

VIROLOGICAL RESPONSES OF VELPATASVIR/SOFOSBUVIR IN PATIENTS WITH HCV GENOTYPE 3

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ABSTRACT:

BACKGROUND & OBJECTIVE: The role of Velpatasvir/Sofosbuvir in the treatment of hepatitis C virus type 3 infection is evaluated in terms of virologic responses. i.e Rapid Virological Response (RVR) End of treatment response (ETR) and Sustained virological response (SVR 12).

METHODOLOGY: This was a descriptive case study conducted in Liver OPD of Benazir Bhutto Hospital during 01 November 2018 to 30 April 2019, in which 100 patients of HCV were enrolled, all of them had HCV genotype 3 infection. Every patient was treated with combination of Velpatasvir/Sofosbuvir 100mg/400 mg Once Daily as part of treatment regimen of HCV infection for 12 weeks. Pre-treatment HCV RNA QUANTITATIVE PCR was done, which was repeated on 4, 12 weeks of treatment and then 12 weeks post treatment.

RESULTS: Among 100 patients, 51 (51%) were male and 49 (49%) were females. Mean age of patients was 43.2 ± 10.4 years (mean \pm SD). Mean BMI of enrolled patients was 21.34 ± 2.40 kg/m². 33% patients were cirrhotic while 67% were non cirrhotic. 53% patients were treatment experienced while 47% were treatment naïve. Rapid Virological Response (RVR) was achieved in 92%, End of treatment response (ETR) was achieved in 96%, while Sustained Virological response (SVR12) was achieved in 99% patients. The results were stratified according to age, gender and BMI. There was no effect of these parameters on the final results.

CONCLUSION: Virological response (RVR, ETR, SVR12) of Velpatasvir /Sofosbuvir and Ribavirin is encouraging.

KEYWORDS: HCV, Genotype 3, RVR, ETR, SVR12, Oral Direct Acting Antivirals, DAA, Velpatasvir, Sofosbuvir.

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INTRODUCTION:

Hepatitis C virus is a major global health concern. Worldwide above 170 million patients have HCV infection with more than 70 million people progress to chronic HCV infection and HCV related liver diseases ^[1]. There are 6 genotypes of HCV infection among which most abundant is HCV genotype 1, but genotype of major concern in our part of world is HCV genotype 3 which is found to have infected 30.1% patients ^[2].

HCV infection can be acute, but in majority cases it progresses to chronic infection which leads to cirrhosis predisposing to hepatocellular carcinoma posing greater health concerns and significant impact on morbidity and mortality ^[3]. Treatment guidelines of HCV management have evolved rapidly in current decade, since the start of use of direct acting oral antivirals (DAAs) in management of HCV infection.

There are two goals of HCV infection treatment. One is to achieve virological responses in term of sustained virological response which is defined as persistent absence of HCV RNA in serum after 12 weeks of completion of treatment with medications, other goal is to prevent complications of HCV such as development of cirrhosis and decompensated liver disease ^[4].

Among recently approved combination Velpastavir/Sofosbuvir combination was approved by FDA in 2016. Velpatasvir is NS5A targeting agent and Sofosbuvir is NS5B targeting drug, both NS5A and NS5B are viral replication proteins ^[5].

The efficacy of Epclusa (Velpatasvir/Sofosbuvir) was evaluated in ASTRAL-1, ASTRAL-2, ASTRAL-3 and ASTRAL-4. SVR 12 was concluded to be 98% in ASTRAL1,2, and 3 after 12 weeks of treatment in ASTRAL 4, Epclusa for 12 weeks and 24 weeks achieved 83% and 86% SVR 12 respectively ^[6,7,8].

Currently there are no local studies available for evaluation of virological responses to Velpatasvir/Sofosbuvir combination. The aim of this study is to evaluate the efficacy of Velpatasvir/Sofosbuvir (Epclusa) in achieving virological responses in HCV genotype 3.

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METHODOLOGY:

This descriptive case study was conducted in Liver Clinic OPD of Medicine Unit-II, Benazir Bhutto hospital from 01-11-2018 to 30-04-2019 over six months' time. The study has been approved by the Ethical review committee of Benazir Bhutto hospital, Rawalpindi. Patients of HCV genotype 3 presenting in Liver clinic were enrolled in this study after taking informed consent via non-probability consecutive sampling technique. Patients with or without cirrhosis, and both treatment naïve and treatment experienced patients were included in study. Age of included patients was between 18-70 years with BMI >18kg/m². All Patients had pretreatment HCV RNA Quantitative levels >1000 IU/L. Patients with HBV, HIV co-infection, pregnant women, and patients with decompensated liver disease were excluded. As a part of treatment regimen, Tab Velpatasvir/Sofosbuvir (EPCLUSA) in dose of 100mg/400mg once daily was given to all patients for 12 weeks. HCV RNA PCR QUANTITATIVE was done at 4 weeks of treatment for Rapid Virological Response, at 12 week of treatment for End of Treatment Response (ETR) and 12 weeks post treatment for Sustained Virological Response (SVR12) ^[9].

