Original Article

Response of peg IFN and ribavarin in HIV-HCV co-infection

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ABSTRACT

Background: *Hepatitis C infection is one of most common co-infection in HIV. HIV infection influences the natural evolution of chronic hepatitis by higher rate of viral persistence, accelerating fibrosis, cirrhosis progressing to end-stage liver disease.*

Objective: *This retrospective study was conducted in order to see the response to Peg- IFN α-2b with Ribavarin in HIV HCV co-infection.*

Material and Methods: *Alanine aminotransferase and Aspartate Aminotransferase, HCV RNA quantitative and Genotype study, Fibroscan, CD4 were collected from the medical records of ART centre.*

Results: *The mean baseline viral load (log10) was 5.76, 3.00 at 1st month, 0.44 at 3rd month, 0 at 6th month and 12th month. RVR was observed in 77.7%, EVR in 88.8%, SVR of 100% at 6th and 12th month. The mean OT and PT reduction at 3rd month was 116.11(57.79%) and 132 (61.68%) respectively, at 6 month was 158 (78.65%) and 177.56 (82.97%) respectively, at 12th month was 159(79.14%) and 176.56 (82.50%). Fibrosis at the start of treatment was 19.0 KPa, 10.00 KPa at 6th month and 8.20 KPa at 12th month.*

Conclusion: *Study shows that SVR can be achieved in HCV HIV co infected patients with IFN and Ribavarin therapy which in turn reduces the morbidity and mortality due to liver disease. Inspite of virological response, few patients continue to have deranged AST and ALT and progressive liver fibrosis.*

Key Words: *Human immunodeficiency virus, hepatitis C virus, HCV RNA, fibroscan*

Introduction

Chronic Hepatitis C infection is one of most common co-infection in people with HIV. Worldwide, Hepatitis C infection accounts for approximately 170 million chronic infections, with an overall 3% prevalence. 4 to 5 million persons are co-infected with HIV. Complication related to HIV-HCV co-infection have become an increasingly important medical issue because consequences from HCV infection leading to HCC and end stage liver disease are now leading cause of death in people with HIV.

Human immunodeficiency virus (HIV) and Hepatitis C Virus (HCV) share the same parenteral routes of transmission. The prevalence of HCV infection in HIV patients ranges from 8% in homosexual men, [1] to 60% in haemophiliacs, [2] or 80% in intravenous (IV) drug users. [3] As HIV has become a chronic illness due to the effectiveness of highly active antiretroviral therapy (HAART), HCV related liver disease has emerged as a major cause of morbidity and mortality among HIV infected patients in the developed world. [4] HCV-related liver disease may be more severe in HIV-infected people than in non–HIV-infected individuals. [5-8] The prevalence of cirrhosis may be 3-fold higher in HIV-HCV co-infected patients than in HIV-negative HCV-infected patients [8, 9] and one third of co-infected patients is at risk of dying of liver disease. A number of studies have

demonstrated the association of HIV co-infection with an increased risk of morbidity and mortality caused by end-stage liver disease (ESLD). HIV accelerates HCV-related liver disease. Progression that typically takes up to 30 years or longer in HCV-mono-infected individuals has been shown to take less than half that time in co-infected individuals. The impact of HAART on the progression of HCV liver disease is controversial. One possibility is that antiretroviral therapy could increase hepatic necroinflammatory activity and thereby accelerate the progression of HCV-related liver disease.

The association of chronic HCV with hepatotoxicity during HAART is well established. Hepatitis C is an independent risk factor for hepatotoxicity with HAART. [10-16] Overall, significant liver enzyme elevations are seen in approximately 15% of individuals receiving antiretroviral drugs. Severe hepatotoxicity, however, leading to drug discontinuation, occurs in less than 10% of cases. Two mechanisms have been involved, the first of which represents a hypersensitivity reaction, often affecting the skin and other organs, and occurring a few days to weeks after beginning antiretroviral therapy. A second mechanism with delayed onset typically appearing several months after beginning therapy is limited to the liver, and represents an intrinsic toxic effect of the drugs in use, and therefore is dose related. [16]

Serum HCV-RNA titres are 1.5 to twofold higher in HIV/HCV co-infected individuals with respect to individuals with HCV mono infections, [17-19] probably due to an impairment in the control of HCV replication in the setting of immunodeficiency. Whether this increase in HCV viral burden contributes to explaining the greater liver injury noticed in HIV/HCV co-infected patients is unknown, although there is no clear correlation between the extent of liver fibrosis and the level of HCV RNA.

