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Original Article

Efficacy and Safety of Direct-Acting Antiviral Drugs in Hepatitis C Virus Infection Genotype-3 in South Punjab Pakistan

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Abstract

Objective: To find out the safety and efficacy of direct anti-viral agents for the treatment of cHCV genotype-3 infection.

Methods: This retrospective study included record 1536 cHCV patient who were treated at medical outpatient department (MOPD) of Medical Unit-1 of Bahawal Victoria Hospital, Bahawalpur from April 2018 to April 2020. Polymerase chain reaction (PCR) was done 3 months after completion of treatment to note sustained virologic response (SVR). Patients were compared for various demographical characteristics, laboratory findings, comorbidities, types of direct anti-viral agents (DAAs) and treatment related adverse-effects.

Results: In a total of 1536 patients, 725 (47.2%) were male and 811 (52.8%) female. Overall, mean age was noted to be 43.2+12.8 years. Overall, SVR was noted in 1447 (94.2%) patients while there was no statistically significant difference between SVR of different DAAs (p=0.0656). Significantly linked factors with No-SVR were found to be older age (46.2+12.3 vs. 43.8+10.4 years, p=0.0368), higher BMI (27.7+3.1 vs. 26.8+2.3, p=0.001), cirrhosis (49.4% vs. 8.4%, p<0.001) and non-responders/relapsers (23.6% vs. 11.5%, p=0.001). Generalized weakness was noted to be the most frequently reported on-treatment side-effect in 471 (30.7%) while body aches & pain and fever were the other most frequently reported side-effects in 230 (14.5%) and 145 (9.4%).

Conclusion: Overall sustained virologic response with various kinds of direct-acting antiviral agents for chronic hepatitis C virus infection genotype-3 was noted to be good and comparable with real world data from different parts of the world. Increasing age, higher BMI, cirrhosis and non-responders/relapsers were found to have significant association with non-achievement of SVR. Adverse-effects related to different direct anti-viral agents were few and mild in nature.

Keywords: Direct acting anti-viral agents, genotype-3, hepatitis C, sustained virologic response.

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Introduction

Globally, around 200 million people are estimated to have hepatitis C virus (HCV) infection. The HCV infection is known to be the most frequent etiology behind chronic liver disease (CLD) and decompensated liver disease while its impact is pronounced among developing countries.[1,2] Genotype-1 is estimated to be the most common HCV genotypes contributing in around 46% globally while genotype-3 is estimated to have a share in around 22% HCV cases. Local data indicated HCV prevalence to be 6.7% while more than 10 million people are estimated to have HCV and genotype 3 is found in 79% cases.[3,4]

Documented evidence highlight that around 85% of HCV patients stay permanently infected once they have HCV infection.[5] Introduction of interferon in the late 1980s transformed the way HCV patients were treated whereas pegylated interferon alpha with ribavirin remained the standard treatment for many years. Interferon based therapy for chronic HCV (cHCV) had unwanted adverse-effects and the sustained viralogic response (SVR) was also not satisfactory.[6,7] The introduction of new generations of "direct-acting antiviral agents (DAAs)" targeting difference HCV proteins

revolutionized the cHCV treatment. As multiple combinations of DAAs are available, it is now possible to achieve SVRs in high majority of cHCV cases while side-affects accompanying these DAAs are very few and mild.[8]

A recent meta-analysis analyzing 34 trials from 22 countries found pooled SVR rate of 92.1% while SVR with sofosbuvir (SOF)+declatasvir (DCV)+ Ribavirin (RBV) was 91.2%, 95.1% with SOF+Velpatasvir (VEL) + RBV, 85.0% with SOF+VEL+Vosilaprevir (VOX) and 98.5% with Glecaprevir (GLE)+Pibrentasvir (PIB).[9] A local multi-central study evaluating 993 patients revealed overall SVR rates form different combinations of SOF, DCV and RBV to be 98%.[10] Researchers from around the world have emphasized difference in characteristics of patients for routinely used DAAs aiming treatment of cHCV So this study was planned to find out safety and efficacy of DAAs in our routine practice in patients with cHCV.

