Original Article

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Response of Daclatasvir and Sofosbuvir in Treatment-Naïve, HCV Genotype 3, Non-Cirrhotic Pakistani Population: 1 Year Follow-Up Experience

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Author`s Contribution

[1,4,,5] Substantial contributions to the conception or design of the work; or the acquisition Concept and design, Collection and assembly of data, Analysis and interpretation of the data, intellectual content [2,3] Active participation in active Methodology, Drafting of article Critical revision of the article

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ABSTRACT

Objective: To evaluate the comparative effectiveness of a combination treatment using daclatasvir and sofosbuvir in treatment-naive, non-cirrhotic HCV genotype 3 Pakistani population.

Methodology: From January 2017 to February 2019, HCV patients who met the inclusion criteria were included in this open-label, non-randomized, uncontrolled observational trial at HBS General Hospital in Islamabad. A 12-week course of oral daclatasvir and sofosbuvir therapy was administered to each participant. Each patient got 400mg of sofosbuvir and 60mg of daclatasvir. Treatment outcomes included sustained virological response (SVR12 and SVR24), rapid virological response (RVR), and end-of-treatment response (ETR) as primary and secondary respectively.

Results: There were 105 participants in the study, of which 72.3% were male and 27.6% were female. RVR for male was 92% (p=0.002), while it was 89.65% for female (p=0.004). 96.05% of the male and 93.1% of the female achieved ETR (p=0.002). Both 93.1% of female and 93.4% of male had SVR12 (p=0.001). A single male patient experienced relapse after achieving SVR12 (p=060). SVR24 rates for male and female were 92.1% (p=0.003) and 93.1%, (p=0.003) respectively. The combination therapy was well-tolerated, with the primary side effect being fatigue (36% in males, 44% in females).

Conclusion: The combination therapy of daclatasvir and sofosbuvir demonstrated both safety and efficacy in treating treatment-naïve, non-cirrhotic individuals with HCV genotype 3 in Pakistan. The study underscores the potential of direct-acting antiviral agents in addressing the challenge of HCV infections.

Key words: HCV, RVR (Rapid Virological Response), ETR (End-of-Treatment Response), SVR (Sustained Virological Response), DAA (Direct Acting Antivirals)

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Introduction

Viral hepatitis is one of the leading causes of mortality worldwide. Annually, it is responsible for more deaths than malaria and HIV.[1] In May 2016, WHO endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis 2016–2021 which targets the elimination of viral hepatitis as a public health threat by 2030 by reduction of new infections by 90% and decrease in fatalities by 65%.[2]

Pakistan sits second on the list of countries with the highest prevalence rates of HCV. A comprehensive review of the latest data shows that HCV seroprevalence among the general adult Pakistani population is 6.8%.[3] That means approximately 10 million patients of HCV are present in the country. In certain sub-groups the figures are alarmingly high (in IV drug abusers and thalassemic patients the prevalence is 72% and 55% respectively).[4] A look at the frequency distribution of genotypes

demonstrates that genotype 3 (69.1%) is the most prevalent genotype in Pakistan, followed by genotype 1 (7.1%).[5] Genotype 3 is generally regarded as more difficult to treat and is associated with rapid fibrosis and early hepatocellular carcinoma.[6]

In 2011, new direct acting antivirals (DAAs) became available against HCV which added another dimension to the treatment options for these patients. The first-generation DAAs were primarily protease inhibitors which were ineffective against genotype 3. However, the newer DAAs, such as sofosbuvir act on the nucleotide analogue NS5B polymerase inhibitor and show pan-genotypic activity.[7] Before the availability of DAAS, interferon and ribavirin were the only drugs available for HCV treatment in Pakistan. Local studies show that patients receiving these medications had sustained virological response of around 50%.[8] Treatment outcome with pegylated interferon was also not much better with figures of 57.6% reported in Pakistani population.[9]

The landmark ALLY 3 + trial showed that the combined use of sofosbuvir and daclatasivir in HCV genotype 3 patients was safe and efficacious. Researchers observed SVR 12 of 92% in treatment-naïve patients and 89% in previously treated patients.[10] An investigation carried out by Dalgard et al, utilizing retrospective data sourced from 17 medical facilities within Scandinavia, highlighted that the application of sofosbuvir-based therapy within a real-life context exhibited the potential to yield Sustained Virological Response (SVR) rates exceeding 90% among patients suffering with HCV genotype 3 infection, even in cases characterized by advanced liver disease.[11]

According to the best of our knowledge, as there is no published data on the efficacy of DDAs in the local population of Islamabad so far, the purpose of this study was to determine the comparative effectiveness of daclatasivir and sofosbuvir in treatment-naïve, HCV genotype 3, non-cirrhotic local population of Islamabad.

Methodology

The investigation was carried out at HBS General Hospital in Islamabad during the period from January 2017 to February 2019. The administration of all prescribed medications adhered to the protocols outlined by the Asia Pacific Association for the Study of Liver (APASL) pertaining to the management of HCV patients. The study received approval from the hospital's ethical review board, and comprehensive informed consent was obtained from all participating patients.

