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# EFFICACY OF SOFOSBUVIR PLUS VALPATASVIR BASED THERAPY IN THE TREATMENT OF TREATMENT NAIVE CHRONIC HEPATITIS C GENOTYPE-3 IN KASHMIR.

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**Abstracts**

**Objectives:** Direct acting antivirals (DAAs) have dramatically changed our approach towards management of chronic hepatitis C by yielding a high sustained virological response (SVR). Genotype-3 is the most common genotype found in Kashmir (Northern India) besides having an aggressive nature with increased risk of steatosis and hepatocellular carcinoma. We assessed the efficacy and safety of sofosbuvir plus valpatasvir based therapy in chronic hepatitis C genotype-3 infection in Kashmiri population.

**Aims and objectives:** An observational, prospective, open label, hospital based study was carried over a period of two years which included 230 treatment naïve chronic hepatitis-C genotype-3 patients. Patients were divided in two groups. Group-A: Non-cirrhotics who received sofosbuvir (400 mg daily) with valpatasvir (100 mg) in fixed–dose combination for 12 weeks. Group B included CPT class A cirrhotics who received sofosbuvir (400mg daily) with valpatasvir (100 mg daily) and weight based ribavarin for 12 weeks. The primary end point was a sustained virologic response at 12 weeks after the end of therapy.

**Results and observations:** We observed 98.57 % (138/140) SVR 12 in non-cirrhotics who received valpatasvir plus sofosbuvir treatment regimen. Cirrhotics who received Sofosbuvir plus valpatasvir with ribavirin observed SVR of 96.6 % (87/90). All patients tolerated the drug regimens well without any serious adverse effect.

**Conclusion**: Once daily oral Sofosbuvir plus valpatasvir based fixed dose rerimen is highly efficient and safe in treatment of both cirrhotics and non-cirrhotic hepatitis C patients.

**Keywords:** Direct acting antivirals; sustained virological response; Genotype; chronic hepatitis C

## Introduction

WHO estimated that in 2015, 71 million persons were living with chronic HCV infection worldwide (global prevalence: 1%) and that 399 000 had died from hepatitis C related cirrhosis or hepatocellular carcinoma (HCC) [1].

India harbors an estimated 10–15 million chronic carriers of HCV, which is one of the major causes of liver-related mortality and morbidity in the country.[2]

Unlike HCV genotype 1, genotype 3 is common in low-income regions in Asia, sub-Saharan Africa, Latin America, and Eastern Europe [3]. In fact genotype 3 is the most common genotype in India and Kashmir.

Patients with HCV genotype 3 and cirrhosis have lower sustained virologic response rates than other populations treated with direct-acting antiviral agents [4].

The primary goal of any HCV therapy is to cure the infection, i.e. to achieve a sustained virologic response (SVR) which is defined as undetectable HCV RNA 12 weeks after treatment completion (SVR12). Long-term follow-up studies have shown that an SVR corresponds to a definitive cure of HCV infection in more than 99% of cases [5].

Treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) had been standard care for HCV patients for a more than a decade giving sub-optimal results and lot of morbidity, until the arrival of oral drugs direct acting antivirals (DDA) changed the whole scenario of hepatitis C management. A number of DAA s have been approved over last few years compelling liver societies to change guidelines more frequently as per the rapidly growing literature favouring newer DAA s.

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 clinical practice guidelines. Besides sofosbuvir plus daclatasvir has a lower SVR 12 in genotype 3 with cirrhosis.

Sofosbuvir is a nucleotide analogue NS5B polymerase inhibitor that was approved in 2013 for the treatment of HCV infection. Velpatasvir is a NS5A inhibitor with antiviral activity against all HCV genotypes. On June 28, 2016, the US Food and Drug Administration approved the first pan-genotypic fixed-dose combination velpatasvir (VEL)/SOF for adult patients with CHC virus infection with or without

cirrhosis, but in India, this combination was approved by Drug Controller General of India on May 4, 2017.

In this study, we report our experience with sofosbuvir-valpatasvir fixed dose combination based treatment regimens of chronic hepatitis-C genotype-3 infection in Kashmiri population.

**Patients and Methods**

This prospective study was conducted in the Department of Gastroenterology, Government Medical College, Srinagar Kashmir India and over two years from July 2017 to June 2019.

