ORIGINAL ARTICLE

EFFICACY OF THE COMBINATION OF DACLATASVIR AND SOFOSBUVIR FOR THE MANAGEMENT OF HCV GENOTYPE 3 PATIENTS

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ABSTRACT

Objective: To determine the frequency of sustained virologic response (SVR) of Daclatasvir (DCV) plus Sofosbuvir (SOV) for the management of HCV genotype 3 infections in non-cirrhotic patients.

Study Design: Prospective, observational study.

Place and Duration of Study: Gastroenterology department, Shifa International Hospital Islamabad, 06 months (May to November 2019).

Methodology: Total 75 diagnosed and treatment- naive patients of chronic HCV genotype 3, in whom liver cirrhosis was ruled out by abdominal ultrasound, were included in the study, by non-probability convenience sampling. A combination of DCV (60mg) and SOV(400mg) orally once daily for 12 weeks was given to all and were followed up in the OPD for 12 weeks after treatment. After 12 weeks of completion of treatment, HCV PCR was checked to evaluate the SVR after 12 weeks (SVR-12).

Results: Out of 75 patients, male patients were 56% while female patients were 44%. The mean age was 48.65 ± 13.72 years. Diabetes mellitus was present in 62.7% of the patients. SVR-12 was achieved in 85.3% which showed insignificant association with gender (p-value 0.916), diabetes mellitus (p-value 0.455) and age (p-value 0.076).

Conclusion: Achieving an SVR-12 rate of 85.3% depicts that the combination of DCV and SOV is extremely efficient in treating the HCV genotype 3, Its efficacy is consistent across patients, regardless of age, gender, or diabetes mellitus.

Key words: *Daclatasvir, Genotype, Hepatitis C, chronic, Sofosbuvir, Sustained virologic response.*

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INTRODUCTION

Chronic infection with the Hepatitis C virus (HCV) is a global health concern. The World Health Organization(WHO) recognizes it as a huge public health issue. The estimated worldwide prevalence is 2.8 %, affecting almost 71 million people globally. This Virus can cause acute & chronic hepatitis, liver cirrhosis, hepatocellular carcinoma(HCC), as well as end-stage liver disease(ESLD). The prevalence of chronic HCV in Pakistan is about 6.5% and in some areas, it is around 14%. It is a silent infection, mostly diagnosed when the patient has already developed complications. Almost 20% of chronic cases of HCV present after developing cirrhosis[1,2,3,4,5]. There are about 58 million chronic HCV carriers in the world, according to some recent studies. The disease is causing 290,000 deaths a year[3].

Of the 11 HCV genotypes, found worldwide, HCV genotype 3 is the 2nd most prevalent. Its global prevalence is 30% and even higher than 60% in parts of Southeast Asia[6]. The prevalence of HCV genotype-3 in Pakistan is higher, with a frequency between 75% to 90% of cases[2,7]. This genotype is more aggressive in increasing the risk of liver cirrhosis & HCC[2]. Patients with elevated alanine aminotransferase (ALT) levels, those above

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the age of 18, those with positive HCV RNA, and those with compensated and decompensated liver disease are among those who should receive treatment. Sustained Virologic Response (SVR) is a negative HCV RNA, 24 weeks after the completion of antiviral treatment[2,7]. Late relapse after achieving SVR is extremely low (less than 1%). With an SVR, patients come up with reduced inflammation, fibrosis and liver complications. With SVR reached, HCC and death rate will be very low[2].

Although the direct-acting antiviral agents (DAAs) have contributed to improving SVR, management of those infected with genotype 3, & having compensated or decompensated liver cirrhosis remains difficult. Regardless of treatment history, genotype 3-HCV-related cirrhosis continues to provide a therapeutic challenge. This genotype's inadequate virological response has been linked with higher hepatic steatosis & fibrosis [7,8].

CAPSULE SUMMARY

The combination of Daclatasvir and Sofosbuvir is very effective in treating HCV genotype 3, as evidenced by the high SVR-12 rate in this study. Its effectiveness was constant across patients, irrespective of age, and gender. Effect modifiers had no significant influence.