The study was designed as an open-label, non-randomized, and uncontrolled investigation. Inclusion criteria encompassed individuals aged above 15 years, those testing positive for quantitative PCR for HCV, and individuals displaying normal liver structure according to ultrasound results and Hild Pugh classification indicative of early liver disease (Child Pugh-A). Further, candidates with normal blood complete profiles, serum albumin levels, and prothrombin time were considered eligible. Conversely, exclusion criteria encompassed patients with a history of previous treatment failure, advanced cirrhosis, anemia, leucopenia, and thrombocytopenia, renal failure, lactating or pregnant females, individuals undergoing cancer treatment, those on immune suppressive regimens, and patients with concurrent hepatitis B virus infection. Primary outcome of the study was “End of Treatment Response” (ETR) and secondary outcome was “Sustained Virological Response” (SVR) at post treatment week 12 or 24.

The participants of the study were given 60 mg of daclatasvir and 400mg of sofosbuvir for a period of 12 weeks and followed after 4 and 12 weeks with PCR by real time assay. A viral load of less than 50 IU/ml was considered negative. SVR 12 was monitored after 12 weeks of completion of treatment while SVR 24 was done after 24 weeks of completion of treatment, using analysis of the groups.

The collected data was subjected to thorough statistical analysis using appropriate methods. Descriptive statistics were utilized to summarize demographic and clinical characteristics. The primary endpoints, including Rapid Virological Response (RVR), End-of-Treatment Response (ETR), and Sustained Virological Response (SVR12 and SVR24), were calculated as percentages of participants achieving these outcomes. Relapse rates and adverse effects were also assessed using descriptive statistics. Furthermore, subgroup analyses were conducted to explore potential variations in treatment response based on gender and age.

Results

The study enrolled a total of 105 treatment-naïve individuals with hepatitis C genotype 3 infection without cirrhosis. Of these participants, 76 (72.3%) were male, and 29 (27.6%) were female. The male participants had an age range of 18 to 70 years. The minimum age among female patients was 18 and maximum was 55 years. The laboratory variables of the study participants are given in Table I.

Table I: Laboratory parameters of the study participants

Lab Parameters	Male	Female
Hemoglobin (g/dL)	14.4g/dl	12.2g/dl
TLC x 10^3	3.8	4.6
Platelet count x 10^3	140	116
Serum Albumin	4.6g/dl	4.2g/dl
ALT	90	116
AST	78	146
PT (seconds)	13	12

RVR for male was 92% (p=0.002), while it was 89.65% for female (p=0.004). 96.05% (p=0.005) of the male and 93.1% (p=0.002) of the female achieved ETR. Both 93.1% of female and 93.4% of male had SVR12 (p=0.001). A single male patient experienced relapse after achieving SVR12 (p=060). SVR24 rates for male and female were 92.1% (p=0.003) and 93.1%, (p=0.003) respectively. The details of the viral load, RVR, ETR and SVR in male are given in Table II while the details of these findings in female are given in Table III. The comparison of the efficacy variables are mentioned in figure 1.

The combination of daclatasvir and sofosbuvir was well tolerated and major side effect experienced was fatigue in 36% of males and 44% of females. The details of the other side effects reported by the patients is given in Table IV.

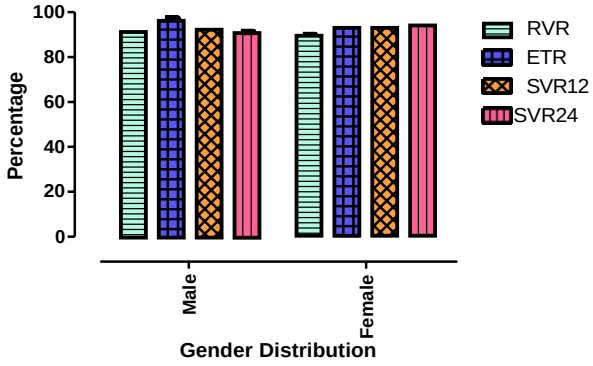

Figure I: Gender wise comparison of the efficacy variables.

Discussion

Chronic HCV infection is, in most of the cases, asymptomatic till its incidentally diagnosis is done.[10] With regards to this infection, Pakistan is a country with an intermediate endemecity.12 Here, the majority of the victims acquire it during their adolescence age or early adulthood.

Our study focused on assessing the effectiveness and safety of direct-acting antivirals (DAAs) within the local population. We observed a robust response to these novel agents with minimal mild side effects. Among the total of 105 patients enrolled in the study, 93.1% achieved Sustained Virological Response (SVR) with a p value 0f 0.005 which was significant statistically and this response was maintained by all except one patient at the 24-week mark after treatment completion. These outcomes

Table II: Frequencies of RVR, ETR and SVR in the Male patients.

