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RESEARCH ARTICLE

EFFICACY OF SOFOSBUVIR PLUS DACLATASVIR BASED THERAPY IN THE TREATMENT OF TREATMENT NAIVE CHRONIC HEPATITIS C GENOTYPE-3 IN KASHMIRI POPULATION

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ABSTRACT

Background: Direct Acting Antivirals (DAAs) have revolutionized the treatment of chronic hepatitis-C infection.Genotype-3 is the most common genotype found in India and Kashmir as well and it has the more aggressive nature and leads to increased riskof steatosis and hepatocellular carcinoma. **Aims and Objectives**: To compare the efficacy and safety in chronic hepatitis C genotype-3 infection in Kashmiri population. **Materials and Methods**: An observational, Prospective, Open label, Hospital based study carried over a period of two years. Treatment naïve Chronic Hepatitis-C genotype-3 patients were included in the study. Patients were divided in two groups. Group-A: Non-cirrhotics who received Sofosbuvir (400 mg daily) with Daclatasvir. Group BCirrhoticswho received Sofosbuvir (400mg daily) with Daclatasvir (60mg daily) and weight based Ribavarin. **Results**:260 patients were enrolled. Both males(n=133) and females(n=127) were almost equal in distribution. We observed 97 % (203/210) SVR12 in non-cirrhoticswho received Daclatasvir plus Sofosbuvir treatment regimen. Cirrhotics who received Sofosbuvir plus Daclatasvir along with Ribavirin observed SVR of 86 % (43/50). All patients tolerated the drug regimens well without any serious adverse effect. **Conclusion:** Once daily oralSofosbuvir plus daclatasvir based therapy is highly efficient and safe in both cirrhotics and non-cirrhotic hepatitis C patients.

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INTRODUCTION

Chronic hepatitis C is a global health problem and one of the main causes of chronic liver disease worldwide[1]. The primary goal of HCV therapy is to cure the infection, i.e. to achieve a sustained virologic response (SVR) defined as undetectable HCV RNA 12 weeks or 24 weeks after treatment completion. SVR12 and SVR24 have been accepted as endpoints of therapy by regulators[2]. HCV genome comprises six genotypes and several subtypes[3] and in our country India Genotype-3 is the most common[4]. Treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) had been standard care for HCV patients for a more than a decade, until the arrival of oral drugs direct acting antivirals (DDA)[5]. The double combination of pegylated IFN-α and ribavirin, the double combination of sofosbuvir and ribavirin and the triple combination of pegylated IFN-α, ribavirin and sofosbuvir are no longer acceptable, according to current EASL Clinical Practice Guidelines. Directing acting antivirals (DAAs) have led to high sustained virologic responses (SVRs) than interferon-based regimens, are shorter in treatment duration, are orally administered and have fewer adverse effects.

In this study, we report our experience with direct –acting antiviral agents (DAAs) based treatment regimens of chronic hepatitis-C genotype-3 infection in Kashmiri population.

Aims and Objectives

- To evaluate the efficacy of Daclatasvir plus Sofosbuvir in chronic hepatitis C genotype-3 infection.
- To assess the safety of this drug regimen.

MATERIALS AND METHODS

This study was conducted in the Department of Gastroenterology, Government Medical College, SrinagarKashmir India from November 2015 to April 2018.
The study was stared after clearance from local institutional ethical committee. Formal Informed Consent was taken after properly discussing the treatment plan, adverse effects and the cost of the treatment along with benefits in the patient's own language. Baseline investigations including hemogram, biochemistry, ultrasonography, weight, height was taken.

The anti-HCV antibodies were detected by using Enzyme Linked Iso-immuno Assay (ELISA) technique.HCV RNA level was measured by COBAS AmpliPrep/COBAS TaqMan HCV test, v2.0 (Roche Molecular Diagnostics, Branchburg, NJ) with a lower limit of quantitation of 15 IU/mLAfter determining the HCV-genotype, patients with genotype 3 were included in the study protocol. Fibroscan (Echosens France) and upper gastrointestinal endoscopy(Olympus 150 series) were also done before starting the treatment protocol. After putting the patients on treatment, HCV-RNA load was measured at 4 weeks, at the end of treatment and 12 weeks post-treatment.

Inclusion criteria: Newly diagnosed adult patients of chronic hepatitis C with genotype-3 cirrhotic as well as non-cirrhotics of either genderwere included in this study.