A recent study found that HCV was the leading non-AIDS cause of death in co-infected persons, and another study found that 50% of deaths in a cohort of patients with HIV in 1998 were the result of end-stage liver disease. [20, 21] The primary goal of HCV treatment is to achieve a sustained virological response that permits fibrosis regression, the disappearance of extrahepatic manifestations, and a reduction of the risk of transmission. Co-infected patients treated with antiretroviral agents have a higher frequency of hepatotoxicity than HIV mono-infected patients.

This retrospective study was done in order to see the response of HCV to standard peg-IFN α-2b and Ribavarin in HIV-HCV co infected patients who were on first line ART. (Tenofovir, Lamivudine and Efavirenz)

Material and methods

A Retrospective study was conducted in the RIMS Hospital, Imphal, and Manipur. The study was intended to include HIV HCV co infected patients who were registered in the Hospital ART centre, undergoing treatment for both HIV and HCV. The study was approved by the ethical committee of the hospital.

Inclusion criteria for the study were any patient aged >18 years having HIV-HCV co-infection registered at the art centre in RIMS Hospital undergoing treatment with First line ART and Peg Interferon α-2B with Ribavarin for HCV, willing to give a valid written consent were included, with Exclusion of patients who were Mono-infected with HIV, or Co-infection with HBV, patients who were on second line ART, not willing to give a valid consent.

The prevalence of HIV HCV co-infection in INDIA is 1.06% [22] with a

confidence limit of 95% the calculated sample size was 4.19. It was intended to include all the patients during the study period who were full filling the inclusion criteria. A total of 43 such patients were under treatment from June 2012 to June 2014 of which only 22 patients were fulfilling the inclusion criteria, out of which the complete data was available for only 9 patients which were included for the final analysis.

The data was collected from the ART centre and Liver Clinic records of the RIMS Hospital. HCV RNA quantitative analysis was performed using Real time PCR by COBAS AMPLIPREP and TAQMAN. With a lower detection limit of 200 HCV RNA copies/mm3. CD4 count was performed using automated analyser, Fluorescence Activated Cell Sorter (FACS) counter. Liver function test (OT and PT) were performed using Reflection Spectroscopy, Calorimetric and UV with PSP respectively. Fibroscan was performed using FIBROSCAN 402 with M probe based on Controlled Pulse Vibration Elastography Technique. HBA1c was estimated by High Performance Liquid Chromatography (HPLC) Method. FBS and PPBS were performed by Hexokinase/ GOD-POD.

OT and PT response were categorised as normal, <3 upper normal limit and >3 upper normal limit. Viral response was defined as Rapid viral response at 4weeks, early viral response at 12 weeks, Sustained viral response at 24 weeks and 48 weeks. Responses were further categorised as complete if HCV RNA was not detectable and partial if decrease was >2log but still detectable HCV RNA. Non responders were those with viral load decrease <2log.

Analysis was done by SPSS v20 software, Descriptive analysis was performed and results were expressed as mean and percentages. Baseline values were compared with on treatment values using Wilcoxon signed rank test.

Results

Of the total 9 patients 7 were male and 2 were female, the mean age of the study population was 42.67±5.70. 3 patients were Hindu and 6 patients Christian. 2 patients were from valley district of Manipur and other 7 patients from tribal districts. The mean age of the start of treatment was 6.1 months. Baseline characteristics of the patients are shown in table no 1.

