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Adverse effects related to Sofosbuvir and Ribavirin related treatment in genotype 3 of Hepatitis C patients

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Abstract

Introduction: Hepatitis C virus (HCV) is a leading cause of chronic liver disease in both industrialized and developing countries. Sofosbuvir and ribavirin is the first all-oral therapy regimen that has been approved in the US by the FDA for use in Genotype 2 and 3 patients and is replacing the conventional therapies.

Aims and Objective: The aim of this study is to assess tolerability and side effects of sofosbuvir and ribavirin in chronic hepatitis C patients with Genotype 3.

Materials and Methods: The study was an interventional study involving chronic hepatitis C patients of Genotype 3. Both Cirrhotic and Non cirrhotic patients were included in this study to receive Sofosbuvir 400mg and Ribavirin weight based (1000mg/day for <75kgs and 1200mg/day for > 75kgs weight) for 24 weeks duration.

Inclusion Criteria: Chronic hepatitis C genotype 3 with age more than 18yrs involving both cirrhotic and non cirrhotic patients, Treatment Naive and experienced patients and Non pregnant and non lactating females.

Results and observation: In our study total number of patients was (n=79). We observed that the mean age (in years) of patients was (40.2 ±11.62) with male patients being 32(40.5%) and the female patients 47(59.5%). Adverse effects attributed to the treatment during the study period were Headache (27%), fatigue (28%), pruritis (12.7%), asthenia (14%), nausea (15%), insomnia (14%), irritability (13%) and were more in Cirrhotic patients as compared to those in non cirrhotic. Drop in hemoglobin attributed to ribavirin was more in cirrhotic patients than in non cirrhotic patients.

Conclusion: The results of our study revealed that side effects were more in cirrhotic patients than non cirrhotic patients although the tolerability was better than the conventional therapy.

Keywords: Sofosbuvir and Ribavirin, Hepatitis C patients

Introduction

Hepatitis C virus (HCV) was discovered in 1989, and is now known to be a leading cause of chronic liver disease in both industrialized and developing countries. Within Europe the seroprevalence increases with age with peak prevalence occurring in 55-64 year old patients; Southern and Eastern Europeans have the highest peak prevalence. The high number of chronically infected individuals, the burden of disease and the absence of a vaccine indicates that treatment will form part of the control of the disease. However the majority of those with persistent infection are unaware of the infection and screening programs to identify patients will be required to prevent silent progression of the disease [1]. Chronic infection with HCV is the leading cause of end-stage liver disease, hepatocellular carcinoma (HCC) and liver related death in the Western world. The majority of patients (57-94%) demonstrate marked improvements in their necro-inflammation and fibrosis scores following SVR [2] However, a small minority (1-14%) of patients have demonstrated fibrosis progression following a sustained virological response [3-5] HCV genome comprises six genotypes and several subtypes. In genotype 3 Peginterferon (PEG-IFN) a-2b (1.5 mg/kg/week) plus ribavirin (RBV) (800-1400 mg/day) or PEG-IFN a-2a(180 mg/week) plus RBV (800 mg/day) for 24 weeks have been the established standard of care regimens [8] The main mechanism of action of most directly acting anti virals (DAAs) is the inhibition of an enzyme (protease or polymerase) [9] although some inhibit the assembly of the replication complex (NS5A inhibitors) or target the host factors that the virus uses (Cyclophilin inhibitors). Such all-oral therapy regimens appear to be very well tolerated and achieve high response rates even

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without the backbone of pegylated interferon.¹⁰Sofosbuvir is a pyrimidine nucleotide analogue with high anti-viral activity against all genotypes and shows a high genetic barrier to resistance^[11].

Regardless of HCV genotype, although in relatively small cohorts of genotype 3, sofosbuvir based triple therapy resulted in SVR rates of 83–100%^[12]. The combination of sofosbuvir (200 mg or 400 mg once daily) and PEG-IFN/RBV for 12 weeks demonstrated efficacy, reaching SVR12 of 91% in HCV-1 and 92% in HCV-2/ HCV-3, while it was 58% in placebo plus PEG-IFN/RBV group^[13]. The tremendous improvement in SVR rates in genotype 1 and genotype 2 has rendered genotype 3 HCV the major challenge, as it continues to globally afflict a large population of patients. Sofosbuvir and ribavirin is the first all-oral therapy regimen that has been approved in the US by the FDA for use in Genotype 2 and 3 patients^[14].

Aims and Objective: The aim of this study is to assess tolerability and side effects of sofosbuvir and ribavirin in chronic hepatitis C patients with Genotype 3.

Materials and Methods: This was a prospective study carried in the department of gastroenterology Sheri Kashmir Institute of Medical Sciences Soura between 2015 to 2016. The study was an interventional study involving chronic hepatitis C patients of Genotype 3. Both Cirrhotic and Non cirrhotic patients were included in this study to receive Sofosbuvir 400mg and Ribavirin weight based (1000mg/day for <75kgs and 1200mg/day for > 75kgs weight) for 24 weeks duration,

Inclusion Criteria

Chronic hepatitis C genotype 3.
Both cirrhotic and non-cirrhotic patients.
Treatment Naive and experienced patients.
Age more than 18 years
Both male and female.
Non pregnant and non-lactating females.
Diagnosis of cirrhosis was based on Fibroscan showing cirrhosis or results >12.5 kPa.

