

RESPONSE RATES TO SOFOSBUVIR AND DACLATASVIR IN CHRONIC HEPATITIS C PATIENTS

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ABSTRACT

Objectives: To evaluate the effectiveness of daclatasvir and sofosbuvir in treating hepatitis C genotype 3a patients

Material and Methods This was a prospective interventional study .Consecutive non probability sampling technique was followed . It was carried out in Department of Medicine KRL hospital Islamabad, Pakistan from February 2017 to June 2018. This study included 80 patients who were infected with hepatitis C virus. Age ranged from 17-83 years. Amongst them 70 were treatment naive while 10 has received Pegylated Interferon and ribavirin in the past. Of treatment experienced 7 out of 10 patients had achieved SVR. Before starting treatment baseline laboratory tests were done and recorded. Quantitative PCR for HCV RNA and Genotyping was done. All patients received treatment for 3 months. Patients had a follow up every two weeks. Quantitative PCR for HCV RNA was performed at the end of treatment,3 months and 6 months after completion of treatment. Response rates were recorded. Data was analysed using statistical package for social sciences version 17 (SPSS 17).

Results: Out of 80 patients 54 (67%) were females and 26 (33%) were males. All patients were of genotype 3a. 70 patients (87%) had never experienced treatment before and 10 patients(13%) had previous treatment with pegylated interferon and ribavirin. End of treatment response was observed in 98.8% of patients while sustained virological response(SVR 12) and SVR 24 was observed in 96.25% of patients. Side effects mainly constitutional symptoms occurred in about one tenth of patients.

Conclusion: Directly acting antiviral drugs(DAA) have improved outlook in hepatitis C treatment while concomitantly reducing the duration of treatment and has high safety profile.

Key words: Patients, Hepatitis C virus, Interferon, Ribavirin, Sustained virological response, Genotype, PCR.

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INTRODUCTION

Hepatitis C virus (HCV) is a small, enveloped, single stranded RNA virus. In 2005, more than 185 million people had hepatitis C virus (HCV) antibodies (prevalence of 2.8 percent)¹. In South Asia moderate prevalences (1.5 to 3.5 percent) was noted¹. In Pakistan out of 5.5% population infected with HCV, 60%-80% had HCV genotype 3^{2,3}. Following infection with the hepatitis C virus (HCV), chronic infection occurs, with approximately 50 to 85 percent of cases developing chronic hepatitis. Approximately 5 to 30 percent of chronically infected

individuals develop cirrhosis over a 20- to 30-year period of time.⁴Risk of developing hepatocellular carcinoma once cirrhosis has developed have varied from 0 to 3 percent per year^{5,6}. Diagnostic tests for hepatitis C virus (HCV) can be divided into two broad categories, serologic assays that detect antibodies to hepatitis C and molecular assays that detect or quantify HCV RNA. The latest, third generation Enzymatic Immunosorbent Assay (EIA-3) generally detect antibodies to recombinant antigens from the core, NS3, NS4, and NS5 proteins. These tests have very high sensitivity and high specificity^{7,8}. For detection and quantification of HCV RNA, polymerase chain reaction (PCR) based method is used. The most sensitive standard PCR assays detect HCV RNA at concentrations of approximately 50 international units/mL of patient serum. Real-time PCR methods have greater sensitivity with lower detection limits of approximately 15 international units/mL⁹. Six

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major genotypes of HCV have been defined, although a viral isolate distinct from all others has been categorized as a seventh genotype¹⁰. Therapies for HCV patients has increased the hope of managing and curing these patients¹¹. Direct-acting antivirals (DAAs) are molecules that target specific nonstructural proteins of the virus and results in disruption of viral replication and infection. There are four major classes of DAAs which include nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors¹². Sofosbuvir is the first NS5B NPIs used in various combinations with other antivirals. It is given as 400 mg tablet once daily. Sofosbuvir shall not be used without other antiviral agents, and dose must not be decreased¹³. Daclatasvir is an NS5A inhibitor used mainly in combination with sofosbuvir. It is given as 60 mg daily with or without food¹⁴. Few studies are available so far in Pakistan regarding the efficacy of Sofosbuvir-Daclatasvir combination in treating Hepatitis C patients. The rationale of this study was to evaluate the efficacy of one of the newer combination of dual oral antiviral treatments in hepatitis C patients comprising of Sofosbuvir and daclatasvir in this case.