Response of OT

The mean OT of 9 patients at the start of treatment was 200.89±92.51, with 3 patients (33.33%) having <3 UNL (41-119) and 6 patients (66.66%) having OT more than >3 UNL (>120). The mean OT at 3rd month of treatment was 84.78, mean reduction by 116.11(57.79%) (P = 0.008) with 8 patients (88.88%) having OT <3 UNL and 1 patient (11.11%) was still having >3 UNL. The mean OT at 6th month 42.89, mean reduction by 158 (78.65%) (P = 0.008) with 4 patients (44.44%) having a normal OT (<40) and 5 patients (55.55%) having OT <3 UNL. The mean OT at 12th month was 41.89, mean reduction by 159 (79.14%) (P = 0.008) with 4(44.44%) patients having a normal OT (<40) and 5(55.55%) patients having OT <3 UNL. The mean reduction from 3rd month to 6th month was 41.89 (P= 0.007) and from 6th month to 12th month was 1 (P = 0.673)

There was an increase by 4 patients (44.44%) in the patient belonging to normal range of OT and an increase by 2 patients (22.22%) in <3UNL and decrease by 55.55% in >3UNL group. [Table no 2, 4] The median OT at start of treatment was 212.00, at 3rd month 87.00, at 6th month was 42.00 and at the end of treatment was 42.00. (Fig. 1)

Table 1: Baseline Characteristics of patients

Characteristics	Values
Total patients	9
Mean age	42.67±5.70
Sex (M/F)	7 male & 2 females
Religion Hindu Christian	 3 6
Time for start of treatment (months)	6.1
Mean HCV RNA (IU/ml) In $2log_{10}$	5.76±0.80
Mean OT (IU/L)	200.89±92.51
Mean PT (IU/L)	214.00±94.49
Mean CD4 count (cells/mm^3)	249.44±48.59
. Fibro scan (KPa) normal (<8) moderate fibrosis (8-12) severe fibrosis (13-18) cirrhosis (>18)	18.40±6.98 0 3 1 5
. Genotype 1 3 Not detected	 3 5 1

Table 2: Percentage normalisation of OT

OT	Baseline	3rd month	6 month	12 months	% change
Normal			4(44.44%)	4(44.44%)	+ 44.44%
< 3 UNL	3(33.33%)	8(88.88%)	5(55.55%)	5(55.55%)	+ 22.22%
> 3UNL	6(66.66%)	1(11.11%)	0	0	- 55.55%

Response to PT

The mean PT of 9 patients at the start of treatment was 214.00, with all the 9 patients (100%) having PT >3 UNL (>90). The mean PT at 3rd month of treatment was 82.00, mean reduction was by 132 (61.68%) (P =0.008) with 6 patients (66.66%) having PT <3 UNL (31-89) and 3 patients (33.33%) having PT >3 UNL (>90).The mean PT at 6th month pf treatment was 36.44, mean reduction by 177.56 (82.97%) (P = 0.008) with 3 patients (33.33%) having PT within normal range <30 IU, and 6 patients (66.66%) having PT < 3 UNL. The mean PT at 12th month of treatment was 37.44, mean reduction by 176.56 (82.50%) (P =0.008), with only 1(11.11%) patient having PT within normal range with other 8 (88.88%) patients having PT <3 UNL. The mean reduction from 3rd month to 6th month was 45.56 (P= 0.008) and from 6th month to 12th month was 1 (P = 0.201). There was an increase by 1 patients (11.11%) in the patient belonging to normal range of PT and an increase by 8 patients (88.88%) in <3UNL and decrease by 100% in >3UNL group. [Table 3, 4] The median PT at start of treatment was 213.00, at 3rd month 62.00, at 6th month 40.00, and at 12th month 40.00. (Fig.1)

Table 3: Percentage normalisation of PT

PT	Baseline	3rd month	6th month	12th month	% change
Normal			3 (33.33%)	1 (11.11%)	+ 11.11%
<3UNL		6 (66.66%)	6 (66.66%)	8 (88.88%)	+ 88.88%
>3UNL	9 (100%)	3 (33.33%)	0	0	- 100%

Table 4: Table showing response of variables with treatment

	BASELINE	3RD MONTH	6TH MONTH	12TH MONTH	P* Value				
					B-3rd	B-6th	B-12th	3rd-6th	6th-12th
OT (IU/L)	200.89±92.51	84.78±24.55	42.89±8.43	41.89±5.92	.008	.008	.008	.007	.673
PT (IU/L)	214.00±94.49	82.00±54.02	36.44±7.58	37.44±5.63	.008	.008	.008	.008	.201
CD4 (cells/mm^3)	249.44±48.59	-	384.67±87.46	601.33±134.91		.008	.008		.008
HCV RNA (IU/mL)	5.76±0.80	0.44±0.96	0	0	.008	.008	.008	.008	.180
FIBRO SCAN (KPa)	18.40±6.98	-	11.31±2.70	8.53±0.93		.008	.008		.012

