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Success of (NS5B/NS5A Inhibitors) Sofosbuvir/Velpatasvir in Management Hepatitis C Studied Tertiary Care Healthcare in Rawalpindi, Pakistan

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Abstract:-

➢ ***Background***

Treatment of Hepatitis C has remarkably changed worldwide with the introduction of Directly Acting Agents (DAA's). Multiple regimens have been employed for the treatment of hepatitis C patients. In 2018, the regimen of sofosbuvir and velpatasvir (SOF/VEL) was approved by World Health Organization to be used.The aim of this study was to assess the efficacy of SOF/VEL in the treatment of chronic hepatitis C patients in a tertiary care hospital in Pakistan.

➢ ***Materials and Methods***

This was a prospective and single arm interventional study conducted from July 2021 to July 2022 at Holy Family Hospital, Rawalpindi after getting ethical approval from Rawalpindi Medical University. Chronic hepatitis C patients regardless of having complications such as hepatocellular carcinoma, decompensated liver disease and previous treatment history were recruited after taking informed consent. All patients were give single tablet combination of SOF/VEL for period of 12 weeks after which sustained virological response (SVR) was measured. Data were collected on a structured proforma and was entered and analyzed in IBM SPSS 23.0.

➢ ***Results***

Among the 154 patients, the mean age of the patients was 50.7±13.2 years and the number of males were 108 (70.1%). After 12 months of treatment SVR was achieved in 96.1%(148/154). SVR was achieved more in patients who had normal liver status, were treatment naïve, had not undergone interferon treatment and did not have hepatocellular carcinoma ($p<0.05$). The mean age of patients who achieved SVR was less compared to those who did not ($p<0.05$).

➢ ***Conclusion***

SOF/VEL combination can be used in patients with chronic hepatitis C effectively.

Keywords:- *Sofosbuvir, Velpatasvir, Hepatitis C, sustained virological response, Pakistan.*

I. INTRODUCTION

Chronic Hepatitis C virus (HCV) infection has estimated to have affects more than 71 million people worldwide. Among the affected there is a significant number of chronic patients who develop liver cancer and/or cirrhosis.[1] Due to high prevalence ranging between 4.5-8.2%, Pakistan stands as the 2nd highest HCV burden-stricken country after Egypt in international prevalence rates.[2] In Pakistan, genotype 3 is the most prevalent (63.5%)compared to the rest. With highest prevalence in Balochistan (25.77%) and overall prevalence of 8.64%, epidemiologist regard blood transfusions and indiscriminate usage of syringes as one of the important factors leading to its spread.[3] HCV poses a huge public threat to Pakistan not only due to the widespread threat but also due to the economic burden it inflicts on a struggling economy.

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The treatment of hepatitis C has evolved over the past 4 decades. In 1990's, the treatment was focused mainly at using Interferon-alpha. However, the drug had multiple side effects and had a low sustained virological response (SVR) of 8% to 9%.[4]TheSVR rates improved to 46% following the addition of Ribavirin.[5] SVR improved further with the usage of Pegylated Interferon (PEG-IFN) and it reached to 56% with a combination with Ribavirin.[6]

In 2014 and 2015, the introduction of hepatitis C genome specific agents called the Directly Acting Agents (DAA) completely changed the SVR rate. Since these drugs are ribavirin and interferon free, the side effects also reduced. The drugs act by inhibiting NS3/4A protease inhibitors (Simeprevir, Telaprevir), NS5A polymerase inhibitors (Daclatasvir, Velpatasvir) and NS5B polymerase inhibitors (Sofosbuvir, Dasabuvir).[7]

According to the WHO guidelines published in 2018 on the treatment of chronic hepatitis C, the proposed treatment regimen that should be followed is based on whether the patient has developed cirrhosis or not.

For adults with cirrhosis it is recommended that the following DAA regimen encompassing all the genomes of hepatitis C should be used:
• Sofosbuvir/velpatasvir 12 weeks
• Sofosbuvir/daclatasvir 12 weeks
• Glecaprevir/pibrentasvir 8 weeks[8]

While for adults with cirrhosis in a compensated state, the following DAA regimens are recommended
- Sofosbuvir/velpatasvir 12 weeks
- Glecaprevir/pibrentasvir 12 weeks
- Sofosbuvir/daclatasvir 24 weeks
- Sofosbuvir/daclatasvir 12 weeks[8]

Sofosbuvir and velpatasvir is now considered as a very promising treatment for Hepatitis C. The drug is delivered in a combination orally as single tablet which comprises of 400 mg of Sofosbuvir while 100 mg of Velpatasvir. Not only does the combination has much less adverse effects compared to combinations with Ribavirin but it also has a pan-genotypic effect. This allows clinicians to use the drug combination widely.[9]

