original article

Identification and management of acute Hepatitis C virus (HCV) infection in end stage renal disease (ESRD) patients on maintenance hemodialysis

Adnan Rafiq, Farhana Yaqoob, ManavWadhawan, Sanjeev Jasuja, Ajay Kumar

Abstract:

Background/Aims: HCV prevalence differs among hemodialysis units according to their geographical location, health care procedures, socioeconomic factors, reuse of lines, hygiene and sterilization of equipment, patient rotation of machines and the undertaking of rigorous universal precaution rules. The present study was undertaken to study the prevalence of acute hepatitis C in end stage renal disease (ESRD) patient on hemodialysis, treatment of acute hepatitis C among these patients with various treatment protocols.

Methodology: The participant in present study included 889 hospitalized patients on maintenance hemodialysis of which 48 (5.4%) were found to be anti HCV positive. Of 48 patients who were anti HCV positive, 43 had anti HCV positive in previous more than 6 months. So they were excluded from the study. 5 patients who had anti HCV negative in previous 6 months and 8 patients with deranged liver enzymes but negative anti HCV were tested by HCV RNA quantitative and had detectable HCV RNA counts.These patients were diagnosed as acute hepatitis C and included in the study.

Results: In our study end of treatment response was 50% across all the groups (p-0.465) with 33.3% in group A (no treatment group), 40% in group B (3 mu treatment group) and 75% in group C (5 mu treatment group). When comparison between the groups was done for ETR, group A and group B showed statistically significant results (p-0.036) which could not be duplicated between group A and C (p-1.215) and group B and C (p-1.102). Sustained virological response across the groups was 58.3% (p-0.539), in group A was 33.3%, group B was 60% and group C was 75%. Again when SVR was compared between the groups,statistically insignificant results were obtained between all the group i.e. group A and B (p-0.533), group A and C (p-1.215) and group B and C (p-0.225)

Conclusion: To conclude HCV infection is being diagnosed more commonly in patients with CKD on maintenance hemodialysis. As is evident from our study HCV infection can be treated better with high dose Interferon than low dose standard Interferon.

Introduction:

Hepatitis C virus (HCV) is an RNA virus member of the family Flaviviridae[1]. The known sources of transmission are blood transfusion, needle stick injury, intravenous drug abuse and sexual exposure[2-5]. HCV prevalence differs among hemodialysis units according to their geographical location, health care procedures, socioeconomic factors, reuse of lines, hygiene and sterilization of equipment, patient rotation of machines and the undertaking of rigorous universal precaution rules. These features influence the risk of nosocomial transmission of HCV to hemodialysis patients[6,7]. The goals of treating patients on dialysis as well as those with less severe degrees of renal impairment are to reduce progression of liver disease and/or to clear HCV infection in those who might later need to undergo renal transplantation. The present study was undertaken to study the prevalence of acute hepatitis C in end stage renal

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Hepatitis C Virus, Hemodialysis, End stage renal disease

disease (ESRD) patient on hemodialysis , treatment of acute hepatitis C among these patients with standard Interferon and comparison of no treatment , 3 MU daily vs. 5 MU daily treatment protocol in these patients.

Materials & Methods:

The participant in present study included 889 hospitalized patients on maintenance hemodialysis. Of 889 patients 643(72.32%) patients were males and 246 (27.68%) patients were females . 48 (5.4%) of these 889 patients were found to be anti HCV positive, 11 of which were females and 37 were males. 841 (94.6%) of 849 patients were anti HCV negative, 235 of which were females and 606 were males.

Of 48 patients who were anti HCV positive, 43 had anti HCV positive in previous more than 6 months. So they were excluded from the study. 5 patients who had anti HCV negative in previous 6 months and 8 patients with deranged liver enzymes but negative anti HCV were tested by HCV RNA quantitative and had detectable HCV RNA counts. These patients were diagnosed as acute hepatitis C and included in the study.

Data collection technique and tools:

Acute HCV infection was defined as raised AST/ALT >2 times upper limit normal (Normal limits- 5-40 IU/L) with positive HCV-RNA irrespective of HCV antibody status. Patients undergoing dialysis at Indraprastha Apollo Hospital were screened for presence of acute HCV infection. These patents underwent monthly LFT and 3 monthly HCV antibody testing (Elisa Microwell-BIO-RAD/Murex). Those with either of these tests positive underwent HCV-RNA qualitative analysis. HCV-RNA was done one day prior to dialysis as heparin is known to interfere in detection of HCV-RNA by PCR technique. Anti HCV positive patients at baseline were included if a documented antibody test was negative within 6 months of positive result. Patients included in the study population underwent HCV genotyping (Nucleotide Sequence Based HCV Genotyping) and quantitative analysis (HCV Quantitative Real Time-PCR) at baseline. A repeat HCV RNA quantitative was done at 4-8 wks from first positive result (Detectable limit >100 viral copies/ml). Patients with positive RNA counts were started on IFN therapy.

