EFFECTIVENESS AND SAFETY OF SOFOSBUVIR AND DACLATASVIR COMBINATION FOR THE TREATMENT OF HEPATITIS C

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ABSTRACT

Objective: To determine the effectiveness and safety of sofosbuvir and daclatsvir combination for the treatment of hepatitis C.

Methodology: This study, of 145 patients, was done in the OPDs of Gastroenterology Unit, LRH & HMC of Khyber Pakhtunkhwa, from January 1st 2017 to December 1st, 2017. HCV infected Patients aged more than 18 years, of either gender, irrespective of previous treatment status having normal hematological tests and ultrasound were included.

Results: Ninty three patients (64.13%) were male and 52 (35.86%) female. Mean age was 39.27 ±10.95. Genotype 3 was the most common genotype, present in 130 (89.65%) patients. All patients with HCV Genotype 3, Genotype 2 and Genotype 1 and untypeable had undetectable HCV RNA at week 4, while 122 (93.84%) patients with HCV Genotype 3; 6(85.71%) patients with Genotype 2; and 4(100%) each with Genotype 1 and untypeable had undetectable HCV RNA twelve weeks after treatment completion. Ten (6.89%) patients developed fatigue, 9(6.20%) patients developed nausea while 8(5.51) patients complained of headache.

Conclusion: Combination of sofosbuvir and daclatasvir was found highly effective with high safety profile in HCV infected patients in our set up.

Key Words: Sofosbuvir, Daclatasvir, Hepatitis C

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INTRODUCTION

Hepatitis C virus (CV) infection is one of the life threatening public health issues worldwide, infecting about 170–200 million people[1] including about 17 million from Pakistan[2] and is considered the leading cause of cirrhosis liver and hepatoma. It is causing approximately 27% of cirrhosis liver and 25% of hepatoma cases throughout the world[3]. Every year about 350,000 persons die due to infection with HCV[4] which is a small enveloped, single stranded RNA virus, classified as a separate genus hepacivirus in the Flaviviridae family[5]. Worldwide about 2.2% of the world's population is infected with hepatitis C virus[3]. The disease is becoming a big public health problem of developing nations, including our country which has the second highest prevalence rate of HCV ranging from 4.5% to 8%[8]. This high prevalence rate in our country is most probably because of deficiency in basic health care resources and lack of public awareness about the disease and the spread of the disease. Similarly, quackery and unhygienic conditions e.g. barber shops are also considered to be the cause of high prevalence rate of Hepatitis C in Pakistan.

Pegylated interferon-alpha in combination with ribavirin was the only recommended treatment regimen for patients having chronic HCV infection till 2011 which was giving a sustained virologic response (SVR) rate of 56-60% in patients having genotype 1[9], and 70 to 80% in genotype 2 and 3[10]. The treatment has now changed with the development of oral protease and polymerase inhibitors to interferon free oral regimen which are more effective and safe than interferon based treatment regimen[11].

The approval of Sofosbuvir, an NS5B polymerase inhibitor in 2013 by FDA was a breakthrough in the management of patients suffering from chronic HCV infection and is the backbone of current therapeutic regimen. Similarly Daclatsvir, NS5A inhibitor was officially announced by FDA in 2015 for the management of Hepatitis C virus infection and currently Sofosbuvir based regimens are the new standard of care which have high antiviral activity, giving broad genotypic coverage and having high barrier to resistance[11,12].

Though the Sofosbuvir and Daclatasvir combination is not the preferred first line regimen for the treatment

of chronic HCV infection currently but because of its low cost, easy availability and low rate of adverse effects, it is the most commonly used pan-genotypic regimen for the treatment of chronic HCV infection in our local set up these days.

The aim of this study was to find out the effectiveness and safety of Sofosbuvir and Daclatasvir combination for the treatment of chronic HCV infected patients by knowing HCV RNA level at week 4 of treatment, and 12 weeks after the completion of treatment and observing the patients for the occurrence of any adverse effects as locally we don't have the exact data about the efficacy and safety of this antiviral drug combination and by knowing the effectiveness and safety of this combination ,we can recommend this drug combination for our local HCV infected patients who can't afford more effective first line antiviral drug combinations.

METHODOLOGY

This descriptive study, comprising of 145 patients, was done in the OPDs of Gastroenterology Units of LRH & HMC Khyber Pakhtunkhwa, from January 1st 2017 to December 1st 2017 on Chronic HCV patients who visited our OPDs for antiviral treatment.

Patients having age more than 18 years, of either gender, irrespective of previous treatment status and having normal hematological tests and ultrasound were included. Decompensated cirrhotics, compensated cirrhotic patients with hepatocellular carcinoma, pregnant HCV infected patients and those not willing for treatment were excluded. After informed consent, all patients were assessed for treatment candidacy with Sofosbuvir and Daclatsvir combination clinically, by doing necessary blood tests including CBC, liver function tests, renal function tests, serum albumin, PT/INR, RNA level, Genotype testing, abdominal ultrasound and OGD where indicated.