Methods

This retrospective study included record 1536 cHCV patient who were treated at "The Medical outpatient department (MOPD) of Medical Unit-1, Bahawal Victoria Hospital", affiliated with "Quaid e Azam Medical College (QAMC), Bahawalpur, Pakistan", from April 2018 to April 2020. Approval from "Institutional Ethical and Research Committee" was acquired.

We included a total 1536 patients of either gender aged > 18 years with cHCV genotype-3 infection as found by detectable HCV RNA of genotype-3 on qualitative polymerase chain reaction (PCR). All patients having co-infection with HBV, incomplete data, discontinuation of DAAs treatment or lost during 12-weeks follow up were excluded from the study.

Baseline evaluation and investigations like hematological and biochemical profiles, genotyping and quantitative PCR were done from the study institute. SOF (400mg once daily) and RBV (1000mg/day in patients with < 75Kg body weight or 1200mg/day >75Kg in 3 doses daily) for 12 or 24 weeks, SOF (400mg) and DCV (60mg) with or without RBV for 12 or 24 weeks, or fixed dose combination of SOF+VEL (400mg+ 100mg) once daily with or without ribavirin for 12 or 24 weeks were given. Use of Ribavirin was determined by the treating physician as per clinical evaluation and experience along with keeping in mind the practice guidelines. PCRs were done 3 months after completion of treatment to note SVR.[4]

SPSS version 26.0 was employed for statistical analysis. Quantitative data was shown as mean and standard deviation (SD) while quantitative data was represented as frequency and percentage. Patients were compared for various demographical characteristics, laboratory findings, comorbidities, types of DAAs and treatment side-effects. Analysis of Variance (ANOVA) and independent sample student t-test were used to compare quantitative variables whereas chi-square test was employed to compare qualitative variables. P-value < 0.05 was taken as significant.

Results

In a total of 1536 patients, 725 (47.2%) were male and 811(52.8%) female. Overall, mean age was noted to be 43.2+12.8 years. Residential status of 968 (63.0%) patients was rural. There were 166 (10.8%) patients who had cirrhosis. There were 188 (12.2%) patients who were treatment experienced. Figure 1 is showing distribution of patients with respect to allotted DAAs treatment regimens.

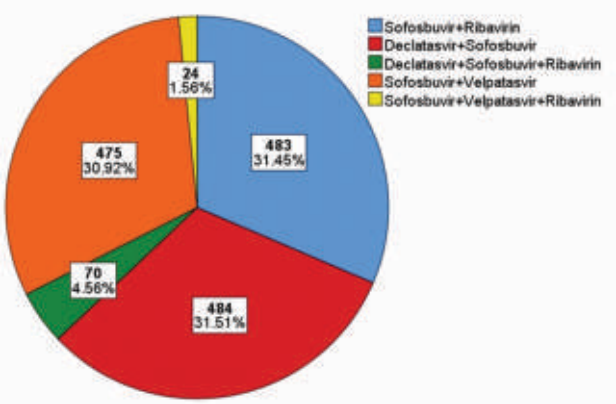

Figure 1: *Distribution of Patients with Respect to DAAs*

Table I is showing distribution of demographical, clinical profile, comorbid conditions and laboratory parameters among patients treated with different DAAs.

Table II is showing SVR among patients of cHCV infection treated with different DAAs. Overall, SVR was noted in 1447 (94.2%) patients while there was no statistically significant difference between SVR of different DAAs (p=0.0656).

Table III is showing assessment of SVR among patients treated with different DAAs. Significantly linked factors with No-SVR were found to be older age (46.2+12.3 vs. 43.8+10.4 years, p=0.0368), higher BMI (27.7+3.1 vs. 26.8+2.3, p=0.001), cirrhosis (49.4% vs. 8.4%, p< 0.001) and non-responders/relapsers (23.6% vs. 11.5%, p=0.001).