IFN therapy and Follow-up:

Patients were informed of the possible risks and benefits of IFN treatment. Three patients refused therapy and were assigned to the control group (Group 1), and five patients each were randomly allocated to one of two IFN treatment groups (Group 2 & 3). IFN-α therapy was started if the following criteria were met: (i) informed consent obtained; (ii) patient age less than 65 years; (iii) female patients of childbearing age who were not pregnant, or agreed to avoid pregnancy during therapy; (iv) the patient was free of autoimmune, thyroid, psychiatric, or malignant disorders; (v) an HIV antibody test was negative; and (vi) the white blood cell count above 3000/mm^3 and platelet count above 60000/ mm^3.

Group 2 patients were started on IFN- α at a dose of 3 MU subcutaneously daily for 4 weeks. Patients were tested for HCV RNA at 4, 8, 12 & 24 weeks after starting treatment. Patients in Group 3 were started on IFN-α at a dose of 5 MU subcutaneously daily for 4 weeks. All patients were treated for duration of 24 weeks. The IFN dose was tapered in patients who experienced serious side effects, such as serious flu-like symptoms, white blood cell count below 2500/ $mm^{3,}$ absolute polymorphonuclear leucocyte count below 1000/ mm^3, and platelet count below 50000/ mm^3. Therapy was discontinued if side-effects do not resolve after the dose reduction.

Following clinical information was collected at the time of enrolment in the study: patient age, gender, duration of haemodialysis, haemodialysis treatment centre, ALT peak level, history of blood transfusion within 6 months prior to AL T elevation, presence of hepatitis B surface antigen, time elapsed between ALT elevation and IFN treatment, HCV -RNA quantitative, HCV genotype.

Follow up after recruiting in the study was as follows: LFT and a complete blood count weekly in the first month, 2 weekly during the second and then monthly for 18 months following the IFN treatment. Serum HCV -RNA was assessed quantitatively before treatment, at 4 weeks, 12 weeks, 24 weeks of treatment and at 6 months post-treatment.

Virologic and biochemical response

End of Treatment response

Biochemical- normal AST/ALT at the end of treatment

Virological - negative HCV RNA at the end of treatment

Sustained viral response

Biochemical- normal AST/ALT at 6 months after end of treatment

Virological - negative HCV RNA at 6 months after end of treatment

Data analysis:

Quantitative data was expressed as mean (±SD) or median and analyzed using Mann Whitney test as

applicable. Qualitative data was analyzed by the Chi-square test.Comparisons between control and IFN-treated patient groups was analyzed using one-way ANOVA. Significant difference was defined as p<O.O5. SPSS software (SPSS Inc., Chicago, Illinois, USA) was used for data entry and analysis.

Results:

In our study end of treatment response was 50% across all the groups (p-0.465) with 33.3% in group A (no treatment group), 40% in group B (3 mu treatment group) and 75% in group C (5 mu treatment group).When comparison between the groups was done for ETR, group A and group B

	Groups		END OF TREATMENT RESPONSE (Yes=1/ No-0)		
			NO	YES	Total
Groups: A-No treatment,B-3 MU,C-5MU	Groups: A-No treatment	Count	2	1	3
		% within Groups: A-No treatment,B-3 MU,C-5MU	66.7%	33.3%	100.0%
	Groups: B-3 MU	Count	3	2	5
		% within Groups: A-No treatment,B-3 MU,C-5MU	60.0%	40.0%	100.0%
	Groups: C-5MU	Count	1	3	4
		% within Groups: A-No treatment,B-3 MU,C-5MU	25.0%	75.0%	100.0%
Total		Count	6	6	12
		% within Groups: A-No treatment,B-3 MU,C-5MU	50.0%	50.0%	100.0%

Table 1: ETR in different treatment groups

Groups			SUSTAINED VIRAL RESPONSE (Yes-1, No- 0)		
			NO	YES	Total
Groups: A-No treatment,B-3 MU,C-5MU	Groups: A-No treatment	Count	2	1	3
		% within Groups: A-No treatment,B-3 MU,C-5MU	66.7%	33.3%	100.0%
	Groups: B-3 MU	Count	2	3	5
		% within Groups: A-No treatment,B-3 MU,C-5MU	40.0%	60.0%	100.0%
	Groups: C-5MU	Count	1	3	4
		% within Groups: A-No treatment,B-3 MU,C-5MU	25.0%	75.0%	100.0%
Total		Count	5	7	12
		% within Groups: A-No treatment,B-3 MU,C-5MU	41.7%	58.3%	100.0%

Table 2: SVR for different treatment groups

showed statistically significant results (p-0.036) which could not be duplicated between group A and C (p-1.215) and group B and C (p-1.102). Sustained virological response across the groups was 58.3% (p-0.539), in group A was 33.3%, group B was 60% and group C was 75%. Again when SVR was compared between the groups,statistically insignificant results were obtained between all the group i.e. group A and B (p-0.533), group A and C (p-1.215) and group B and C (p-0.225).Side effects in the form of physical intolerance e.g. flu-like symptoms, fever , GI complaints etc. were seen more commonly seen in group C patients (80%) as compared to group A(60%) and B (0%). Also haematological intolerance as expected was seen more commonly in group C patients (60%) which needed temporary dose modification in 60% of patients as group B patients(40%) and 40 % of these patients need modification.