The ASTRAL series of phase 3 clinical trials assessed the efficacy of Sofosbuvir and Velpatasvir combination using the sustained virological response (SVR) rates. Not only 100% was achieved in all genotype of hepatitis C but different stages of fibrotic diseases were treated by the same regimen. A single pill daily improves the adherence to treatment and absence of gluten and lactose in the combination makes it suitable for patients with intolerance. In case of decompensated disease, SOF/VEL combination with ribavirin results in 94% SVR rates.[10]

After being approved for treatment in Pakistan since 2018, minimal studies have been conducted in the country to assess the efficacy of the combination in the treatment of hepatitis C. Nevertheless, a widescale study was conducted to assess the combination efficacy when compared to SOF/DCV in treating genotype 3 patients.[11] However, minimal studies have been conducted which take into account factors such as genotype, presence of hepatocellular carcinoma, liver status, previous treatment exposure, METAVIR score and interferon usage in the same sample of study. Hence, the current study provides an additional narrative to the current evidence in literature.

II. MATERIALS AND METHODS

A. Study Design

This was a prospective, single arm and interventional study which was conducted in the department of Gastroenterology of Holy Family Hospital, Rawalpindi. The trial was conducted after the approval of the ethical review committee of Rawalpindi Medical University and was designed on the basis of Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study was conducted from July 2021 to July 2022.

B. Participants

A total of 154 participants were included in this study. The patients were enrolled by non-probability convenient sampling according to the selection criteria of the study. All those patients between the age of 20-70 years regardless of gender, presence of hepatocellular carcinoma, fibrotic stage, liver status, previous treatment history and interferon treatment history were included in this study. Diagnosed cases of hepatitis C through RT-PCR who remained positive for greater than 6 months were termed as chronic hepatitis C patients. Patients with concurrent hepatitis B infection, history of the human immunodeficiency virus (HIV) and history of a liver transplant were excluded from this study.

C. Study Process

After taking informed written consent from the 154 patients, they were given fixed dose of Sofosbuvir and Velpatasvir in the concentration of 400 mg and 100 mg respectively. The treatment was given for a period 12 weeks and 24 weeks. Prior to giving the treatment, the principal investigator of the study took a detailed history of the patients to deduce whether the patients had received treatment before or not, was there any interferon used, and the demographic status. All the patients underwent liver biopsy, liver ultrasound and necessary blood tests to calculate the METAVIR score, to rule out hepatocellular carcinoma and degree of liver disease. The patients underwent RT-PCR after the duration of treatment which was noted by the principal investigator. The results were used to report SVR which was considered as the primary end point of the study.

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III. STATISTICAL ANALYSIS

Data were entered and analyzed in IBM SPSS version 23.0. Quantitative variables such as age were reported as mean and standard deviation. Qualitative variables such as gender, genotype. liver status, METAVIR score, duration of treatment, hepatocellular carcinoma. interferon treatment and previous treatment history were reported as frequency and percentages. The primary outcome variable SVR reported as frequency and percentage. The data were stratified according to SVR. Post-stratification Chi-square test was applied for qualitative variables and independent T-test was applied for quantitative variables.

IV. RESULTS

Among the 154 patients who underwent treatment with the combination of SOF/VEL, the mean age of the patients was 50.7±13.2 years. The number of males in the study were 108 (70.1%). Table 1 shows the demographic and past medical history related variables of all the patients.

Table 1 the demographic and past medical history related variables

		Number (Percentage)
Genotype	I	140 (90.9%)
	II	11 (7.1%)
	III	3 (1.9%)
Liver Status	Normal	85 (55.2%)
	Chronic Liver Disease	36 (23.4%)
	Decompensated Chronic Liver Disease	33 (21.4%)
METAVIRScore	F0 (No fibrosis)	82 (53.2%)
	F1 (Portal fibrosis without septa)	1 (0.6%)
	F2 (Portal fibrosis with few septa)	8 (5.2%)
	F3 (Portal fibrosis with numerous septa without cirrhosis)	31 (20.1%)
	F4 (Cirrhosis)	32 (20.8%)
Duration of Treatment	12 weeks	103 (66.9%)
	24 weeks	51 (33.1%)
Hepatocellular Carcinoma	Not Present	141 (91.6%)
	Present	11 (7.1%)
	Present with Portal Vein Thrombosis	2 (1.3%)
Interferon Treatment History	Yes	44 (28.6%)
	No	110 (71.4%)
Previous Treatment History	Yes	10
	No	144

Table 1: Demographic and history related variables of the patients

- *Sustained Virological Response Rate*

The response rate among the patients in this study was 96.1% (148 patients). Response rate varied according to the baseline and history related variables as shown in table 2.