No major adverse effects related to DAAs were observed in any of the patients while on-treatment reported adverse-effects were generally mild in nature. Generalized weakness was noted to be the most frequently reported on-treatment side-effect in 471 (30.7%) while body aches & pain and fever were the other most fre-

Table 1: *Demographics, Clinical Profile, Comorbidities and Laboratory Parameters among Patients (n=1536)*

Characteristics		SOF+RBV (n=483)	SOF+DEC (n=484)	SOF+DEC+RBV (n=70)	SOF+VEL (=475)	SOF+VEL+RBV (n=24)	P-Value
Gender	Male	227 (47.0%)	223 (46.1%)	38 (54.2%)	225 (47.4%)	12 (50.0%)	0.7825
	Female	256 (53.0%)	261 (53.9%)	32 (45.8%)	250 (52.6%)	12 (50.0%)	
Age in Years *		40.2±12.5	41.2±13.0	46.7±10.3	42.5±13.7	47.2±9.7	<0.001
BMI in Kg/m²*		26.1±2.1	26.4±2.6	27.3±2.5	27.1±2.6	27.4±2.5	<0.001
Residence	Rural	303 (62.7%)	291 (60.1%)	44 (62.9%)	313 (65.9%)	17 (70.8%)	0.3962
	Urban	180 (37.3%)	193 (39.9%)	26 (37.1%)	162 (34.1%)	7 (29.2%)	
Cirrhosis		34 (7.0%)	41 (8.5%)	18 (25.7%)	64 (34.2%)	9 (37.5%)	<0.001
Non-responders / relapsers		24 (5.0%)	38 (7.9%)	24 (34.3%)	94 (19.8%)	8 (33.3%)	<0.001
Diabetes		33 (8.6%)	38 (7.9%)	7 (10.0%)	37 (7.8%)	2 (8.3%)	0.7517
Hypertension		82 (17.0%)	76 (15.7%)	17 (24.3%)	68 (14.3%)	3 (12.5%)	0.2705
Hemoglobin in g/dl		12.6±2.4	12.3±2.7	12.1+2.6	12.4+2.6	12.7+2.7	0.308
ALT in IU/L		68.8±58.2	73.7±62.7	69.0+64.3	71.2±58.0	64.5±52.9	0.734
Platelet Count in ×10⁹/L		241.1±96.4	236.8±91.2	225.1±99.6	234.0±84.2	227.5±97.9	0.573

Table 2: *Sustained Virologic Response (SVR) among Patients of Chronic Hepatitis C Virus Infection Treated with Different DAAs*

SVR	SOF+RBV (n=483)	SOF+DEC (n=484)	SOF+DEC+RBV (n=70)	SOF+VEL (=475)	SOF+VEL+RBV (n=24)	P-Value
	451 (93.4%)	468 (96.7%)	64 (91.4%)	441 (92.8%)	23 (95.8%)	0.0656

Table 3: *Assessment of Sustained Virologic Response Among Patients Treated with Different DAAs with respect to Various Study Variables*

Characteristics		SVR (n=1447)	No-SVR (n=89)	P-Value
Gender	Male	690 (47.7%)	35 (39.3%)	0.1252
	Female	757 (52.3%)	54 (60.7%)	
Age in Years*		43.8±10.4	46.2±12.3	0.0368
BMI in Kg/m²*		26.8±2.3	27.7±3.4	0.001
Residence	Rural	920 (63.6%)	48 (53.9%)	0.0672
	Urban	527 (36.4%)	41 (46.1%)	
Cirrhosis		122 (8.4%)	44 (49.4%)	<0.001
Non-responders / Relapsers		167 (11.5%)	21 (23.6%)	0.001
Diabetes		110 (7.6%)	7 (7.9%)	0.9276
Hypertension		227 (15.7%)	19 (21.3%)	0.1577
Hemoglobin in g/dl		12.5+2.6	12.2±2.5	0.2898
ALT in IU/L		66.2+58.6	73.4+70.3	0.2667
Platelet Count in ×10⁹/L		238.1+101.4	231.5±92.8	0.5494

quently reported side-effects in 230 (14.5%) and 145 (9.4%). Table IV is showing details of most frequently reported on-treatment adverse-effects and no statistically significant difference was observed is different types of DAAs (p=0.9740).

