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Comparison of Efficacies of Sofosbuvir/Daclatasvir with Sofosbuvir/Ribavirin for Hepatitis C Virus Genotype 3 Treatment in a Tertiary Care Center in Karachi

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Abstract

Hepatitis C virus infection (HepCV) is a significant health issue globally, which leads to several liver diseases, including cirrhosis and hepatocellular carcinomas. There is a class of drugs knowns as DAA, which has changed the spectrum of chronic HepCV treatment modality. HepCV genotype 3 is more prevalent in Pakistan and more aggressive, leading to HCC. We studied the drug response in SVR or sustained virological response in HepCV-infected patients on daclatasvir and sofosbuvir compared to sofosbuvir ribavirin in the local population. Over two years, this retrospective study was performed at the Department of Gastroenterology, Ziauddin Hospital, North campus. It was a prospective cohort study. All patients harboring HepCV genotype 3a infection were classified into A and B groups. Group A was treated with a combination of sofosbuvir and daclatasvir, while group B was treated with sofosbuvir and ribavirin. Both groups included cirrhotic and non-cirrhotic patients and measured the outcome as SVR3 after 12 weeks of the end of therapy. Three hundred patients were included in the study, out of which 182 (60.06%) were male while 118 (39.33%) were females. We observed that non-cirrhotic patients achieved SVR3 of 100% when

they received daclatasvir/sofosbuvir therapy compared to 93.6% in patients who received Sofosbuvir and ribavirin. On the other hand, cirrhotic patients achieved SVR3 of 92% when receiving Sofosbuvir and Daclatasvir compared to 72% in those who received Sofosbuvir and ribavirin. Sofosbuvir, along with daclatasvir, was more effective than sofosbuvir and ribavirin alone in genotype-3 infected hepatitis C patients.

Keywords

Cirrhosis, Ribavirin, Daclatasvir, SVR, Sofosbuvir.

List of Abbreviations

- **HepCV**
  - Hepatitis C virus
- **SVR3**
  - Sustained virologic response at three month/twelve weeks
- **FDA**
  - Food and drug administration authority
- **DCLTV**
  - Daclatasvir
- **SOFOS**
  - Sofosbuvir
- **RBV**
  - Ribavirin
- **EASL**
  - European Association for the Study of the Liver
- **PCR**
  - Polymerase chain reaction
- **DAA**
  - Direct-acting antiviral
- **HCC**
  - Hepatocellular carcinoma

Introduction

Chronic hepatitis C virus (HepCV) is a common reason for chronic hepatic disease leading to cirrhosis, liver cancers, and liver-related mortality worldwide (1). It is estimated that more than 70 million people are suffering from HepCV infection annually, and more than 3.5 million die (2). Pakistan ranks second in the list of HepCV -infected highest-burden countries, having a prevalence of 4.5–8.2% (3). HepCV genotype 3a is the most common (69.1%) type in Pakistan (4). The

disease can be transmitted through injection reuse, transfusion, surgical procedures, tattooing, piercing, and unhygienic shaving at barbershops. However, no national hepatitis surveillance system is currently working in Pakistan, a significant health concern (5).

Previously, the most effective treatment option available was interferon-based therapy for HepCV. However, it has been reported to have a lower sustained virological response rate (SVR) with undesirable side effects (6). On the other hand, Pakistan said around 70% of HEPCV-infected patients achieved complete response with therapy based on IFN (7).

The advent of direct antiviral agents or directly-acting antivirals (DAA) is a complete revolution in anti HepCV therapy globally, with the ability of these drugs to stop the replication process of the HepCV. The three classes of FDA-approved drugs are presently available to treat HepCV infection, including NS3/NS4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors. It has been reported that with the combination regimens of these FDA-approved DAAs, greater than 90% SVR rates can be achieved successfully (8).

As far as Pakistan is concerned, sofosbuvir-based DAAs for HepCV infections have been included in the "National Chronic Hepatitis C Infection Treatment Guidelines." Daclatasvir (DCLTV), an HepCV NS5A inhibitor, is included in the National Hepatitis Control Program and can give to the HepCV genotype 3a patients along with sofosbuvir (SOFOS) as a combination regimen for 12 weeks. With the addition of daclatasvir, better efficacy and treatment outcomes were observed (9).

A small number of HepCV genotype 3a patients are included in clinical trials, raising concern about the efficacy of presently available DAA agents. Furthermore, limited data is currently available on therapeutic regimens based on SOFOS/DCLTV compared to SOFOS and ribavirin (RBV). Our study aimed at identifying the effective antiviral treatment with generic DAA administered to the HepCV genotype 3a patients in a private hospital in Karachi.

Material and Method

This retrospective cohort included 300 confirmed HepCV genotype 3a patients treated with DAAs from 2016 to 2018. Gender, age, abdominal ultrasound, previous treatment status, anti-HepCV antibody status, HepCV RNA status by real-time PCR, and HepCV genotype was retrieved from Gastroenterology Department, Ziauddin Hospital. Patients with hepatitis C virus genotype 3a, regardless of cirrhosis of the liver or previous treatment with interferon, were included in this study. Patients were divided into Group-A, which was treated with Sofosbuvir (400mg daily) and

Daclatasvir (60mg daily), Group B patients were treated with Sofosbuvir (400mg daily) and ribavirin (400mg, 500mg, or 600mg twice daily if weight up-to 75kg, 76-100kg or >100 kilograms).