MATERIAL AND METHODS

It was a prospective interventional study of 12 weeks duration. Consecutive non probability sampling technique was followed. It was carried out in Medicine out-patient of KRL Hospital Islamabad from February 2017 to June 2018. Study was approved by the ethical review board of KRL Hospital Islamabad, Pakistan. Informed consent was taken from all participants and their baseline characteristics including age, gender, comorbid conditions, family history, risk factors and previous treatment status were recorded on specifically designed questionnaires along with their complete addresses and contacts. Eligible patients included those with genotype 3a with age ranging from 17-83 years. They were either treatment naïve or treatment-experienced. Patients having chronic liver disease due to viruses other than HCV, genotypes other than 3a, hepatocellular carcinoma and chronic kidney disease (CKD) stage IV, V were excluded from this study. Patients with cirrhosis and decompensated liver disease are being studied separately.

Before starting treatment Quantitative PCR for HCV-RNA was done to document the baseline level of viremia (i.e., baseline viral load) along with HCV genotype. Quantitative PCR for HCV-RNA was done using

Qiagen artus® HCV RG RTPCR kit for quantification. For HCV genotyping, viral RNA was extracted using QIAamp Viral RNA Mini kit following the manufacturer’s instructions. Then HCV genotype was determined by using RNA UltraSense One-Step Quantitative RT-PCR system and in-house designed primers. Baseline complete blood picture (CBC), Liver Function Tests (LFTs), Prothrombin Time (PT), serum albumin, ultrasound abdomen and thorough physical and systemic examination along with psychological assessments were done and routinely followed every two weeks. Patients were given 12 weeks treatment with sofosbuvir and daclatasvir. Adherence to treatment and side effect profile was checked and questions regarding development of adverse effects were asked at every follow up visit. End of treatment response (EOTR) and sustained virological response at twelve weeks (SVR 12) and twenty four weeks (SVR 24) were recorded. Statistical Package for Social Sciences (SPSS) version 17 was used for data analysis.

RESULTS

Current study included 80 patients having HCV confirmed by PCR. Mean age was 49.2 ± 15.31 years, with age ranging from 17 to 83 years. Family history of positive contacts included first degree relatives including spouses. Spouse history was available only after marriage. All other details are illustrated in table 1. Dental exposure was the commonest known risk factor (22%). Multiple risk factors included more than one kind of exposure. Figure 1 shows details of risk factor for HCV transmission. Table 2 illustrates comorbid conditions of study population. No comorbid condition was found in 50 (62.5 %) cases. Diabetes Mellitus was positive in 8 (10 %) followed by Hypertension 7 (8.8 %). Figure 2 illustrate response rates to sofosbuvir and daclatasvir treatment in terms of EOTR, SVR12 and

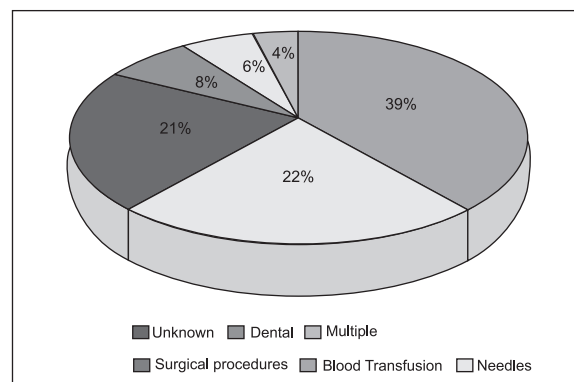


Fig 1: Risk factors for HCV transmission

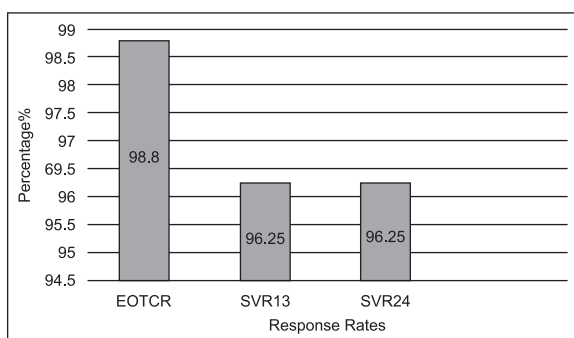


Fig 2: Response rates to Sofosbuvir and daclatasvir treatment

Table 1: Characteristics of study population

| Characteristics | | No. of Patients & %ages |
|--------------------------|---------------|-------------------------|
| Total Number of Patients | 80 | |
| Age | Mean ± SD | 49.2 ± 15.31 |
| | Minimum age | 17 Years |
| | Maximum age | 83 Years |
| Gender | Male | 26 (33%) |
| | Female | 54 (67%) |
| Education | Educated | 47 (59%) |
| | Un-educated | 33 (41%) |
| Family History | Positive | 28 (35%) |
| | Negative | 52 (65%) |
| Spouse History | Positive | 12 (15%) |
| HCV Genotype | 3a | 80 (100%) |
| | Others | 0 (0%) |
| Treatment status | Naïve | 70 (87%) |
| | Relapser | 07 (9%) |
| | Non-responder | 03 (4%) |