Recent advancements in HCV infection treatment plans, either alone or in conjunction with Ribavirin and pegylated interferon-alpha, have significantly increased the pharmacological capacity to attain SVR. However, due to the severe adverse effects associated with these drugs, non-compliance is common and patients even discontinue treatment. Among the novel antiviral treatments, a highly effective drug Sofosbuvir(SOV), a pangenotypic NS5B nonstructural protein inhibitor, has recently been approved for treating HCV genotype 3. It works particularly well against HCV genotype 3 when combined with Ribavirin or Pegylated Interferon (Peg-IFN) plus Ribavirin. Another potent option, Daclatasvir (DCV), a pangenotypic NS5A inhibitor, has also demonstrated encouraging outcomes when combined with SOV and Ribavirin[7]. Daclatasvir was approved in 2015 by the Food and Drug Authority to be used in combination with SOV for treating HCV genotypes 1 and 3. Due to the scarcity of alternatives and concerns over their cost, it is still utilised in many government settings. In addition, the government provides it as part of a hepatitis control program[9,11]. Sofosbuvir is prescribed with DCV for the treatment of HCV with/without ribavirin, and treatment has been dramatically changed with the advent of new antivirals[2,10]. In the 2016 ALLY-3 Phase III trial, which compared SOV-DAC combination therapy concluded that SVR is higher in non-cirrhotic patients' treatment-naive about 96% and 86% for treatment-experienced patients[11]. There is a dearth of information on this combination in this region of the world, although few trials have evaluated the safety & efficacy of DAA-based therapy of adult patients having chronic HCV infection, notably regimens based on DCV and SOV with or without Ribavirin[12]. The National Hepatitis Control Program includes DCV, which is administered in conjunction with SOV for 12 weeks to combat genotype 3. DCV was added at the government level, which improved compliance and produced positive treatment results[13].

Given the low effectiveness of antiviral treatment in this subgroup of HCV patients, particularly in genotype 3, analysis of the viral response in de-compensated cirrhosis warrants particular consideration. A small number of advanced liver disease cases have been included in a few trials that have assessed the use of DCV/SOV in genotype 3-HCV-infected patients in clinical practice[14]. The DCV/SOV-based regimen also showed promising results in different coinfections like HIV and special populations like kidney transplant recipients among the immunosuppressive status of patients[15]. From 2020 onwards, the SOV/DCV regimen has become the preferred DAA treatment for HCV in low- & low-middle-income countries, accounting for around 2/3rd of the global prevalence [16].

Pakistan is included in the low-income countries list. Moreover, SOV/DCV regimen is provided at many public hospitals through the National Hepatitis Control Program. Assessing the efficacy of this DAA combination is the foremost rationale of this study in a resource-limited setting like our country. This study assessed the efficacy of combining SOV and DCV for treating HCV genotype 3 infection in our population.

METHODOLOGY

This prospective, observational study was done at the Deptt. of Gastroenterology, Shifa International Hospital, Islamabad, from 24-05-2019 to 24-11-2019. Institutional Review Board provided the ethical approval for this research (Reference number: 421-364-2017, Date: 12-1-2017).

All patients in the age range 18-70 years reporting to the outpatients department (OPD), diagnosed with chronic HCV genotype 3, were screened for cirrhosis by ultrasound abdomen and baseline HCV RNA. Total 75 patients who were non-cirrhotic on ultrasound and had baseline HCV RNA >15 IU/ml were included by nonprobability convenience sampling. All patients were treatment-naive. Pregnant, lactating, patients having cirrhosis, un-typeable genotype and prior hypersensitivity to drugs were excluded.

All data were recorded through structured proforma. After informed consent, demographic information of patients (name, age, gender) was recorded. Basic labs were checked namely Complete Blood Count (CBC), Liver Function Tests(LFTs), Serum Creatinine level & International Normalized Ratio (INR). SVR was operationally defined to be achieved if HCV PCR is <15 IU/ml, 12 weeks after treatment completion. The selected patients were started with DCV 60mg and SOV 400mg orally once daily and were followed up in OPD for 12 weeks. Then the patients were advised to follow-up after 12 weeks of the end of treatment and HCV PCR were checked. The primary endpoint was an SVR after 12 weeks (SVR-12) of the end of treatment, assessed with a sensitive molecular method.