Table 2 Response rate varied according to the baseline and history related variables

		SVR Achieved or Not		**P-value**
		Yes	**No**	
Gender	Male	103 (69.6%)	5 (83.3%)	0.419
	Female	45 (30.4%)	1 (16.7%)	
Genotype	I	135 (91.2%)	5 (83.3%)	0.621
	II	10 (6.8%)	1 (16.7%)	
	III	3 (2.0%)	0 (0.0%)	
Liver Status	Normal	84 (56.8%)	1 (16.7%)	0.021*
	Chronic Liver Disease	35 (23.6%)	1 (16.7%)	
	Decompensated Chronic Liver disease	29 (19.6%)	4 (66.7%)	
METAVIRScore	F0 (No fibrosis)	81 (54.7%)	1 (16.7%)	0.215*
	F1 (Portal fibrosis without septa)	1 (0.7%)	0 (0.0%)	

	F2 (Portal fibrosis with few septa)	7 (4.7%)	1 (16.7%)	
	F3 (Portal fibrosis with numerous septa without cirrhosis)	30 (20.3%)	1 (16.7%)	
	F4 (Cirrhosis)	29 (19.6%)	3 (50.0%)	
Duration of Treatment	12 weeks	103 (69.6%)	0 (0.0%)	0.001**
	24 weeks	45 (30.4%)	6 (100.0%)	
Hepatocellular Carcinoma	Not Present	141 (95.3%)	0 (0.0%)	<0.001*
	Present	7 (4.7%)	4 (66.7%)	
	Present with Portal Vein Thrombosis	0 (0.0%)	2 (33.3%)	
Interferon Treatment	Yes	38 (25.7%)	6 (100%)	<0.001**
	No	110 (74.3%)	0 (0.00%)	
Previous Treatment History	Yes	7 (4.7%)	3 (50.0%)	0.004**
	No	141 (95.3%)	3 (50.0%)	

When comparing the age according to SVR, the ones who achieved it had a mean age of 49.1±13.1 years and the ones who did not achieve it were 61.7±12.6 years (p=0.028)

V. DISCUSSION

Since the introduction of DAA's, the treatment protocol for hepatitis C has widely changed all over the world. DAA's have been preferred over the interferon and ribavirin combination considering the lesser side effects it inflicts on the patients as well as the greater SVR rates that are achieved.

SVR is the measure of prognosis and treatment efficacy when assessing outcomes of hepatitis C treatment. In this study, SVR was achieved in a total of 148 patients (96.1%) of the patients. The current study has multiple factors which have impacted the SVR of the patients. The current study includes multiple factors which include previous treatment history, interferon treatment, presence of hepatocellular carcinoma, duration of treatment, liver status, METAVIR score, genotype and gender.

The treatment duration generally was divided into two groups in this study. For 103 (66.9%) patients the treatment was given for 12 weeks while it was given for 24 weeks to 51 (33.1%) patients. Among the patients who received the treatment for 12 weeks, all achieved SVR but those who received for 24 weeks had an SVR rate of 88.1%. However, the overall SVR was reported to be high as much as 96.1%. This is comparable to the widescale study conducted in Pakistan comprising of a total 1,388 participants, out of which 415 patients received SOF/VEL. The SVR was reported to be 94.7% in the group. Non-SVR was reported to be more in patients with old age and with cirrhosis.[11]

Similarly, another study reported that SVR was achieved in 94.4% of the cases of genotype II or hepatitis C while it was achieved in 92.0% of genotype III. The study reported in the multivariate model that previous treatment experience and presence of decompensated liver disease were among the reasons which led to low SVR rates.[12]This was comparative to this study as SVR rates were low in patients with treatment experience as well as decompensated liver disease.

A real-world experience reported in Canada in a trial to treat 2,812 patients suffering from Hepatitis C resulted in a SVR rate of 94.6%. The SVR rates varied in genotype 1, genotype 2 and genotype 3 and were reported as 94.6%, 94.5% and 96.4%, respectively. Factors that were reported to have contributed to non-SVR were younger age, treatment experience and infected with HIV.[13] This was comparative to our study as non-SVR was reported in patients with treatment experience in our study as well. However, our study reported lower SVR rates in older age groups while this study reported lower SVR rates in younger age groups.