Exclusion Criteria:

- Co-infection with Hepatitis-B or Hepatitis-D or HIV.
- Children, pregnant patients and ESRD/patients on hemodialysis
- Evidence of liver disease because of other etiology.
- Study Design: All the patients selected for this were randomized into two groups:

Group-A (non-cirrhotic) received sofosbuvir (400mg per day) and daclatasvir (60mg per day) for a period of 12weeks.

Group-B (Cirrhotic) received sofosbuvir (400mg per day) and daclatasvir (60mg per day) with ribavarinbody weight based for a period of 24 weeks. Assessment of liver stiffness with transient elastography is a reliable tool to detect significant fibrosis or cirrhosis in patients with chronic hepatitis-C (6). The cut off value of 12.8 kpa is taken for cirrhosis (7). All the patients were assessed for the safety by means of physical examination and review of adverse events and clinical laboratory testing of blood samples. Statistical Analysis: It was a randomized, open label, prospective, hospital based, comparative study.

RESULTS

In cirrhotic group 43/50 ie 86% achieved SVR.Among non-cirrhotics 204/210 ie 97 % achieved SVR. Only 8/260 (3.1%) patients developed headache, other minor adverse effects observed were fatigue, fever, dry-mouth, dyspepsia and insomnia in 3/260 (1.15%) patients.

Baseline Characteristics of the patients

Variable	
Age, median (range) years	42 (22-65)
Male: female %	51: 49
Cirrhosis n (%)	50 (19%)
Bilirubin Total (mg/dl) mean±SD	0.8 (0.6)
ALT(ULN:40U/L) mean ± SD	35 (15)
AST(ULN:40 U/L) mean ± SD	32 (13)
Albumin (g/dl)mean ± SD	4.2 (0.5)
INRmean ± SD	1.1 (0.3)
TLC(x1000/mm3),mean ± SD	6.5 (0.8)
Hemoglobin(g/dl),mean ± SD	13.2 (1.2)
Platelets(x1000/mm3),mean ± SD	280 (130)
Creatinine (mg/dl), mean ± SD	0.9 (0.3)
HCV RNAmean ± SD	650000 (150000)
BMI, Mean kg/m^2 (SD)	26 (3.5)
MELD score, median (range)	13 (8-27)

Distribution of amongcirrhoticsandnon-cirrhotics

	n	%	Treatment protocol
Non-cirrhotics	210	80.7%	S+D x 12weeks
Cirrhotics	50	19.3%	S+D+R x 24 weeks
	260	100%	

Overall response to treatment (SVR) among cirrhotic and non-cirrhotic patients

Group	SVR Achieved		SVR Not Achieved	
	No.	%age	No.	%age
Cirrhotic	43	86	7	14
Non-cirrhotic	204	97	6	3
Total	247	95.6	13	4.4

Adverse Effects	Frequency	Percentage
Headache	8	3.1
Dry Mouth	1	1.1
Fever	1	1.1
Dyspepsia	1	1.1
Fatigue	1	1.1
Insomnia	1	1.1
AE leading to discontinuation	0	0
Death	0	0

DISCUSSION

Patients with HCV genotype 3 infections are considered a special population and have become one of the most challenging subpopulations to treat. Studies have shown that genotype 3 is associated with faster progression to cirrhosis and, thus, has a higher likelihood of hepatocellular carcinoma in comparison to the other genotypes (https:// www. ncbi.nlm.nih.gov/pmc/articles/PMC5089232/#B03). In addition, few effective treatment options are available. Patients with HCV genotype 3 infection and cirrhosis have the lowest SVRs even in the DAA era.