Discussion:

That hemodialysis patients are at high risk of HCV infection is well known. However there is large variation in prevalence of HCV infection in different regions of world, even variation in same regions in different hospitals. Similar to immunocompetent patients, IFN-based treatment for acute hepatitis C is the mainstay therapy in HD population.

The present study was done to identify and manage the patient of acute hepatitis C in a cohort of mantenance hemodialysis patients. The prevalence of anti HCV positivity in our study was 5.4% and prevalence of acute hepatitis C was 1.46%. In a review of so far published data in 1999, Wreghitt[8] described a range from 4% in the UK to 71% in Kuwait for anti HCV positivity among a HD population.

One patient in our study had spontaneous clearance of virus without receiving any treatment. Gerlach et al[9] showed that spontaneous HCV clearance was observed in 52% of patients with acute symptomatic hepatitis C whereas all asymptomatic patients developed chronic hepatitis C.

Most patients with chronic kidney disease have a sense of fatigue at some point in time, and it seems that subjective symptoms of acute hepatitis such as anorexia and prostration are complained less severely, compared to normal individuals contracting acute viral hepatitis. Serum ALT elevations are less remarkable[10-12] and jaundice usually mild, bilirubin seldom rising above 10 mg/dl [12]. Thus identification of acute hepatitis C in these patients is uncommon and so the opportunity for treatment. The goal of treating patients with acute hepatitis C is to prevent these patients from progressing to chronic liver disease. In dialysis patients, periodic measurement of serum aminotransferases level and anti HCV antibodies increases the chances of early diagnosis of HCV infection.

A recent Cochrane Database Systemic Review involving randomised controlled trials of transfusion associated AHC showed an increase in sustained virological response (SVR) rate of 29% [13]. Interferon treated patients had a SVR of 32% as opposed to 4%. The relatively low rate of response may be related to the suboptimal dose and duration of treatment with interferon (interferon a2b 3 MU 3 times weekly for 12 weeks). A meta-analysis from Licata et al further supports that induction strategy and use of high dose interferon therapy improve SVR[14].

Camma et al [15], in a meta analysis of nine studies, concluded that short course of low dose interferon administered to patients with acute HCV infection is significantly more effective than no treatment in obtaining viral clearance and normal aminotransferases 12 months after stopping treatment. Similar conclusions have been made in other studies [16-17].

Duarte et al[18], in a study of interferon therapy in hemodialysis patients with acute HCV infection comparing the outcome in 16 patients treated with low dose (3 million units) and 20 with high dose (6-10 million units) three times per week, there was no statistically significant difference in the sustained virological response between the two groups compared to 17 controls who received no treatment.

Gursoy et al, [19], in a study population of 67 patients, 14 patients were excluded due to side-effects or because they were lost to follow-up, 17 patients who received no specific treatment were used as controls (Group 1), 16 and 20 patients received low-(3 MU) and high-dose (6–10 MU) IFNα-2b three times weekly for 3 months (Groups 2 and 3, respectively). Virological end-of-treatment response (ETR) was observed in 1 (5.6%), 13 (56.5%), and 17 (65.4%) patients in Groups 1, 2, and 3, respectively, and virological sustained response (SR) was observed in 1 (5.6%), 6 (26.1%), and 13 (50%) patients in the three groups. The rates of ETR and SVR in the treated groups were significantly higher than those of the control group ($P < 0.01$ for all comparisons).

In our study, end of treatment response was 50% across all the groups (p-0.465) with 33.3% in group A (no treatment group), 40% in group B (3 mu treatment group) and 75% in group C (5 mu treatment group). When comparison between the

groups was done for ETR, group A and group B showed statistically significant results (p-0.036) which could not be duplicated between group A and C (p-1.215) and group B and C (p-1.102)

Sustained virological response across the groups was 58.3% (p-0.539), in group A was 33.3%, group B was 60% and group C was 75%. Again when SVR was compared between the groups, statistically insignificant results were obtained between all the group i.e. group A and B (p-0.533), group A and C (p-1.215) and group B and C (p-0.225).

Side effects in the form of physical intolerance e.g. flu-like symptoms, fever , GI complaints etc. were seen more commonly in group C patients (80%) as compared to group A(60%) and B (0%). Also haematological intolerance as expected was seen more commonly in group C patients (60%) which needed temporary dose modification in 60% of patients as compared to group B patients(40%) and 40 % of these patients needed dose modification.

Our study although showed that patients in high dose group i.e. 5 mu had better SVR rates as compared to 3 mu group, there were some limitations also. First and foremost was the small sample size, so no firm conclusions can be drawn from our study. Also our hospital is the tertiary care hospital with most patients coming from good educational and economic background so compliance may not have been the major issue in our patients. Another important factor in the management of acute hepatitis C patients is drop out rate because of side effects of interferon treatment, which was low in our patients.

Conclusion:

To conclude HCV infection is being diagnosed more commonly in patients with CKD on maintenance hemodialysis. As is evident from our study HCV infection can be treated better with high dose Interferon than low dose standard Interferon. However larger studies with good number of patients are needed to come at firm conclusion.

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