Similarly, researchers have discussed the clinical outcomes treating patients of genotype I and genotype II patients with decompensated cirrhosis with SOF/VEL. In one of the studies, overall SVR rate was reported to be 92.3%. This study reported a good virological activity of SOF/VEL in patients suffering from decompensated liver disease.[14]The usage of the combination was also proven to be beneficial in patients with end stage renal disease. SVR was achieved in 96% of the patients after a treatment of 12 weeks. There were no major side effects reported that can be detrimental to end stage renal disease patients.[15] In addition to this, a study conducted in Taiwan also advocated the safety and efficacy of the combination treatment in compensated liver disease by reporting an SVR rate of 92.6%.[16]These results were synonymous to our study in which 87.88% of the patients suffering from decompensated liver disease successfully reach SVR by the end of the treatment.

In terms of cirrhosis, the current study reported that SVR rates did not vary according to the METAVIR score. Patients regarded with a F4 level signifying cirrhosis and F3 level signifying portal fibrosis with numerous septa without cirrhosis, both reported SVR rates of 96.8% and 90.6% respectively. This was also affirmed by studies conducted previously in literature which reported SVR rates of 96% (212/220), and 99% (278/281) in patients with cirrhosis and advanced fibrosis respectively.[17]This was also affirmed by another study conducted in Taiwan using the fibrosis-4 (FIB-4)

index which reported there was no significant difference in the SVR rates between patients with FIB-4 scores of ≤ 3.25 and those with scores of > 3.25.[18]

According to a study conducted in Rawanda, an SVR of 97% was achieved in treatment naïve patients who presented with genotype IV of hepatitis C.[19] A study on treatment experienced patients reported that SOF/VEL was an effective combination for treating patients with and without cirrhosis belonging to genotype III group. In compensated liver disease patients taking 100 mg velpatasivir regimen, SVR was achieved in 100% of the patients. While patients with decompensated liver disease, the SVR was achieved in 96% of the patients.[20]Previous treatment has also been regarded as one of the contributing factors to treatment failure in hepatitis C patients for other regimens than SOF/VEL. In literature, it has been reported that patients who are treatment naive are equally likely to respond to treatment when compared to treatment experienced patients. The current study, however, differs given there is a significant difference in achieving SVR rates when the treatment naïve and treatment experienced patients were compared.

Our study has several limitations which may impact the overall results of the study. Patients who were included in the study were majorly from the genotype 1 and only a few patients from genotype II and genotype III. Adding further, the study has all limitations associated with non-probability convenience sampling.

In conclusion, our population was found to be responsive towards the treatment by SOF/VEL. However, the rate of SVR does vary according to factors such as presence of hepatocellular carcinoma, history of interferon treatment, liver statusand previous treatment history.