Discussion

The FDA has recommended SOF+DEC+RBV as the 1st line DAAs regimen for treating all kinds of HCV genotypes.[11] The "European Association for the Study of the Liver (EASL)" also endrose SOF+DEC+RBV or SOF+VEL+RBV depending upon the treatment experienced or presence of cirrhosis among patients with genotype-3.[12] We had 10.8% patients with cirrhosis while 12.2% were treatment experienced so most of our patients received double drug regimens. In the present study, SOF+DEC and SOF+RBV were the most commonly utilized DAAs regimens accounting for 31.5% patients each. A recent local study by Mushtaq S et al evaluating DAAs in the treatment of cHCV shared that 95% of their patients received SOF+DEC which shows that this combination is among the prefe-rred ones by clinicians in Pakistan.[10] The same study also

Table 4: *Frequency of Most Common On-Treatment Side-Effects Among Patients Treated with Different DAAs*

Side-Effects	SOF+RBV (n=483)	SOF+DEC (n=484)	SOF+DEC+RBV (n=70)	SOF+VEL (=475)	SOF+VEL+RBV (n=24)	P-Value
Generalized Weakness	158 (32.7%)	124 (25.6%)	21 (30.0%)	164 (34.5%)	4 (16.7%)	0.9740
Body Aches & Pain	74 (15.3%)	63 (13.0%)	12 (17.1%)	78 (16.4%)	3 (12.5%)	
Fever	54 (11.2%)	42 (8.7%)	6 (8.6%)	41 (8.6%)	2 (8.3%)	
Nausea	35 (7.2%)	24 (5.0%)	4 (5.7%)	38 (8.0%)	2 (8.3%)	
Cough	21 (4.3%)	18 (3.7%)	2 (2.9%)	14 (2.9%)	1 (4.2%)	

found an overall SVR of 98% with DAAs. Very similar to our study, Mushtaq S et al included all patients of cHCV regardless of their status about presence of cirrhosis or past history of treatment. A real-world data from Taiwan has showed achievement of SVR in SOF + RBV, Ledipasvir+SOF+RBV and DEC+ Asunaprevir+RBV to be 98.2%, 97.2% and 85.0%.[13]

After approval of SOF in 2013 by FDA, SOF has been the most experienced DAA followed by DEC. According to Leroy V et al in ALLY-3+ trial evaluating efficacy of DEC, SOF and RBV, SVR rates of 92% and 89% were achieved with SOF+DEC among treatment naïve patients an relapsers/non-responders respectively.[14] A multi-central local study shared that out of 1388 patients of HCV genotype-3, overall SVR rates of 96.5% was achieved with either SOF+DEC+RBV or SOF+ VEL+ RBV.[15] Researchers from Iran showed in the past that DAAs resulted in higher SVR rates (92%) even in cirrhotic patients which correlates well in with the present findings.[16]

In the present study, older age (p=0.0368), higher BMI (p=0.001), cirrhosis (p<0.001) and non-responders/ relapsers were found to be significantly linked with No-SVR. A study by Abdulla M et al from Behrain evaluating 167 patients treated with either SOF based regimens or Ombitasivr/Paritaprevir/Ritonavir based regimens found that SVR was achieved in 94.1% and 92.4% patients respectively while SVR rates were significantly higher among patients without liver cirrhosis as per multiple logistic regression (OR=16.1, 95% CI: 1.96 to 131.9, p=0.01).[17] Local data has documented age above 60 years as well as cirrhosis to be significant predictors of non-SVR with DAAs.[15] A recent study from Spain highlighted higher BMI to be significantly liked with non-achievement of SVR which is quite consistent with the present findings.[18] Data from world over has shown that no uniformity exists regarding predictor of non-SVR while evaluating effectiveness of DAAs which makes it more challenging to compare factors regarding non achievement of SVR. Multiple studies have indicated baseline characteristics such as liver cirrhosis, history of previous HCV treatment, HCV genotype-1 or 3, high viral loads or raised liver enzymes to be most compelling contributors to failure in achievement of SVR among cHCV patients.[19-21]

Out study had some limitations. Although, sample size in the present study was good but still being a single center study, our findings cannot be generalized. Retrospective study design has its own limitations. We were unable to evaluate viral load among patients at baseline as not all patients had their viral load recorded. Inclusion of RBV was on treating physician's discretion which might have created some imbalance in the different regimens evaluated. Despite all these limitations, the present study presents one of the biggest cohort of patients treated with variety of DAAs from Pakistan.

Conclusion

Overall SVR with various kinds of DAAs for cHCV genotype-3 infection was noted to be good and comparable with real world data from different parts of the world. Increasing age, higher BMI, cirrhosis and non-responders/relapsers were found to have significant association with non-achievement of SVR. Adverse-effects related to different direct anti-viral agents were few and mild in nature.

Conflict of Interest: None

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