Results and observations

In our study which was a prospective study carried in the department of Gastroenterology Sheri Kashmir Institute of medical sciences soura between 2015 to 2016 involving chronic hepatitis C patients of Genotype 3. The total number of patients was (n=79). We observed that the mean age (in years) of patients was (40.2 ±11.62). The age distribution of study patients is depicted in (Table1) we observed that the number of male patients in our study was thirty two (40.5%) and the number of female patients was forty seven (59.5%). This observation showed predominance of female patients in our study (Table 2). Baseline laboratory parameters observed in the patients is presented in (Table 3). In our study the adverse effects attributed to the treatment during the study period were accessed and compared among the treatment naïve and treatment experience patient's. The results of this observation are depicted in Table4. We also observed that the adverse effects attributed to the treatment were more in Cirrhotic patients as compared to those in non-cirrhotic. This difference was statistically non-significant though. These observations are presented in Table 5. In our study we accessed the drop in hemoglobin attributed to

ribavirin and observed that in cirrhotic patients (n=29) the drop in hemoglobin (g/dl) at four weeks of treatment had a mean of 0.51 (±0.429) and the drop in hemoglobin (g/dl) among non-cirrhotic patients (n=50) had a mean of 0.25 (±0.547). The drop-in hemoglobin in cirrhotic patients at four weeks of treatment was more in cirrhotic patients than in non-cirrhotic patients and this difference was statistically significant (P-value 0.031). The drop-in hemoglobin at an intervals of four, eight and twelve weeks of treatment is depicted in Table 6.

Table 1: Age distribution of study patients

Age (years)	Frequency	Percentage
19-29	11	13.9
30-39	31	39.2
40-49	21	26.6
50-59	10	12.7
≥ 60	6	7.6

Mean±SD=40.2±11.62

Table 2: Gender distribution of study patients

Gender	Frequency	Percentage
Male	32	40.5
Female	47	59.5
Total	79	100

Table 3: Showing descriptive statistics of baseline laboratory parameters

Parameter	Mean	SD	Min	Max
HB	12.84	1.95	8.45	17.85
TLC	5.9	2.06	2.7	12.1
PLT	28.22	40.34	1.03	174
BIL	1.33	1.13	0.3	6.45
AST	48.31	25.46	11	104
ALT	114.01	93.23	18	612
PRO	7.83	0.78	6	10.45
ALB	4.19	0.53	2.5	4.9
INR	1.19	0.17	1	1.83

Table 4: Showing side effects among treatment naïve and treatment experienced patients

Side Effects	Treatment Naïve [n=63]		Treatment Experienced [n=16]	
	Number (n).	%age	Number (n).	%age
Headache	17	27.0	6	37.5
Fatigue	18	28.6	4	25.0
Pruritis	8	12.7	2	12.5
Asthenia	9	14.3	4	25.0
Nausea	15	23.8	4	25.0
Insomnia	14	22.2	1	6.3
Irritability	13	20.6	1	6.3
Rash	0	0.0	0	0.0

Table 5: Showing side effects among cirrhotic and noncirrhotic patients

Side Effects	Cirrhotic [n=29]		Noncirrhotic [n=50]		P-value
	Number (n).	%age	Number (n).	%age	
Headache	10	34.5	13	26.0	0.424
Fatigue	8	27.6	14	28.0	0.968
Pruritis	5	17.2	5	10.0	0.351
Asthenia	6	20.7	7	14.0	0.440
Nausea	6	20.7	13	26.0	0.595
Insomnia	7	24.1	8	16.0	0.374
Irritability	9	31.0	5	10.0	0.018*
Rash	0	0.0	0	0.0	-

Table 6: Comparison based on drop in Hemoglobin among cirrhotic and noncirrhotic patients

Hb Drop	Cirrhotic [n=29]		Noncirrhotic [n=50]		P-value
	Mean	SD	Mean	SD	
4 Weeks	0.51	0.429	0.25	0.547	0.031*
8 Weeks	0.91	0.613	0.71	0.631	0.179
12 Weeks	1.45	0.923	1.23	0.842	0.282

Discussion

In our study of chronic hepatitis C genotype we observed following adverse effect profile; Headache (27%), fatigue (28%), pruritis (12.7%), asthenia (14%), nausea (15%), insomnia (14%), irritability (13%). In Valence study¹⁵ the adverse events observed by patients in a group which received treatment for twenty four weeks and the percentage is as: Headache (30%), fatigue (30%), pruritis (27%), asthenia (21%), nausea (13%), insomnia (16%), arthralgia (12%), irritability (10%). The adverse events observed in our study were more or less similar to those observed in valence study. None of the patients in our study had discontinuation of treatment owing to adverse events however in Valence study (4%) of patients had to discontinue treatment due to adverse events. This observation can be explained on the basis of small sample size in our study. The sample size in valence study was large (n=419) and the number of patients in the group who received sofosbuvir and ribavirin for twenty four weeks (n=250). In contrast to this the total number of patients in our study were (n=79). In Valence study¹⁵ the mean reduction in hemoglobin level at the end of treatment was 2.1 g per deciliter in patients who received treatment for twenty four weeks. In our study we observed that the mean reduction in hemoglobin level at the end of treatment was 1.45 g per deciliter in cirrhotics and 1.23 g per deciliter in non cirrhotic patients. Again these observations can partly be explained by small number of patients in our study as compared to Valence study. In Valence study out of two hundred thirty five patients there was no requirement of ribavirin dose reduction or interruption in two hundred patients (85%). However in our study we observed that none of our patient had reduction or interruption of ribavirin dose owing to adverse events. This can be partly explained by small sample size (n=79) in our study, further host genetic factors may be responsible for this difference.

Conclusion

The results of our study revealed that side effects were more in cirrhotic patients than non cirrhotic patients although the tolerability was better than the conventional therapy.

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