In Kashmir, DAAs like Sofosbuvir (NS5B inhibitor) became available by the end of 2014 and Daclatasvir (NS5A inhibitor) became available by the end of 2015 which made possible all-oral, interferon-free regimens. In this study, we report our experience with direct –acting antiviral agents (DAAs) based treatment regimens of chronic hepatitis-C genotype-3 infection in Kashmiri population. We enrolled 260 patients of chronic hepatitis C genotype 3 on sofosbuvir and daclatasvir combination, to assess and compare the efficacy and tolerability of this treatment regimen. These regimens have the advantage of being safe even in patients of decompensated cirrhosis. In our study there was an almostequal gender distribution, males (n=133) and females (n=127). The mean age was 42 years(22-65) and most of them had BMI in normal range.All of the patients enrolled in this study were asymptomatic, found incidentally or on screening or with some trivial liver enzyme elevations. In our study most of the patients had no family history of acute or chronic hepatitis C infection. Majority, 80% of patients had no underlying co-morbidity. Among the patients studied diabetes mellitus (4.4%), hypertension (3%), leukemia (2%) and carcinoma ovary (1.1%) were the comorbid illnesses. We enrolled two hundred sixty (n=260) patients in our study and most of them were non-cirrhotic, 81%(210/260).Cirrhotics were only 19 % patients (n=50).Non-cirrhotic group received treatment regimen of Sofosbuvir along with Daclatasvir (S+D) for 12 weeks, while as cirrhotic group was treated with Sofosbuvirand daclatasvir plus Ribavirin (S+D+R).

The SVR12 rate was highest in non-cirrhotic 97% (204/210). The cirrhotics who received Sofosbuvir plus Daclatasvir along with Ribavirin (S+D+R) achieved SVR 12 of 86 %. In the landmark ALLY-3 study[9],101 treatment naıve and 51 treatment experienced were treated with DCV 60 mg plus SOF 400 mg once daily for 12 weeks. SVR12 rates were 90% (91 of 101) and 86% (44 of 51) in treatment-naıve and treatment-experienced patients, respectively. Baseline characteristics, including gender, age, HCV-RNA levels, and interleukin-28B genotype, did not impact virological outcome. DCV plus SOF was well tolerated; there were no adverse events (AEs) leading to discontinuation. They concluded that 12-week regimen of DCV plusSOF achieved SVR12 in 96% of patients with genotype 3 infection without cirrhosis and was well tolerated. Hezode C et al from France[10] in a multicentre observational study evaluated SOF plus DCV with or without RBV for 12 or 24 weeks in naive or treatment-experienced patients with HCV genotype 3.SOF (Sofosbuvir) plus DCV (Daclatasvir) for 12 weeks provides very high SVR rates in non-cirrhotic patients (94–97%), but in those with cirrhosis the overall SVR of 59–69% is less than satisfactory.

The addition of RBV increases the SVR rates in cirrhotic patients to above 80% and extending treatment to 24 weeks raises SVR rates to 90%. Nevertheless, it remains unclear if 12 weeks is enough for all patients or 24 weeks is the best option for some special populations, such as cirrhotic patients. In a RCT conducted by Sulkowski et al. (2014) which included patients of hepatitis C genotypes 1-3 who were treated with Sofosbuvir and Dcalatasvir with or without Ribavarin,they found SVR 12 of 89 %. In our study we observed by addition of ribavirin todaclatasvir and sofosbuvir combination achieved high SVR-12. The combination of SOF plus DCV for 24 weeks is recommended by the EASL and the AASLD guidelines for the treatment of cirrhotic patients with HCV genotype 3 infection (European Association for Study of the Liver, 2012; http:/www.hcvguidelines.org. Accessed 7 March 2017). In our study we added ribavirin with sofosbuvir plus daclatasvir combination and extended the treatment for the period of 24 weeks. Our results indicate that regimens based on DAAs that are currently available in India are highly effective for treatment of genotype-3 HCV infection, including patients with cirrhosis.

In our study we have not found any effect on hemoglobin and creatinine in both cirrhotic and non-cirrhotic patients due to treatment regimens. The baseline investigations were done at 0 week, at 4 week and at end of treatment. In our study only3 out of 90 patients, 3.3% developed headache. Other minor adverse effects noted were fever, fatigue, and dry-mouth in one patient. Daclatasvir has been reported to be safe and well-tolerated in combination with other anti-viral and DAAs like PEG-IFN/RBV, SOF[14,15].In our study most of the patients tolerated well the drugs. There was no major side effect observed in our patients and none of them discontinued treatment due to adverse effects. We examined patients physically as well as by laboratory before starting treatment, at 4 weeks, 12 weeks and the end of treatment regimens. There was no significant fall of hemoglobin and impairment of renal functions. We have also not observed any effects on liver functions. In summary, a 12-week regimen of DCV plus SOF achieved a very high SVR12 intreatment-naivenon-cirrhotic patients with genotype 3 infection.

This regimen, with the addition of RBV demonstrated high SVR12 rates even in patients with cirrhosis. It was well tolerated in both the groupsof patients.

Convflict of interest: All the authors declare that they have no conflict of interest.

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