The evaluation of sustained virological response was conducted by utilizing real-time PCR following the conclusion of therapy and again after a period of three months (SVR3 commonly referred as SVR12) from the end of treatment. Statistical analysis was performed using SPSS version 20.0.

Results

Three hundred (300) patients were included in the study, out of which 182 (60.06%) were male while 118 (39.33%) were females. The mean age was 44.8± 16.45. All subjects included in the study did not receive any therapy in the past. 80 (26.66%) patients were cirrhotic (Table-1). The patients were divided equally into two groups. Group-A patients were given sofosbuvir plus daclatasvir, and group-B patients were given sofosbuvir and ribavirin. The primary outcome of treatment was to achieve SVR3.

SVR3 was achieved in all patients without cirrhosis and in 92.50% cirrhotic when treated with sofosbuvir and daclatasvir. While 93.63% of non-cirrhotic patients achieved SVR3 compared to 72.50% cirrhotic patients in the group- B, as shown in tables 2 and 3.

Variables		**Number (300)**	**%**
Age (years)	Mean ± SD	44.8 ± 16.45	
Gender	Male	182	60.06%
	Female	118	39.33%
Liver status	non-cirrhotic	220	73.33%
	cirrhotic	80	26.66%

Table-1 Patients included in the study.

Abbreviation: SD, standard deviation.

Patients	**SVR3**
Group-A (150)	147 (98.00%)

Non-cirrhotic (110)	110 (100%)
Cirrhotic (40)	37 (92.50%)

Table-2: SVR3 achieved by group-A patients.

Abbreviation: SVR3, sustained virological response after 12 weeks of treatment.

Patients	**SVR3**
Group B (150)	132 (88.00%)
Non-cirrhotic (110)	103 (93.63%)
Cirrhotic (40)	29 (72.50%)

Table-3: SVR3 achieved by group-B patients.

Abbreviation: SVR3, sustained virological response after 12 weeks of treatment.

Discussion

Dramatic changes have been observed in HepCV therapy after shifting from the use of interferon with poor SVR and unwanted drug effects to convenient DAAs with better SVR and more minor unwanted drug reactions. EASL (European Association for the Study of the Liver) has recommended using SOFOS and DCLTV for HepCV infection irrespective of treatment history. Studies reported from the Asia Pacific region showed varying SOFOS and DCLTV treatment observations. For example, 96% found SVR rates regardless of cirrhosis status in patients harboring genotype 3 when treated with a combination of DCLTV and SOFOS for 24 weeks. Similarly, SVR rates of 97% were observed in non-cirrhotic HepCV genotype three patients when treated with DCLTV and SOFOS for 12-weeks (10). Another study by Mushtaq et al. showed SVR3 in all of the non-cirrhotic patients treated with DCLTV/SOFOS as compared to 96.7% patients receiving SOFOS, whereas cirrhotic patients obtained 80% of SVR with SOFOS/DCLTV as compared to SVR of 50% in cirrhotic patients who received SOFOS/RBV (11). These results are per our observations. Another study showed that the SOFOS/DCLTV regimen exhibited less SVR3 rates of 86% in cirrhotic patients after 24 weeks (12).

In our study, 98% of patients treated with SOFOS and DCLTV showed SVR3 and 88% SOFOS/RBV. Interestingly, 72.5% of cirrhotic patients on SOFOS/RBV therapy achieved SVR3

in the non-cirrhotic patients. This is in slight conflict with a study by Osinusi et al., who showed 90% of patients of HepCV genotype 1 with liver fibrosis achieved SVR24, but only 68% of patients irrespective of stages of cirrhosis achieved SVR24 (13). Genotype 3 is the most common genotype found in Pakistan. Considering the higher SVR3 rates observed in non-cirrhotic patients in this study with SOFOS/DCLTV, this regimen can be used in areas with limited availability of NS5A inhibitor and is recommended in non-cirrhotic HepCV patients with HepCV infection in limited resources areas.

In one study, SOFOS/RBV regimen in HepCV genotype 3 showed SVR3 of 85% (14). In our study, all non-cirrhotic patients reported SVR3 on the DCLTV/SOFOS regimen. The regimens used in the study, irrespective of cirrhosis status, showed overall SVR3 rates of or above 88%; however, better results were obtained with the SOFOS/DCLTV regimen. Therefore, SOFOS and DCLTV regimens can be safely used for the HepCV genotype three management in real-world settings where there are fewer resources available irrespective of the cirrhosis status of the liver.

In conclusion, this study provides a clear recommendation for clinical practice and emphasizes the superior advantages of sofosbuvir and daclatasvir, demonstrating their value when present treatment options are scarce in nations with limited resources.

Contributions of the author

The study protocol was created by SS and FNK. The study design was created by SMQA. JM analyzed, produced data tables, and interpreted the dataset, which was generated by IB and RS. The data was fully accessible to all authors, who also provided critical feedback on the manuscript and participated in data interpretation.

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