All the categorical variables like gender, RVR, ETR, SVR were described as frequencies and percentages while for age, BMI which are continuous variables, mean and SD was calculated. Effect modifiers including age, gender, BMI were controlled by stratification.

RESULTS:

Total of 100 patients of HCV were evaluated. Mean age of patients was 43.2 ± 10.4 years (mean ± SD).

The age was further distributed into two categories the distribution is given below in the graph (Figure I).

Out of 100 patients, 51 (51%) were males and 49(49%) were females.

The following pie chart (Figure II) shows the distribution of male and female patients. The BMI was 21.34 ± 2.40 kg/m². 33 patients were having evidence of liver cirrhosis and Ultrasound at time of enrollment, whereas 67 patients were non-cirrhotic. 47% patients (47/100) were treatment naïve, whereas remaining 53% (53/100) had already taken. Rapid Virological Response(RVR) was achieved in 92% of patients (92/100), whereas End of treatment response was achieved in 96% (96/100) Patients and Sustained Virological Response (SVR12) was achieved in 99% (99/100) patients. The following pie chart (Figure III) shows the distribution RVR, ETR and SVR among patients.

The data was stratified according to age, gender and BMI. There was no effect of these parameters on the final results. The following table (Table I) shows the comparison between groups for efficacy after stratification.

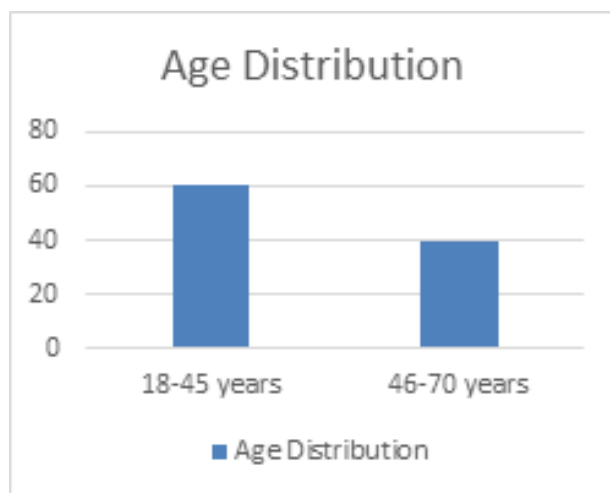


Figure-I

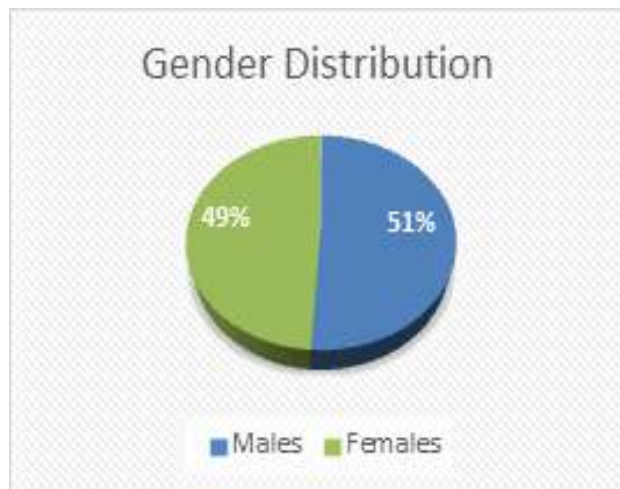


Figure-II



Figure-III

Table-I. RVR, ETR SVR status after stratification.

		RVR	ETR	SVR
Age	18-45 years	55/60 (90%)	57/60 (95%)	60/60 (100%)
	46-70 years	37/40 (92.5%)	39/40 (97.5%)	39/40 (97.5%)
Gender	Male	47/51 (92.1%)	49/51 (96%)	50/51 (98%)
	Female	45/49 (91.8%)	47/49 (95.9%)	49/49 (100%)
BMI	18.5-24.9	67/73 (91.7%)	70/73 (95.8%)	73/73 (100%)
	25-29.9	25/27 (92.5%)	26/27 (96.3%)	26/27 (96.3%)

DISCUSSION:

HCV infection has emerged as a significant global problem as its burden is on rise with passage of time. This disease is no more confined to few epidemiological locations, rather it is now considered to be present in almost every country of world contributing to socio-economic burden^[10].

