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SHORT REPORT

Efficacy and safety of hepatitis C antiviral therapy in moderate and severe chronic kidney disease

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Abstract Hepatitis C virus (HCV) infection is an important cause of liver-related morbidity and mortality in patients with end-stage renal disease (ESRD). Though indicated, antiviral therapy adds to the existing financial burden and is poorly tolerated in these patients. We studied HCV treatment outcomes in patients with moderate and severe chronic kidney disease (CKD) between June 2010 and June 2012. Out of 46 patients with CKD, only 16 (genotype 1:6, 3:9, indeterminate 1) received interferon treatment (conventional 9, pegylated 7; with low-dose ribavirin 5). End of treatment response was achieved in 50 % and sustained viral response in 44 %. Adverse effects such as tuberculosis, anemia, and cardiac failure resulting in discontinuation of therapy were seen in three. The dropout rate was 38 %. Though interferon therapy was efficacious and safe, it was received by only 35 % of patients with CKD. We suggest that antiviral therapy be offered under close monitoring in the absence of contraindications in patients with moderate and severe CKD.

Keywords Chronic kidney disease · End-stage renal disease · Hepatitis C virus

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Introduction

Hepatitis C virus (HCV) infection is a major health problem in patients with chronic kidney disease (CKD), especially in those with end-stage renal disease (ESRD) who are undergoing hemodialysis contributing to liver-related morbidity and mortality [1]. In Indian patients with ESRD, HCV PCR positivity has been reported to be 28 % [2]. Treatment of hepatitis C (HCV) in ESRD patients is recommended prior to renal transplantation in treatment guidelines proposed by major liver societies for HCV [3] as the presence of HCV infection has been found to be associated with poor patient and graft survival following renal transplantation (RT) [4]. Meta-analysis has confirmed the poor tolerability and increased risk of graft dysfunction when the treatment is given after RT [5]. Hence, the ideal time to treat HCV in ESRD patients is prior to RT [6]. But with the available treatment modalities which require interferon injections to be given for 24 to 48 weeks depending on the genotype, there are many medical, financial, and practical difficulties which preclude successful antiviral therapy. In fact, a recent report from Dialysis Outcomes and Practice Patterns Study of 49,762 hemodialysis (HD) patients in 12 nations enrolled between 1996 and 2011 has shown that only one percent of the total of 4,739 ESRD patients with HCV were receiving antiviral treatment [7].

In this article, we narrate our experience with antiviral therapy in ESRD patients listed for RT and a few patients with moderate CKD.

Materials and Methods

From June 2010 to June 2012, out of 429 patients with HCV infection seen in the department of Hepatology, patients referred from Nephrology with moderate and severe CKD were analyzed in a retrospective manner after obtaining clearance

from the institutional review board. CKD was defined as per the Kidney Disease Improving Global Outcomes practice guidelines 2012 [8]. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation [9].

HCV PCR positivity was considered requisite to be diagnosed as HCV infection. HCV RNA quantification was done using the Abbott Real-Time HCV PCR (Abbott, Weisbaden, Germany). HCV genotyping was performed using a nested PCR with primers specific for the NS5B region followed by sequencing of the 350-base pair product [10].

Liver biopsy was done by the transjugular route to rule out cirrhosis when there was no evidence of the same with blood tests or ultrasonogram. As a policy, HCV antiviral therapy was offered to all patients planned for RT in our hospital. Treatment duration was guided by European Association for the Study of the Liver guidelines [3] and the type of IFN (pegylated or conventional) used was dependent on patients' affordability. Ribavirin was used whenever tolerated.

Treatment responses were assessed at various time points—rapid virological response (4 weeks), early virological response (12 weeks), end of treatment response (24 or 48 weeks), and sustained virological response (after 24 weeks of therapy). Therapy was planned for 24 weeks in genotype 3 and 48 weeks for genotype 1. In addition, we adopted the response-guided rule in which continuation of therapy beyond 12 weeks was only in the presence of early viral response (EVR).

Results

There were 46 patients with moderate and severe CKD. More than half of these patients (n=25) did not receive HCV antiviral therapy for various reasons as shown in Fig. 1. Twenty-one of the 46 patients (47 %) consented for treatment. Of these, five patients dropped out soon after initiation of treatment due to various reasons as mentioned in Fig. 1. These early drop outs were excluded from further analysis. Thus, a total of the 16 patients (35 %) only proceeded with the treatment. The baseline details are provided in Table 1. Transjugular liver biopsy was done in nine patients (56 %). None had established cirrhosis, though focal periportal fibrosis was seen in four patients.