**Study Design:** A total of 230 patients included in this study were randomized into two groups:

*Group-A (non-cirrhotic)*: included 140 patients who received sofosbuvir (400mg per day) plus valpatasvir (100 mg per day) fixed dose combination for a period of 12weeks.

*Group-B (CPT class A Cirrhosis):* included 90 patients who received sofosbuvir (400mg per day) plus valpatasvir (100 mg per day) fixed dose combination with ribavarin body weight based for a period of 12 weeks.

Newly diagnosed adult patients (age > 18 years) of chronic hepatitis C with genotype-3 non-cirrhotics and Child-Turcotte-Pugh (CTP) class A cirrhotics of either gender were included in this study.

Decompensated cirrhosis, co-infection with Hepatitis-B or HIV, Children, pregnancy and ESRD/patients on hemodialysis were excluded from the study

Baseline investigations including hemoglobin,white blood cell count, platelet count Liver function tests, renal function tests, 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, v 2.0 (Roche Molecular Diagnostics, Branchburg, NJ) with a lower limit of quantitation of 15 IU/mL

Assessment of liver stiffness was done with transient elastography (Echosens France) and a cut off value of 12.5 kPa was taken for cirrhosis. Upper gastrointestinal endoscopy (Olympus GIF Q 150 series) was also done before starting the treatment protocol.

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.

After putting the patients on treatment, HCV-RNA load was measured at 4 weeks, at the end of treatment and 12 weeks post-treatment (SVR-12) . Reassessment of liver stiffness was done with Fibroscan at SVR (12 weeks after completion of the treatment)

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. The study was stared after clearance from local institutional ethical committee. All authors participated in the acquisition, analysis and interpretation of the data, had access to the study data and reviewed and approved the final manuscript.

**Objectives**

1. To evaluate the efficacy of Sofosbuvir plus valpatasvir based therapy in chronic hepatitis C genotype-3 infection.
2. To assess the safety and tolerability of this drug regimen.

**Statistical Analysis:** It was a randomized, open label, prospective, hospital based, comparative study. Collected data was compiled and entered in spread sheet Microsoft excel and exported to Data editor of SPSS computer software, version 20 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables were summarized as frequency and percentage.

**Results**:

The present study included 230 treatment naïve hepatitis C genotype 3 patients who were grouped into cirrhotic and non-cirrhotic groups. Non-cirrhotics received sofosbuvir-valpatasvir therapy for 12 weeks while cirrhotics received weight based ribavarin in addition to sofosbovir-valpatasvir. Mean age of the study patients was 42 years. Males constituted about 55%. 39% patients were cirrhotic based on liver stiffness value (fibroscan) > 12.5 k Pa. There were 12 patients with intravenous drug abuse (5 non-cirrhotics and 7 cirrhotics ).

**Table 1:** Patient demographics and baseline characteristics

| Variable | |
|---|---|
| **Age (**years) **mean (SD)** | 42 (22-65) |
| **Gender Male: female**,(%) | 55: 45 |
| BMI ($kg/m^{2)}$, mean (SD) | **26 (3.0)** |
| **Cirrhosis. n (%)** | 90 (39%) |
| **Bilirubin total** (mg/dl) mean (SD) | 0.8 (0.6) |
| **ALT** (ULN:40U/L) mean (SD) | 54 (15) |
| **AST** (ULN:40 U/L) mean (SD) | 48 (13) |
| **Albumin** (g/dl) mean (SD) | 4.2 (0.5) |
| **INR** mean (SD) | 1.1 (0.3) |
| **TLC**(x1000/mm3), mean (SD) | 6.5 (0.8) |
| **Hemoglobin(**g/dl), mean (SD) | 12.2 (1.8) |
| **Platelets(**$x10^3/\mu L$), mean (SD) | 190 (130) |
| **Creatinine** (mg/dl), mean (SD) | 0.9 (0.3) |
| **HCV RNA (log 10 $^5$ iu/ml)** | 28±13 |
| Fibroscan score (kPa) , mean (SD) | 13.5 ± 4.2 |
| Intravenous drug abusers | 12 (5.3 %) |

ALT, alanine aminotransferase; AST aspartate aminotransferase; BMI, body mass index; DAA,direct-acting antiviral; RBV, ribavirin; SD, standard deviation; INR, International normalized ratio; TLC ,total leucocyte count