REFERENCES

[1]. Lim AG, Qureshi H, Mahmood H, Hamid S, Davies CF, Trickey A, Glass N, Saeed Q, Fraser H, Walker JG, Mukandavire C. Curbing the hepatitis C virus epidemic in Pakistan: the impact of scaling up treatment and prevention for achieving elimination. International journal of epidemiology. 2018 Apr 1;47(2):550-60.
[2]. Miller MH, Ferguson MA, Dillon JF. Systematic review of performance of non-invasive biomarkers in the evaluation of non-alcoholic fatty liver disease. Liver International. 2011 Apr;31(4):461-73.
[3]. Arshad A, Ashfaq UA. Epidemiology of hepatitis C infection in Pakistan: current estimate and major risk factors. Critical Reviews™ in Eukaryotic Gene Expression. 2017;27(1).
[4]. Poynard T, Leroy V, Cohard M, et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology. 1996;24(4):778–789.
[5]. Lai MY, Kao JH, Yang PM, Wang JT, Chen PJ, Chan KW, Chu JS, Chen DS. Long-term efficacy of ribavirin plus interferon alfa in the treatment of chronic hepatitis C. Gastroenterology. 1996 Nov 1;111(5):1307-12.
[6]. Chen CH, Yu ML. Evolution of interferon-based therapy for chronic hepatitis C. Hepatitis research and treatment. 2010;2010.
[7]. Geddawy A, Ibrahim YF, Elbahie NM, Ibrahim MA. Direct acting anti-hepatitis C virus drugs: clinical pharmacology and future direction. Journal of translational internal medicine. 2017 Mar 1;5(1):8-17.
[8]. World Health Organziation. Guidelines For The Care And Treatment Of Persons Diagnosed With Chronic Hepatitis C Virus Infection. 2018.
[9]. Greig SL. Sofosbuvir/velpatasvir: a review in chronic hepatitis C. Drugs. 2016 Oct;76(16):1567-78.
[10]. Grebely J, Dore GJ, Zeuzem S, Aspinall RJ, Fox R, Han L, McNally J, Osinusi A, Brainard DM, Subramanian GM, Natha M. Efficacy and safety of sofosbuvir/velpatasvir in patients with chronic hepatitis C virus infection receiving opioid substitution therapy: analysis of phase 3 ASTRAL trials. Clinical Infectious Diseases. 2016 Dec 1;63(11):1479-81.
[11]. Mushtaq S, Akhter TS, Khan A, Sohail A, Khan A, Manzoor S. Efficacy and safety of generic sofosbuvir plus daclatasvir and sofosbuvir/velpatasvir in HCV genotype 3-infected patients: real-world outcomes from Pakistan. Frontiers in Pharmacology. 2020 Sep 2;11:550205.
[12]. Belperio PS, Shahoumian TA, Loomis TP, Mole LA, Backus LI. Real-world effectiveness of daclatasvir plus sofosbuvir and velpatasvir/sofosbuvir in hepatitis C genotype 2 and 3. Journal of hepatology. 2019 Jan 1;70(1):15-23.
[13]. Wilton J, Wong S, Yu A, Ramji A, Cook D, Butt ZA, Alvarez M, Binka M, Darvishian M, Jeong D, Bartlett SR. Real-world effectiveness of sofosbuvir/velpatasvir for treatment of chronic hepatitis C in British Columbia, Canada: a population-based cohort study. InOpen forum infectious diseases 2020 Mar (Vol. 7, No. 3, p. ofaa055). US: Oxford University Press.
[14]. Tada T, Kurosaki M, Nakamura S, Hasebe C, Kojima Y, Furuta K, Kobashi H, Kimura H, Ogawa C, Yagisawa H, Uchida Y. Real-world clinical outcomes of sofosbuvir and velpatasvir treatment in HCV genotype 1-and 2-infected patients with decompensated cirrhosis: A nationwide multicenter study by the Japanese Red Cross Liver Study Group. Journal of Medical Virology. 2021 Nov;93(11):6247-56.
[15]. Taneja S, Duseja A, Mehta M, De A, Verma N, Premkumar M, Dhiman RK, Singh V, Singh MP, Ratho RK, Ramachandran R. Sofosbuvir and Velpatasvir combination is safe and effective in treating chronic hepatitis C in end-stage renal disease on maintenance haemodialysis. Liver International. 2021 Apr;41(4):705-9.

[16]. Liu CH, Chen PY, Chen JJ, Lo CC, Su WW, Tseng KC, Liu CJ, Huang CS, Huang KJ, Yang SS, Peng CY. Sofosbuvir/velpatasvir for patients with chronic hepatitis C virus infection and compensated liver disease: real-world data in Taiwan. Hepatology International. 2021 Apr;15(2):338-49.
[17]. Asselah T, Bourgeois S, Pianko S, Zeuzem S, Sulkowski M, Foster GR, Han L, McNally J, Osinusi A, Brainard DM, Subramanian GM. Sofosbuvir/velpatasvir in patients with hepatitis C virus genotypes 1-6 and compensated cirrhosis or advanced fibrosis. Liver International. 2018 Mar;38(3):443-50.
[18]. Huang YT, Hsieh YY, Chen WM, Tung SY, Wei KL, Shen CH, Chang KC, Lu CK, Yen CW, Lu SN, Hung CH. Sofosbuvir/velpatasvir is an effective treatment for patients with hepatitis C and advanced fibrosis or cirrhosis in a real-world setting in Taiwan. BMC gastroenterology. 2021 Dec;21(1):1-9.
[19]. Kateera F, Shumbusho F, Manirambona L, Kabihizi J, Murangwa A, Serumondo J, Makuza JD, Nsanzimana S, Muvunyi CM, Kabakambira JD, Sylvain H. Safety and efficacy of sofosbuvir-velpatasvir to treat chronic hepatitis C virus infection in treatment-naive patients in Rwanda (SHARED-3): a single-arm trial. The Lancet Gastroenterology & Hepatology. 2022 Jun 1;7(6):533-41.
[20]. Pianko S, Flamm SL, Shiffman ML, Kumar S, Strasser SI, Dore GJ, McNally J, Brainard DM, Han L, Doehle B, Mogalian E. Sofosbuvir plus velpatasvir combination therapy for treatment-experienced patients with genotype 1 or 3 hepatitis C virus infection: a randomized trial. Annals of internal medicine. 2015 Dec 1;163(11):809-17.