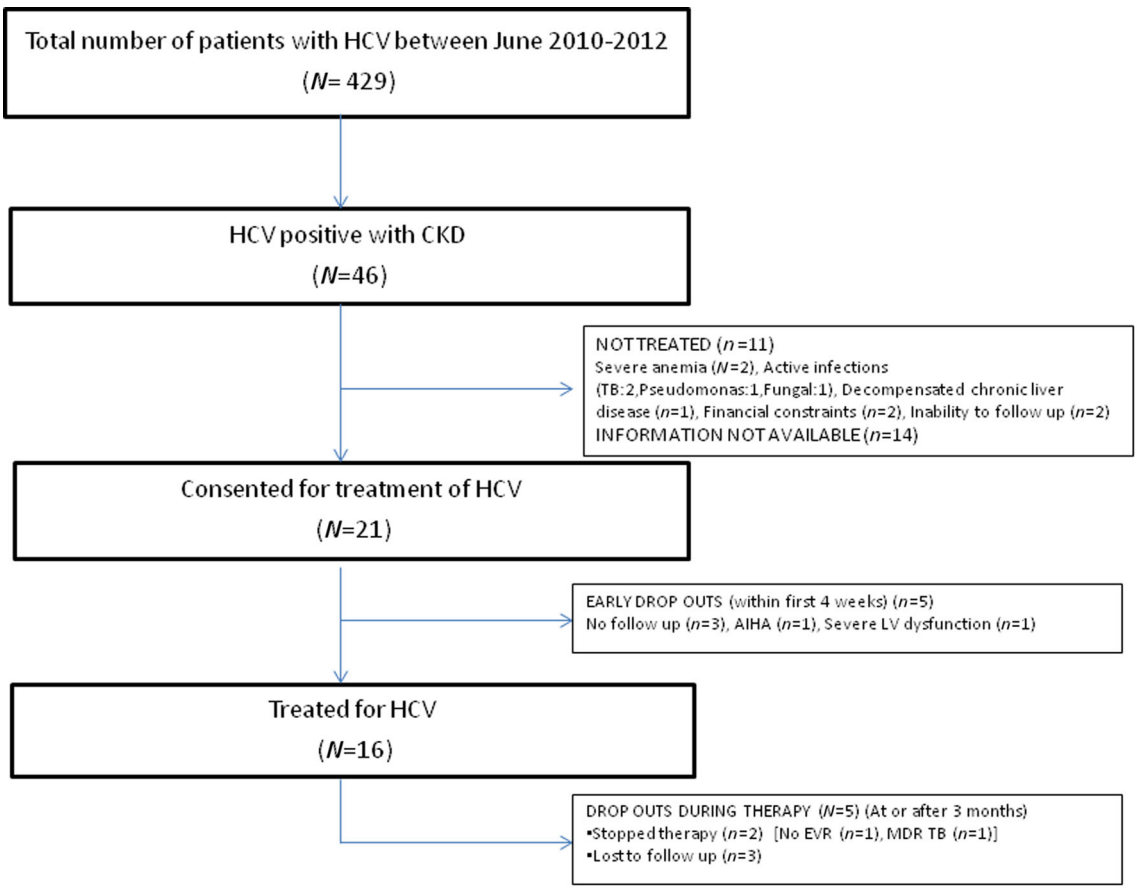

Fig. 1 Flowchart of the patients treated. *AIHA* autoimmune hemolytic anemia, *CKD* chronic kidney disease, *HCV* hepatitis C virus, *LV* left ventricular, *MDR TB* mutlidrug-resistant tuberculosiss

Table 1 Patient characteristics and treatment details

Patient characteristics	Values
Median age	36 years (21–60 years)
Males/females	12/04
CKD stage 3/4*/5*	02/01/13
HCV genotype** 1/3/indeterminate	06/09/01
HCV RNA (IU/mL) [median (range)]	6.3 $\log_{10}$ (3.85–7.52)
ALT (IU/L) [median (range)]	60 (18–208)
Ultrasonography	
Normal liver	12
Fatty liver	1
Early chronic liver disease	3
Treatment details	
Drug details	
Conventional interferon	9
Conventional followed by pegylated interferon	3
Pegylated interferon	4
Ribavirin	5
Side effects of therapy	
Anemia	13
Infections	2
Hypothyroidism	1
Psychosis	1

ALT alanine aminotransferase, *CKD* chronic kidney disease, *HCV* hepatitis C virus

*All these patients were on hemodialysis (ESRD)

**Genotype could not be determined due to low viral load

Treatment details

Nine patients received conventional (interferon alpha 2a 3MU three times a week) and seven received pegylated interferon (interferon alpha 2a 135 μg or 2b 50 μg/week). Ribavirin (200–600 mg) was used in five patients (two stage 3 and three stage 5 patients) in combination with interferon. Four of them received 200 mg of ribavirin once daily, of which two tolerated the same and achieved partial EVR and sustained viral response (SVR), respectively. One patient received 600 mg which had to be stopped after 3 months.