All the Patients fulfilling the criteria were given Sofosbuvir 400mg and Daclatasvir 60mg in a single daily dose for 12 weeks. All patients were followed during the treatment duration for compliance and toxicities and managed accordingly. Quantitative HCV RNA (from the laboratories with a lower level of detection 25 IU/ml) level was done at 4 weeks, and 12 weeks after treatment completion. SPSS version 10 was used for data analysis.

RESULTS

Total patients included in the study were 145; 93 (64.13%) were male and 52 (35.86%) were female. Male to female ratio was 1.78:1. Minimum age was 18 years in our study and maximum age was 68 years with mean age of 39.27 ±10.95 years. Most of the patients (n=81, 81, 55.86%) were having age in the range of 31-45 years, as shown in Table 1.

Genotype 3 was the most common genotype in this study, present in 130 (89.65%) patients. Frequencies of other genotypes are shown in Table 2.

All of the 145 (100%) patients with HCV had undetectable HCV RNA at week 4, while 122(93.84%) patients with HCV Genotype 3, had undetectable HCV RNA twelve weeks after treatment completion (SVR12), Table 3.

Ten (6.89%) patients complained of fatigue during the treatment duration; however no death or serious adverse effects leading to treatment discontinuation occurred, Table 4.

Table 1: Age wise distribution of patients (n=145)

Age Range (Years)	Number	Percentage
18-30	28	19.31
31-45	81	55.86
46-68	36	24.82
Total	145	100%

Table 2: Genotype wise distribution of patients (n=145)

Genotype	Number	Percentage
3	130	89.65
2	7	4.82
1	4	2.75
Untypeable	4	2.75
Total	145	100%

Table 3: Distribution of patients according to response rate (n=145)

HCV RNA	Genotype	Number	Percentage
At week 4 of Treatment (RVR)	3	130	100
	2	7	100
	1	4	100
	Untypable	4	100
Twelve weeks after Treatment Completion (SVR)	3	122	93.84
	2	6	85.71
	1	4	100
	Untypable	4	100

Table 4: Distribution of patients according to side effects (n=27)

Side Effects	Number	Percentage
Fatigue	10	6.89
Nausea	9	6.20
Headache	8	5.51

DISCUSSION

Sofosbuvir, a nucleotide inhibitor of viral NS5B RNA polymerase has been approved for the treatment of chronic hepatitis C, in combination with other drugs and its approval represents the first key step towards the new era in the treatment of CHC patients, since it is the first approved DAA with potent activity and high genetic barrier against all HCV genotypes[13]. Similarly Daclatasvir, an NS5A inhibitor approved by FDA for the management of HCV in 2015, is also an effective drug given in combination with sofosbuvir. Our study showed that Sofosbuvir and Daclatasvir comination was very effective against hepatitis C virus infection in clinical practice in our local population infected with hepatitis C, giving a high response rate in the form of rapid virological and sustained virological response rate and ultimate cure of HCV and less side effects occurrence associated with this treatment regimen. This high response rate achieved in our study is comparable to other studies done on similar combination regimens like ALLY-3 Phase III Study done by Nelson et al[13] where SVR rate of 90% was achieved in Genotype 3 treatment naïve patients and the study done by Wyles et al[14] in HCV/HIV co-infected patients which gave an SVR rate of 97% in all genotypes.

Our study results are also in accordance to the study done by Mark et al[15] where 89% SVR was achieved in genotype 3 patients, 98% in Genotype 1 patients while 92% SVR rate was achieved in Genotype 2 patients. Results of our study are also comparable to the study done by Pajin et al[16] which gave response rate of 92.86% in Genotype 3 and 100% in Genotype 1 treated with Sofosbuvir and Daclatasvir combinations for 12 weeks.

However, we noted some difference in the safety profile of Sofosbuvir and Daclatasvir combination in our study and other studies like ALLY-3 Phase III Study done by Nelson DR et al[13] where 20% of patients experienced headache ,19% of patients suffered from fatigue and 12% of patients experienced nausea with this drug combination while side effects occurred less frequently in our study which also needs further exploration in the form of large studies.

LIMITATIONS OF OUR STUDY

The sample size in our study was small and may not be a true representative of the community so further large studies should be carried out to elaborate the safety and efficacy of this combination in our local hepatitis C infected patients.

CONCLUSION

The combination of sofosbuvir and daclatasvir was found highly effective and safe in patients infected with hepatitis C in our local set up and can be safely recommended keeping in view its low cost and easy availability and lesser side effects as compared to other first line anti viral drugs which are more costly as well as having issue of availability.

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CONTRIBUTORS

DK conceived the idea, planned the study and drafted the manuscript. FA, MI and MKH helped acquisition of data, did statistical analysis and critically revised the manuscript. HK and AG did literature search, statistical analysis and finalization of manuscript. All authors contributed significantly to the submitted manuscript.