial of DAA in dialysis population, there is an ongoing trial of sofosbuvir and ribavirin in hemodialysis population. Our own personal experience suggest that this combination is likely to show a very good response if carefully given in these patients (unpublished data).

Our study has limitation of being a retrospective study. However, due to cost of therapy limiting the enrollment of patients, unless the cost of treatment is supported by funding agency or sponsor, it will be difficult to do a prospective study of patients on hemodialysis HCV infection, more so in Indian context.

Conclusion

Peg-INF monotherapy in patients with HCV infection in Indian population is well-tolerated with reasonable SVR. The response rate was not affected by genotype status. Very few patients required discontinuation of therapy due to side effects and dropout rate had been minimal. RVR was strong predictor of SVR. Until, safety and efficacy of DAA are established in these patients, Peg-INF will remain an acceptable option for treatment before renal transplant.

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Conflicts of interest

There are no conflicts of interest.

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