*Wilcoxon matched paired test. (2-tailed)

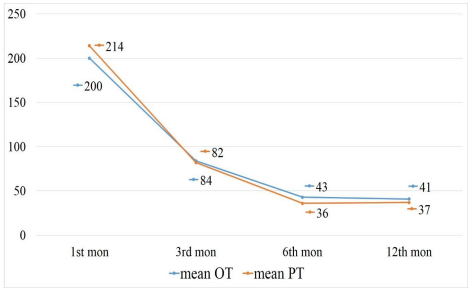

Fig.1 Graph showing response of OT and PT

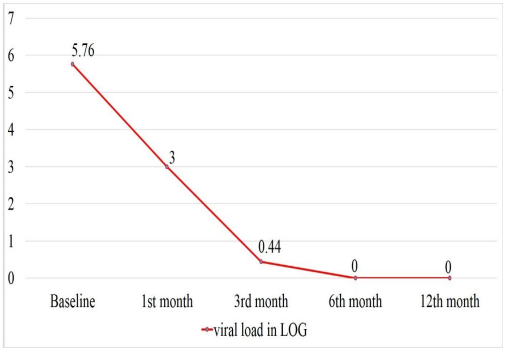

Fig. 2 Graph showing response of Viral load

Viral load

Rapid viral response, as 2log decrease in viral load (partial responders) was observed in 7 patients with the other two patients attaining only 1log decrease (non responders) in their viral load by the end of 1st month of treatment. RVR was seen in 77.77%. (P =0.008)

Early viral response as 2log decrease in viral load as compared to baseline was seen in all the 9 patients who had under gone treatment. EVR was 100% (P = 0.008). HCV RNA was not detectable (complete responders) in 7 patients and detectable but decrease by >2log (partial responders) in other 2 patients at the end of 3 months. With RVR as baseline the response was seen only in 8 (88.88%) patients and one patient didn't attain response with log reduction <1.

Sustained viral response was also seen in all the 9 patients. SVR was 100% (P= 0.008). No breakthrough resistance defined as non-response or increase in viral load was seen in any of the patients. (Fig. 2)

Fibro scan

The median fibrosis at the start of treatment was 19.00 with 5 patients having cirrhosis (>18 KPa), 1 patient having severe fibrosis (13-18 KPa) and 3 patients having moderate fibrosis (8-12 KPa). The median fibrosis at the end of 6 months of treatment was 10.00 with 7 patients having moderate fibrosis and 2 patients having severe fibrosis. The change from baseline to 6th month was statistically significant with P=0.008. The median fibrosis at the end of treatment was 8.20 with 2 patients having no fibrosis (<8 KPa) and other 7 patients having moderate fibrosis. The change from baseline to 6th month was statistically significant with P=0.008. The number of patients normalizing was seen in 2 of the 9(+22%), and for moderate fibrosis 7 (+44%). There was an 11% decrease in the severe fibrosis group and 55% decrease in cirrhosis group. [Table 5]

Table 5: Percentage normalisation of Fibrosis

	Baseline	6 month	12 month	% change
<8KPa			2 (22%)	+ 22%
8-12 KPa	3 (33 %)	7 (77%)	7 (77%)	+ 44%
13-18 KPa	1 (11%)	2 (22%)		- 11%
>18 KPa	5 (55%)			- 55%

CD4 Recovery

The baseline CD4 at the start of treatment was 249.44±48.59, at the end of 6 months it was 384.67±87.46, the mean increase from baseline to 6 months was 135 cells/mm^3 (P= 0.008), the CD4 at 12 months was 601.33±134.91, the mean increase was 352 cells from baseline (P= 0.008) and 6^{th} month to 12^{th} month change was 217 cell/mm^3 (P=0.008). (Table 4, Fig. 3)