Reports were assessed and HCV RNA<15 IU/mL was labelled as achieved SVR-12. All this information was recorded through structured proforma. All lab investigations were done in the hospital laboratory and were verified by pathologists.

Data analysis was done with SPSS 20. Means & Standard Deviation were calculated for the quantitative variables, and frequencies & percentages for the qualitative ones. Data was stratified for age, gender and diabetes mellitus to deal with the effect modifiers. After stratification, a chi-square test was applied setting a p-value of <0.05 as significant.

RESULTS

The study was done on 75 patients, in order to determine the frequency of SVR-12 of DCV plus SOV combination for the management of HCV genotype 3 infection in non-cirrhotic patients.

The minimum & maximum ages of patients were 25 and 70 years respectively. The mean of the age was 48.65 ± 13.72 years. Male patients were in the majority (56%). Diabetes mellitus was identified in more than half of the patients (62.7%). The SVR-12 was achieved by most of the patients. Table 1 and Figure 1 show the detailed results. A chi-square test determined the association of SVR-12 with gender, age and diabetes mellitus.

Table 1: Characteristics of the study participants.

S.no	Characteristic	Subcategory	Frequency (n=75)	Percentage (%)
1.	Gender	Male	42	56
		Female	33	44
2.	Diabetes Mellitus	Present	47	62.7
		Absent	28	37.3
3.	SVR-12 achieved	Yes	64	85.3
		No	11	14.7

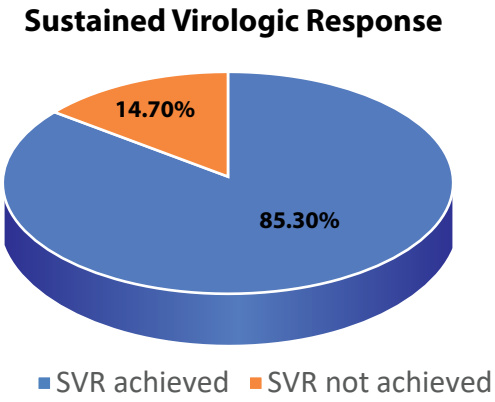

Figure 1: Percentage of sustained virologic response achieved 12 weeks after completion of treatment

Table 2: Association of SRV-12 with different characteristics

Characteristics	Subcategory	SVR achieved n (%)		p – value
		Yes	No	
Gender	Male	36 (48)	6 (8)	0.916
	Female	28 (37.3)	5 (7)	
Age	≥47 years	30 (40)	2 (2.6)	0.076
	<47 years	34 (45)	9 (12)	
Diabetes Mellitus	Present	39 (52)	8 (10.6)	0.45
	Absent	25 (33.3)	3 (4)	

Age was categorized into two groups of > 47 & < 47 years of age. Despite differences in percentages, the analysis showed that gender, age and diabetes mellitus do not have a significant association with achieving SVR. The findings imply that treatment regimens play a more critical role in determining SVR outcomes irrespective of age, gender or presence of diabetes mellitus (Table 2).

DISCUSSION

The frequency of SVR-12 of the DCV plus SOV for the management of HCV genotype 3 infection in non-cirrhotic patients was determined. In our study, SVR-12 was achieved by maximum (85.3%) patients. Our results are comparable to another prospective, observational study, by Jinnah Postgraduate Medical Centre, (JPMC) Karachi [9], which had 300 patients with detectable HCV RNA PCR with the most prevalent genotype 3 (83%). The mean age in their study (40.49 years) was slightly lower than the mean age in ours but the dispersion in the age (SD ± 13.86) was comparable to our results. In contrast to our study, the majority of the patients included were females (58%). Combination therapy with SOV and DCV was administered for either 12 or 24 weeks, with Ribavirin added for treatment-experienced and cirrhotic patients. SVR-12 or SVR-24, was achieved in 88.33% of patients which is slightly higher than the response achieved in our study. Both studies highlight the effectiveness of combination therapy with SOV and DCV across different patient populations and settings. However, differences in demographic profiles such as gender distribution, treatment durations, and patient characteristics, such as cirrhosis, treatment history and presence of Diabetes Mellitus, may account for variations in outcomes. Regardless of these differences, both studies demonstrate high efficacy rates for achieving SVR-12, which supports the utility of this therapeutic regimen in managing HCV.