**Table 2:** Distribution of patients among cirrhotics and non-cirrhotics.

| | n | % | Treatment protocol |
|---|---|---|---|
| **Non-cirrhotics** | 140 | 60.9 % | S+V x 12 weeks |
| **Cirrhotics** | 90 | 39.1 % | S+V+R x 12 weeks |
| | 230 | 100% | |

S: Sofosbuvir; V: Valpatasvir; R: Ribavarin

**Table 3:** Treatment response (SVR 12)

| Group | SVR Achieved | | SVR Not Achieved | |
|---|---|---|---|---|
| | **Number** | **%age** | **Number** | **%age** |
| **Cirrhotic** | 87 / 90 | 96.6 | 3 / 90 | 3.3 |
| **Non-cirrhotic** | 138 / 140 | 98.6 | 2 / 140 | 1.4 |
| **Total** | **225 / 230** | **97.8** | **5 / 230** | **2.2** |
| P-value = | | | | |

In cirrhotic group 87 out of 90 patients (96.6 %) achieved SVR. Among non-cirrhotics 138 out of 140 patients (98.6 %) achieved SVR.

**Table 4:** Profile of adverse events.

| Adverse Events | S +V n (%) | S+V+R n (%) |
|---|---|---|
| Headache | 10 (7.1) | 8 (8.8) |
| Nausea | 4 (2.8) | 6 (6.6) |
| Dry Mouth | 6 (4.2) | 7 (7.8) |
| Fatigue | 8 (5.7) | 13 (14.4) |
| Insomnia | 5 (3.6) | 8 (8.8) |
| Nasopharyngitis | 2 (1.4) | 3 (3.3) |
| Anorexia | 6 (4.2) | 8 (8.8) |
| Dyspepsia | 2 (1.4) | 2 (2.2) |
| Drop in Hb | | |
| <2 gm/dL | 3 (2.1) | 7 (7.8) |
| >2 gm/dL | 0 | 3 ( 3.3) |
| Drop in platelets | | |
| <50 x $10^3$ /µL | 2 (1.4) | 6 (6.6) |
| >50 x $10^3$ /µL | 0 | 2 (2.2) |
| AE leading to discontinuation | 0 | 0 |
| Death | 0 | 0 |
| Total events | **49** | **68** |

Adverse events were more commonly reported among cirrhotics, but all were mild or moderate in severity with none being severe enough to result in discontinuation.

**Discussion**

The global prevalence of genotype 3 hepatitis C virus (HCV) infection is estimated to be 22%–30% of all HCV infections.[6,7]

Unfortunately genotype 3 is the most common genotype in highly populated and resource limited nations like India [2]. Moreover, genotype 3 HCV infection can be associated with a more rapid progression of fibrosis, leading to a higher risk of developing cirrhosis and hepatocellular carcinoma.[8]

No doubt the introduction of directly acting antivirals in the management of hepatitis C infection have rasied the hope of eliminating this infection but genotype 3 has been found to have lower SVR 12 compared to other genotypes. Sofosbuvir plus valpatasvir is the first pangenotypic single-tablet regimen approved for the treatment of hepatitis C infection.

In this prospective study which included 230 treatment naïve chronic hepatitis-C patients 39% (n=90) were cirrhotic while as 61% (n=140) were non-cirrhotics. Non-cirrhotics received sofosbuvir plus valpatasvir in fixed–dose combination for 12 weeks while as cirrhotics received in addition weight based ribavarin for 12 weeks. Our data showed successful real-world use of SOF/VEL regimens in GT 3 non-cirrhotic as well as cirrhotic patients. SVR was achieved in 98.57 % (138/140) in non-cirrhotics while as cirrhotics achieved SVR in 96.6 % (87/90).

Our finding is consistent with previous studies showing similarly high SVR 12 rates among GT 3 cirrhotic patients treated with SOF/VEL, from a retrospective pooled-analysis of the ASTRAL-1, -2, and -3 trials (91% achieved SVR12) [9], as well as from a German multicentre cohort study (98% achieved SVR12) [10].

In the ASTRAL 3 study, the rate of sustained virologic response in the sofosbuvir–velpatasvir group was 95% (95% CI, 92 to 98), which was superior to the rate of 80% (95% CI, 75 to 85) in the sofosbuvir–ribavirin group (P<0.001) [3].

A recent study by Gorkha et al [11] found high efficacy of sofosbuvir plus valpatasvir regimen in genotype 3 hepatitis C patients in both cirrhotics (SVR 12 of 95%) and non-cirhotics (SVR 12 of 100 %)....