The response to treatment at various time points has been shown in Fig. 2.

Rapid viral response

Rapid viral response (RVR) was checked only in 7 of the 16 patients and was achieved in 4 patients. Of the three who had no RVR, one had EVR, end of treatment response (ETR), and SVR. Another had no EVR and hence, the treatment was discontinued. The third one had partial EVR.

Early viral response

A complete EVR seen in 11 patients (69 %) and partial EVR in two. One patient with partial EVR had multidrug-resistant tuberculosis and the other had Enterobacter sepsis at the end of therapy. In the three patients who did not achieve EVR, treatment was discontinued.

End of treatment response

Data for ETR was available in 10 patients out of the 13 with EVR. Of these 10 patients, 8 achieved ETR. Thus, 62 % of the patients who had EVR achieved ETR which amounted to 50 % of the study population. The two patients who had no ETR despite EVR included a male with genotype 3 and a female with genotype 1 infection. Both these patients had high-baseline viral loads and were treated with conventional interferon.

Sustained viral response at 24 weeks

Of the eight patients with ETR, one died due to pseudomonas pneumonia and hence, SVR was not checked. SVR was seen in all others (7/7) amounting to 44 %.

Side effects

The commonest side effect noted was anemia (81 %). It was more commonly seen in patients given ribavirin (drop in hemoglobin between 1.5 and 6 g/dL) and required discontinuation of ribavirin in one. Patients who developed anemia were treated with erythropoietin by the nephrologists. Infections requiring discontinuation of therapy was seen in only one patient who developed tuberculosis. Another patient had Enterobacter sepsis after the completion of therapy. Autoimmune hemolytic anemia (AIHA) due to IFN and severe LV dysfunction were the other reasons for discontinuation of therapy soon after the initiation of therapy. Hypothyroidism and psychosis were noted in one patient each but no treatment withdrawal was necessary.

Drop outs

Five patients dropped out within the first few weeks and five others dropped out within 3 months after initiation of therapy as in Fig. 1. Therapy had to be stopped due to adverse effects in three patients (infections, AIHA, cardiac failure) lack of EVR in one but the other six were lost to follow up.

Treatment experienced patients

Three of the seven patients treated with pegylated interferon had previously been treated with conventional interferon for