Age	No.	Viral Load	RVR N (%)	ETR	SVR	Relapse	P value
18- 24	6	42747	6 (100)	6 (100)	6 (100)	0	0.002*
25- 29	3	39543	3 (100)	3 (100)	3 (100)	0	0.005*
30 -34	12	53291	11 (91.6)	12(100)	11(91.6)	1	0.001*
35 -39	9	295701	8 (88.8)	9(100)	9(100)	0	respectively
40 -44	22	313521	20 (90.9)	21(95.4)	20(90.9)	1	
45 -49	10	17462	10 (100)	9(90)	9(90)	0	
50 -54	6	73621	5 (83.3)	5 (83.3)	5 (83.3)	0	
55 -59	5	21345	5 (100)	5(100)	5(100)	0	
60 -64	2	32541	1 (50)	2(100)	2(100)	0	
65 -70	1	95615	1 (100)	1(100)	1(100)	0	

Table III: Frequencies of RVR, ETR and SVR in the Female patients.

Age	No.	Viral Load	RVR	ETR	SVR	Relapse	P value
18- 24	2	29457	2(100)	2(100)	2(100)	0	0.004*
25 -30	3	35271	2(66.6)	2(66.6)	2(66.6)	0	0.002*
35- 44	7	21543	6(85.7)	7(100)	7(100)	0	0.001*
45 -49	13	54322	12(92.3)	12(92.3)	12(92.3)	0	respectively
50 -54	4	23253	4(100)	4(100)	4(100)	0	

Table IV: Adverse effects experienced by the patients.

Adverse Effects	Males	Females
Fatigue	36	44
Body Aches	16	16
Headache	8	14
Insomnia	22	16
Dyspepsia	12	6
Flu Like Symptoms	6	4

remained consistent regardless of age, gender, and viral load at the onset of treatment.

Our study findings aligned with those of the ALLY 3+ trial, which demonstrated SVR12 rates of 90% (91 out of 101) for treatment-naïve patients and 86% (44 out of 51) for treatment-experienced patients.

Similarly, our results were in line with the research conducted by Welzel et al.[12] Their study assessed the efficacy of daclatasvir and sofosbuvir across all genotypes. They found that HCV RNA was undetectable in 73% of cases at week 4 (Rapid Virological Response), while the End-of-Treatment Response (ETR) was 92%, and 99% of participants achieved SVR24. However, in genotype 3 cases, SVR was 92%.[12] Mehta et al's study on genotype 3 also found similar results, where the treatment response to daclatasvir and sofosbuvir was 97.3%.[13] Among Iranian patients with HCV genotype 3 and cirrhosis, the response to daclatasvir and sofosbuvir treatment was 98%.[14]

However, certain studies reported slightly different outcomes. Ferriera et al's study indicated that SVR achieved in genotype 3 was only 84.7%, significantly lower than our findings.[15] One major difference was that SVR 12 was considered to be the end point of their study, while our focus extended to SVR 24, which enabled us to observe patient relapse post-SVR12 at the conclusion of treatment.

The adverse effects of daclatasvir and sofosbuvir, such as fatigue and insomnia, observed within the Pakistani population, were in comparable with international data from the ALLY 3 study.

In a study that was conducted by umer et al, the efficacy of daclatasvir and sofosbovir in genotype 3 patients. The outcomes of the study were more better with SVR12 of 98% (40/41). In this study, only cirrhotic patients were included.[16] Sulkowski et al. premeditated the outcome of Sofosbuvir plus Daclatasvir treatment naïve genotype 1 chronic hepatitis C infected patients in one arm. They observed that 100% of the patients in that arm attained SVR12 after completion of 12 weeks of treatment.[17]

In another study done by Fontaine and his co-workers, eighty-two genotype 4 infected patients were cured with Sofosbuvir plus Daclatasvir with or without Ribavirin and with or without Simeprevir. The 33 patients who received Sofosbuvir plus Daclatasvir only, were sunjected to statistical analysis. SVR12 was attained in 88.9% of those patients. However, this might be clarified by the fact that the studied group included participants who were difficult to treat, whether because they were treatment-experienced or with advanced liver disease.[18]

Another large study in Egypt documented the high SVR12 in patients receiving generic Sofosbuvir and Daclatasvir.[19] Similarly, in a study, 74% (56/76) of patients who did not achieve SVR12 were non-responders and 26% (20/76) were relapsed after the EOT. The primary nonresponse occurred slightly more among those treated with SOF-DCV than SOF-VEL. However, relapse rates were the same in both groups. The reason could be the cirrhotic patients added in easy to treat group rather in difficult to treat group and increased the non-SVR rate. The SVR rate was later increased to 88% (SOF/VEL) and 83% (SOF+DCV) by the addition of RBV for 24 weeks. Since, the regimen was not found to be a significant predictor of SVR, which is in agreement with the guidelines of EASL's and AASLD for the recommendations of sofosbovir and daclatasvir as a therapeutic regimen against HCV-GT3.[20]

Conclusion

Combination of daclatasvir and sofosbuvir was safe and efficacious in treatment-naïve, HCV genotype 3, non-cirrhotic local population of Islamabad with spontaneous viral remission rates of more than 93%. The results cannot be generalized for the whole country. Therefore, more multi-center studies are suggested to present the actual picture.

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