Table 2: Comorbid conditions

| Comorbid condition | No. of Patients & ages |
|-------------------------|------------------------|
| None | 50(62.5) |
| Diabetes Mellitus | 08(10) |
| Hypertension | 07(8.8) |
| Others (COPD, CVA, IHD) | 06(7.5) |
| Multiple | 09(11.2) |

SVR24. Figure 2: Response rates to Sofosbuvir and daclatasvir treatment side effects were minimal and restricted to constitutional symptoms. 8(10%) patients experienced fatigue and bodyaches while 2(2.5%) patients experienced headache.

DISCUSSION

A systematic review of data reveals HCV seroprevalence amongst adults to be 6.8%¹⁵. In alcohol study lower income group was mostly affected(5.01% vs 2.09%)¹⁶. Genotype 3a was reported to be most common subtype (61.3%)¹⁵. In our study all patients had genotype 3a(100%). Just over half (53 %) of our patients were above 50 years. In a study in Lahore middle aged patients (30 to 50 years) had HCV.¹⁷In another study done in China people aged 50 to 64 had high HCV infection¹⁸. In our study females were affected more than males(67% vs 33%). In a study at Lahore 55 % patients were females.¹⁷In our study 15% of spouses were affected. In a study from China it was found that the proportion of spouses with HCV in cases (10.5%) was significantly higher than that of control group¹⁸. In current study, Dental procedure was the most common risk factor for HCV transmission followed by Surgical treatment. In another study dental treatment (82.0%), intravenous/intramuscular injection (81.0%) surgery (49.0%), endoscopy (42.0%), blood transfusion (29.0%), dialysis (7.0%), sharing needles (6%) and acupuncture (5.5%) were the common risk factors for HCV transmission¹⁷. A study conducted locally showed 75% patients had history of intra-muscular or intravenous injections, 31% had dental procedures, 14% operative procedures and 7% patients had transfusion history¹⁹. In current study Diabetes Mellitus and Hypertension were the most common comorbid conditions among HCV infected patients while in a study done in USA, the most common comorbid conditions were hypertension, gastroesophageal reflux disease (GERD), osteoarthritis, asthma and Diabetes Mellitus²⁰.

The combination of daclatasvir plus sofosbuvir was well tolerated, with a low incidence of adverse events. Common adverse events were fatigue, headache, and bodyaches in about 10% of patients. These results are comparable with phase II study demonstrating the efficacy and tolerability of daclatasvir plus sofosbuvir, with or without ribavirin, in patients with genotype 3 infection²¹. Findings from another study show that in genotype 3–infected patients without cirrhosis, 12-week treatment with daclatasvir plus sofosbuvir is efficacious, compared with the current 24-week regimen containing sofosbuvir/ ribavirin. Inclusion of ribavirin worsens the safety profile without benefit in terms of SVR¹⁴.

In our study a 12-week regimen of daclatasvir and sofosbuvir achieved SVR12 in 96% of treatment-naïve and treatment-experienced patients with genotype 3a

infection without cirrhosis and was well tolerated. In Ally-3 study patients with genotype 3a, 12-week regimen of daclatasvir plus sofosbuvir achieved SVR12 rates of 90% in treatment-naïve patients and 86% in treatment-experienced patients, SVR12 was achieved in 96% of patients without cirrhosis and in 63% of patients with cirrhosis²². A study from India showed EOTR and SVR12 rates of 94.4% and 91.9% respectively.²³ A large scale systematic review study in UK gathered data from clinical trials showed SVR 12 rates of 90.1%(84.8-94.6) among all patients of genotype 3a while SVR 12 approaching 97.6 % in those without cirrhosis.²⁴ Comparable SVR12 rates were observed elsewhere, treatment-naïve(93%) and treatment-experienced (91%)²⁵. Akhter et al showed SVR of 94.4% in genotype 3 patients²⁶.

LIMITATIONS

Limitations of this study were that this study only included genotype 3a patients. Patients with other genotypes were not included.

CONCLUSIONS

Directly acting antiviral drugs(DAA) have improved outlook in hepatitis C treatment while concomitantly reducing the duration of treatment and has high safety profile.

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Response rates to sofosbuvir and daclatasvir in chronic hepatitis C patients

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Ali A: Concept ,design, analysis, and interpretation and data.

Sheikh M: Data collection literature review.

Azim S: Data Collection.

Saeed M: Data Collection.

Abbasi AS: Literature Review.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.