Another observational study conducted at Lady Reading Hospital, Peshawar, from Jan to Dec 2020, presents insights into the effectiveness of SOV and DCV in achieving SVR in patients with HCV [17]. That study had 172 patients, with a mean age of 40 (SD ± 12.23) years, a little lower than in our study. Age distribution showed that 53% were young adults (18–40 years)

and 47% were middle-aged and elderly (>40 years of age). This age distribution was comparable to our study which showed more patients (57%) in age <47 years. Gender distribution was in contrast to our study showing a majority of the female participants (55.8%). Most of the participants in the study were diagnosed with genotype 3(69.8%) and 91.3% had normal liver on ultrasound. This study achieved slightly higher SVR12 rates than our study (93.6% vs. 85.3%). Gender and age showed no significant association with SVR 12(p-value>0.05) which is comparable to our results. Both studies confirm the high efficacy of the SOV + DCV regimen in achieving SVR12 across various patient groups.

Our results are comparable to another study conducted on 835 patients in a resource-limited country. Mean age of 50.5 ± 13.73 was higher than our study with the same dispersion. In contrast to our study, the most represented age group (42.2%) was 50 – 69 years. A male predominance of 60.78% was comparatively more than our study. The study showed a very high treatment efficacy after 12 weeks of treatment. Result of HCV PCR <15 IU/mL was achieved among 99.4%, which is much higher than our response rate [3]. Our results are comparable to another multicenter study conducted across multiple government and private tertiary care hospitals in Pakistan which evaluated the efficacy of SOV and DCV in achieving SVR in HCV genotype 3 infection [13]. This study was done on 972 patients. The mean age 46.5 ± 13.3 years was slightly lower than our participants with the predominance of female participants. Total 94.4% of patients achieved SVR-12, a comparatively higher response than our study. The slightly lower SVR-12 rate in our study may be due to the differences in sample size, patient characteristics, and comorbidities such as diabetes. In contrast to our study, it showed a significant association of age with SVR-12. Age above 60 years was identified as a significant predictor of non-SVR.

Another study done at the Hepatitis Clinic, Medical Unit–II, Jinnah Hospital Lahore, supports the results of our study that DCV in combination with SOV is an efficient strategy for HCV genotype 3. That study had 135 patients. The mean age of the participants was 49.8 ±2.3 years with a predominance of male participants which is comparable to our results. The SVR-12 was achieved by 91.1% of patients which shows higher response than our study [18].

CONCLUSION

SVR-12 was achieved in 85.3% of HCV genotype 3 infection patients who used the DCV plus SOV combination. Effect modifiers had no significant influence. The combination demonstrated high efficacy & good tolerability in HCV genotype 3 infection in the study population.

Non-probability convenience sampling technique and an inadequate sample size were the main limitations of our study. Future research should concentrate on examining the risk variables linked to treatment failures and a low SVR.

ETHICAL APPROVAL: *Reference number: 421-364-2017, Date: 12-1-2017*
CONSENT FOR PUBLICATION: *Written, informed consent was obtained from the study participants.*
AVAILABILITY OF DATA: *Data is available from the corresponding author on a justified request.*
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AUTHORS' CONTRIBUTION:

- ***Sana Tahir Virk:*** *Drafting the article, analysis and interpretation of data*
- ***Sadaf Yousaf:*** *Acquisition of data, Drafting the article*
- ***Kazim Abbas Virk:*** *Conception and design, critical revision*
- ***Zaid Umer:*** *Analysis and interpretation of data*
- ***Abeer Zafar:*** *Acquisition of data, Drafting the article*
- ***Mahwish Ahmad:*** *Conception and design, Critical revision*

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