EASL 2018 guidelines for the management of hepatitis C recommends fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks in treatment-naive and treatment-experienced patients infected with HCV genotype 3 without cirrhosis. It does not recommend this combination in treatment-naive and treatment-experienced patients infected with HCV genotype 3 with compensated (Child-Pugh A) cirrhosis, because suboptimal results have been reported with this combination which is largely based on results of ASTRAL 3 study. The SVR12 rates were 98% (160/163) in treatment-naive patients without cirrhosis.

Lower SVR12 rates of 93% (40/43) were observed in treatment-naive patients with compensated cirrhosis. Treatment-experienced cirrhotics had SVR 12 of 91% only [3].

Thus, the addition of a third drug to this regimen is may be necessary particularly in patients infected with genotype 3 with compensated cirrhosis. EASL 2018 recommends a fixed-dose combination of glecaprevir and pibrentasvir for

12 weeks in treatment-naive patients infected with HCV genotype 3 with compensated (Child-Pugh A) cirrhosis.

While as the AASLD treatment guidelines 2018 recommend the fixed dose combination of sofosbuvir and velpatasvir for both non-cirrhotic as well as compensated cirrhosis patients.

In POLARIS-3 trial which compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir/ velpatasvir among 219 DAA-naive participants with genotype 3 infection and cirrhosis, the SVR12 rate was 96% in both arms; 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir achieved SVR [12].

In another phase 3 trial from India by Sood et al found 97% SVR12 rate for patients with genotype 3 and compensated cirrhosis treated with sofosbuvir/ velpatasvir for 12 weeks [13].

In a large phase II study conducted HCV genotype 3 with cirrhosis, patients were randomized to receive sofosbuvir/velpatasvir with or without ribavirin for 12 weeks. In the sofosbuvir/velpatasvir group 91% (92/101) achieved SVR12 while as in the treatment group receiving sofosbuvir/velpatasvir with ribavirin, 96% (99/103) patients achieved SVR12. The benefit of the addition of ribavirin to the regimen was largely attributable to the difference in relapse rates among patients with baseline NS5A resistance-associated substitutions [14].

Besides these trials, real world data has also demonstrated high SVR 12 rate for patients with genotype 3 and compensated cirrhosis treated with sofosbuvir/velpatasvir for 12 weeks. Mangia et al [15] showed a SVR 12 rate of 95 % (71 patients out of 75 patients).

A study from Pakistan [16] found nearly identical SVR rates with sofosbuvir valpatasvir combination in hepatitis C patients without cirrhosis (92.5%) and with compensated cirrhosis (92.1%).

In general, our study results depict a tolerable safety profile for sofosbuvir-velpatasvir among both patients without cirrhosis and patients with compensated cirrhosis, as the majority of adverse events were of mild-to-moderate severity. None of the adverse events (AEs) was severe enough to demand discontinuation in therapy.

The common side effects in our study were fatigue, headache, insomnia, nausea, dryness of mouth. We observed lower frequency of (AEs) compared to that seen in ASTRAL 3 trial .We did not encounter any case of nasopharyngitis or pruritus. These occur more frequently in the cirrhotic group who received ribavarin in addition to the standard sofosbuvir-valpatasvir combination.

Similarly AEs were generally frequent in patients who underwent RBV-including regimens and the types of AEs were typical of RBV (anemia, insomnia, irritability and coughing) in ASTRAL 3 trial.

Limitations associated with our study are single centre data which may not have generalisability, besides being silent on any information about long-term clinical outcomes of patients who achieved SVR.

## Conclusion

SOF/VEL being a pangenotypic and pan-fibrosis single pill oral regimen is highly efficacious in Hepatitic C infection including non-cirrhotics and compensated cirrhosis. In addition this regimen has few mild adverse events. Surely, it has simplified, or perhaps eliminated the pre-treatment assessments and on treatment monitoring that may not be easily available in resource poor nations. Considering the characteristics of SOF/VEL, this regimen can be considered the ideal partner in the path to HCV eradication.

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**Authors' contribution:** All authors contributed equally

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**Compliance with ethical principles:** The study was conducted according to the Declaration of Helsinki 1975.

The study was approved by the scientific committee at Government Medical College Srinagar, Kashmir, India.

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