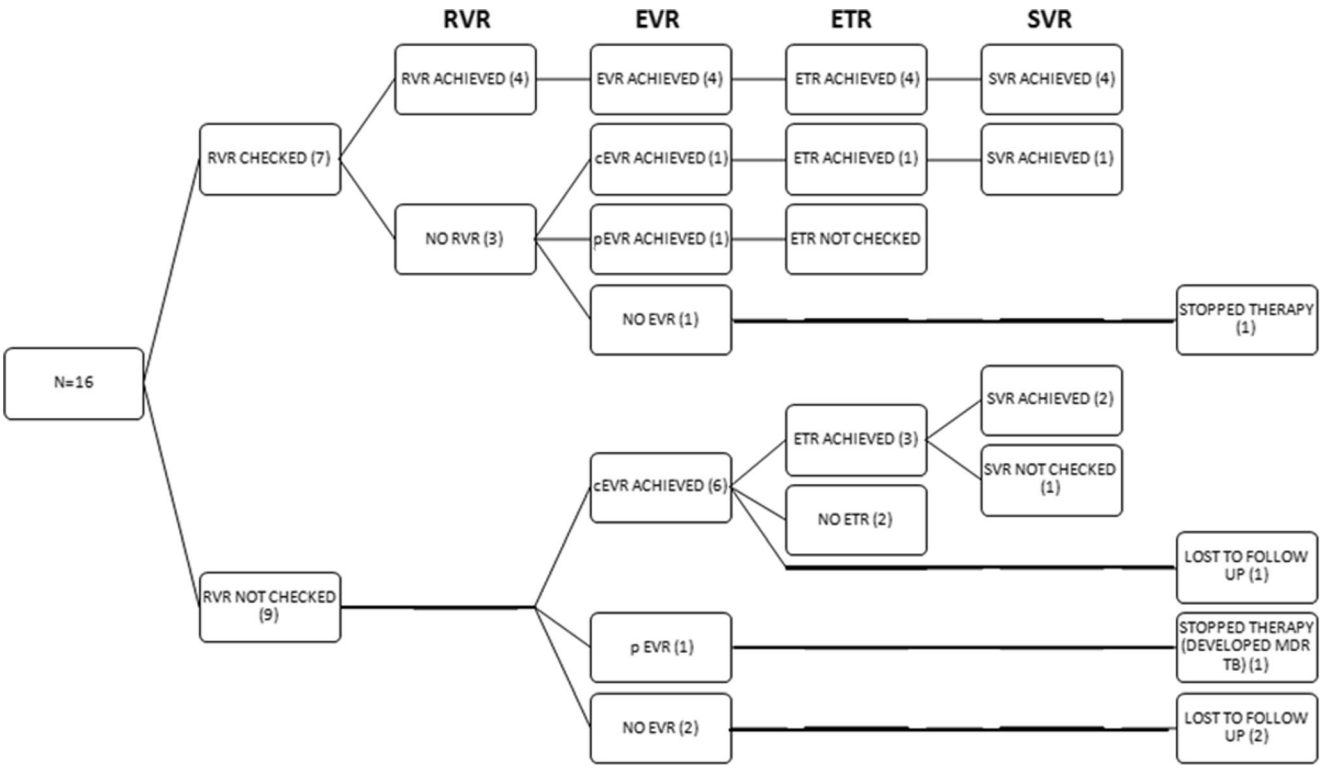

Fig. 2 Response to treatment. *EVR* early virological response (*C* complete, *p* partial), *ETR* end-of-treatment response, *MDR TB* multidrug-resistant tuberculosis, *RVR* rapid virological response, *SVR* sustained virological response

24, 48, and 12 weeks, respectively. Only one of them achieved SVR.

Discussion

For the first time, we have shown from India that this difficult-to-treat group can be shown to achieve SVR on par with the internationally reported rates of 40 % to 45 % with careful selection and close monitoring.

Comparison between HCV-infected ESRD patients on HD and transplanted ones shows that RT offers significantly better survival. With longer duration after RT (3 vs. 5 years), HCV-infected patients have poorer graft survival due to chronic allograft nephropathy [11]. It is clear that better long-term outcome is likely with eradication of HCV in ESRD patients planned for RT.

Currently, there is no recommendation for the use of newer antiviral drugs in CKD patients while on dialysis or post-RT. Though Liu et al. demonstrated in a randomized controlled trial that pegylated IFN alpha 2a is superior to conventional IFN [12], two meta-analyses including 645 and 459 patients have shown no advantage with pegylated IFN when compared with regular IFN with an SVR of 31 % for pegylated IFN vs. 39 % IFN [13] and 37 % for pegylated IFN vs. 41 % IFN [14]. The dropout rates were higher (27 %) in pegylated (Peg) IFN compared to 19 % IFN [13] mainly due to hematological side effects. Controlled pharmacokinetic studies have shown that clearance of injected interferon is significantly delayed in uremic patients [15]. Though concern about drug accumulation and hemolytic anemia have limited the use of ribavirin in this cohort, a recent RCT has shown that combination therapy with Peg IFN and ribavirin 200 mg daily to be superior (SVR 64 % vs. 33 %) to monotherapy but with a higher need for erythropoietin [16] the current standard of care in ESRD patients is interferon either standard or pegylated with or without a small dose of ribavirin.

The number of patients with ESRD and HCV being treated is small in our study not only similar to the rest of India [17] but also well-developed countries like Japan [18]. In view of the comorbidity, ESRD patients are a difficult group to treat with a high incidence of infective, hematological, cardiovascular, and central nervous system side effects with interferon. Our major challenge in treatment of HCV in this group was getting their consent for the same. Only 47 % agreed for the treatment. The financial burden of cost of interferon therapy added to that of extra dialysis sessions during 6–12 months of therapy is one of the major reasons for refusal and loss of follow up on antiviral therapy. This can be overcome to a certain extent by the use of conventional interferon which is less expensive and equally efficacious.

Among those who started the treatment, documentation of adverse effects requiring cessation of therapy was done in

three instances only but six others dropped out without any follow up, resulting in only 35 % receiving at least 3 months of antiviral therapy. It is highly probable that the geographic distance precluded them from reporting the adverse effects of therapy which resulted in discontinuation. If nephrologists and dialysis nurses assume responsibility for monitoring adherence to antiviral therapy and watching out for complications during antiviral therapy, dropout rates can be reduced significantly. The care of ESRD patients with HCV is a bright example of a clinical situation in which hepatologists and nephrologists can work together.

In conclusion, though only one third of patients with moderate and severe CKD and HCV were treated with antiviral therapy, 50 % of them achieved viral clearance at the end of therapy and 44 % achieved sustained viral clearance. We strongly advocate antiviral therapy under close monitoring in the absence of contraindications in HCV-infected patients with moderate and severe CKD.

Conflict of interest JR, RM, BG, PLA, JS, AG, PA, and TV declare that they have no conflict of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 as revised in 2008. We did not obtain informed consent from individual patients as it was a retrospective study. Institutional ethics committee clearance was obtained.

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