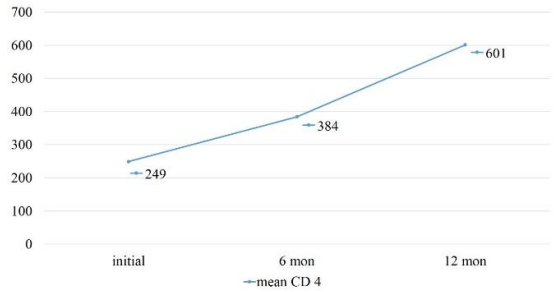

Fig. 3 Graph showing recovery of CD 4 count

Discussion

The most important finding that was observed in this study was SVR of 100%, with all the 9 patients treated achieved undetectable HCV RNA at 24 weeks of treatment. This is in contrast to various study conducted elsewhere such as Marina N [23] et al showed SVR of 49.6%, Fabrice C [24] et al showed SVR of 21%, Laguno M [25] et al showed SVR of 44%, Ballesteros AL [26] et al showed SVR of 28.6%, over all in patients with HIV-HCV co infection. SVR was in the range of 67% to 80% by Gary LD [27] et al, 54.2% by Kaita KDE [28] et al, 35%-72.4% by Marina N [23] et al, 63% by Stephanos JH [29] et al, 13%-38% by John GM [30] et al and various other studies predominantly in HCV mono infected patients. High SVR response in this study could have been due to High CD4 count at the start of treatment (mean 249.44 ± 48.59), Younger age of the study population (mean age 42.67 ± 5.70), Active HCV virus multiplication as shown by high OT and PT at the start of treatment, (mean OT – 200.89 ± 92.51, mean PT – 214.0 ± 94.49), Early start of treatment (mean age of start was 6.1 months). Other studies have shown that response in general has been poor for Genotype 1 and 4 and better for Genotype 2, 3 and 5. Such a difference was not seen as all the 3 patients (33.3%) with genotype 1 in the study attained complete SVR at 24 weeks. RVR was 77.7% with 7 out of 9 patients showing >2log decrease in viral load and other 2 of 9 patients there was no response. EVR was seen in all 9 patients 100%, with complete response in 77.7% and partial in 22.2% of patients. In contrast to studies conducted by Shyam K [31] et al which showed an increase of HCV RNA viral load on initiation of ART, such phenomenon was not observed in any of the patients.

Biochemical response in the form of OT and PT normalisation was seen in only 44.4% and 11.1% of patients respectively. Inspite of patients achieving SVR and maintaining the response till 48 weeks of treatment, failed to achieve biochemical response, with 55.5% and 88.8% of patients having their OT and PT respectively <3UNL. This signifies the persistence of hepatocyte destruction inspite of good virological response, which could have been due to HIV Virus or hepatotoxic effects of the ART drugs or other confounding factors most importantly alcohol consumption. For this reason, the biochemical response in HCV–HIV co-infected patients is not a good marker of virological response. Studies conducted by John GM [30] et al showed that normalization of serum alanine aminotransferase values was associated with undetectable levels of serum HCV RNA in most patients who had sustained virologic responses which was not observed in this study.

Fibrosis regression was seen in 22.2% of patients with 77.7% of patients

having persistent moderate fibrosis at the end of treatment even though they had achieved undetectable HCV RNA. This is similar to the biochemical response which was also not achieved. The prevalence of extensive liver fibrosis (METAVIR fibrosis scores 2, 3, and 4) and moderate or severe activity were higher in HIV-infected patients (60% and 54%, respectively) than in control patients was shown in the study conducted by Yves B [32] et al. Although different system was used in our study (Elastography) to quantify the fibrosis, the progression of fibrosis expressed as percentage of patients was comparable.

From this study it can be observed that SVR can be achieved in HCV patients who are co-infected with HIV and these patients can be benefitted from treatment. Many of these co-infected patients are not treated for the HCV infection due do various reasons such as cost involved in treatment, poor family and social support, increased pill burden, increased incidence of adverse effects etc. By not treating, such patients are at increased risk of liver related morbidity and mortality as has been shown in various studies.

This is a retrospective study with a small sample size and a non-comparative study. Side effect profile was not studied. Response was studied only in those patients who were taking specific combination of drugs in first line ART. The IL28 B polymorphism couldn't be studied in the study population due to financial constraints.

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