Most widely studied genotype across the world is Genotype 1, and majority research data is targeted to this Genotype. However Genotype 3 has also been focused in studies especially due to its resistance to conventional treatment regimes. Developments of new oral antiviral drugs have made treatment of genotype 3 much easier. And these newer medications like sofosbuvir and related compounds are now hot favorite in the treatment of HCV genotype 3^[11, 12]. It has been reported that patients infected with HCV genotype 3 are more prone to develop Hepatocellular carcinoma as compared to patients infected with HCV genotype 1. In a study by Kanwal F, et al^[13] was found that this association of HCV genotype and HCC is independent of patients' age, diabetes, body mass index, or antiviral treatment.

Our study conducted on a sample size of 100 persons, included both male and females in roughly equal percentage (males 51%; females 49%). There were more subjects in the younger age group (60% in 18-45 years age group) as compared to older age group (40% in 45-71 years age group). Our study included both cirrhotic and non-cirrhotic patients. The results of our study were comparable to many other similar studies.

A series of phase 3 trials were conducted to assess efficacy of velpatasvir/Sofosbuvir with or without put ribavirin in patients of HCV genotype 1-

6 with name of ASTRAL trials. These trial encompasses both cirrhotic, non-cirrhotic as well as treatment naïve and treatment experienced patients. In ASTRAL 1 trial, 624 patients of HCV genotype 1,2,3,4 and 6 were included in trial for treatment with Velpatasvir and Sofosbuvir and overall 99% patients achieved SVR12. In ASTRAL II trial, done for HCV genotype 2, combination of Velpatasvir/Sofosbuvir plus Ribavirin Achieved overall SVR 12 of 99%. ASTRAL III was conducted for Genotype 3 of HCV in which SVR12 of 95% was recorded. Whereas in ASTRAL IV trial for patients of decompensated cirrhosis with all genotypes, SVR12 was 85% in genotype 3 with 12 weeks of treatment. Sustained Virological response (SVR 12) in our study was 99% for patients of HCV genotype including cirrhotic, non-cirrhotic, treatment naïve and treatment experienced patients after 12 weeks of therapy with Velpatasvir/ Sofosbuvir. These values are comparable to the ones seen in international studies; the slight difference might be attributed to the small sample size of our study. The evaluated Rapid Virological Response (RVR) and End of Treatment Responses (ETR) in our study were 92% and 96% respectively^[6,7,8]. These results are also similar to results of various other international and national studies^[14,15].

In another trial Velpatasvir with sofosbuvir with or without Ribavirin achieved SVR 12 in 99% patients with HCV genotype 1,2,3^[16]. Many studies support the effectiveness of Velpatasvir plus sofosbuvir in achieving High SVR. Ahmed Husseni in a metaanalysis reported the SVR 12 in patients of HCV genotype 3 to be 94% in patients treated with Velpatasvir and Sofosbuvir^[15]. ASTRAL studies also advocated that combination of Velpatasvir and

Sofosbuvir are more effective as compared to sofosbuvir alone in achieving SVR ^[7,8].

Study done by Rosito Garico *et al* considers Velpatasvir plus Sofosbuvir with or without Ribavirin as highly effective regimen for HCV in Cirrhotic, Liver transplant patients and patients on Haemodialysis and with renal failure ^[17]. Studies done by Schreiber J *et al*, and Everson GT *et al*, reported Velpatsavir sofosbuvir combination to be highly effective ^[18,19].

Currently no local study is available in our country about the efficacy of Velpatasvir and sofosbuvir in HCV genotype 3 infection, however a trial of 502 patients on Sofosbuvir in 2016 has been reported to achieve SVR12 in 85.5% of cases. However this study does not encompass for effect of Velpatasvir on SVR ^[20]. Another analysis by S Iqbal ^[21] (2017) suggested expected SVR to be between 80-100% with DAA.

In my study, the data was stratified according to age, gender and BMI. There was no effect of these parameters on the final results. Similar conclusions were drawn from clinical trials by Ferguson MC ^[22].

CONCLUSION

Sustained virological response of Velpatasvir, sofosbuvir and ribavirin is encouraging. However, more studies are required to ascertain the results.

CONFLICT OF INTEREST: All authors disclose no conflict of interest.

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Authors' Contribution:

Muhammad Sarfraz: Designed, data collection, statistical analysis, final approval of manuscript, and agreement for accountability of all work.

Arshad Rabbani: Data collection, statistical analysis, agreement for accountability of all work, and final approval of manuscript.

Muhammad Shahzad Manzoor: Over all Supervision of data collection, analysis and study writing.

Benish Adil: Help in data collection analysis and final draft of study.

Ramsha Ghazal Arshad: Help in data collection analysis and final draft of study.

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