RESPONSE OF SOFOSBUVIR IN CHRONIC HCV PATIENTS IN KHYBER PAKHTUNKHWA

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ABSTRACT

Objective: The aim of this study is to determine the response of Sofosbuvir in chronic Hepatitis C patients in Khyber Pakhtunkhwa.

Material and Methods: This study was conducted in Kuwait teaching hospital Peshawar. A total of 180 patients were enrolled in this prospective observational study from July 2016 to August 2017. 160 patients (88.8%) were naïve and 20 (12.2%) were treatment experienced patients. PCR test of all of these patients was positive. All of the enrolled subjects were treated with same dose of Sofosbuvir (SOF) 400mg and 800-1200 mg Ribavirin (RBV) daily depending on weight for a period of six month. Biochemical profile was done throughought the length of treatment and end of treatment response (ETR) was noted after six months therapy.

Results: All of the enrolled subjects showed greater response to Sofosbuvir based therapy. Out of 180 total patients 178 (98.8%) were negative for PCR while only 2 (1.11%) patients had positive PCR for HCV RNA. There was direct correlation of response with Alanine Amino Transferase (ALT), while for Hemoglobin (HB) there was greater fluctuation before and end of treatment. Moreover, patients of all age groups and gender were equally responsive to Sofosbuvir and Ribavirin combination therapy.

Conclusion: A significant response was noted for all of the enrolled subjects. This was too high as compared to previous IFN based therapy.

Key Words: Sofosbuvir, Ribavirin, PCR, ALT and HB

INTRODUCTION

Hepatitis C is among the leading cause of health related problems. Worldwide, about 3% of the population has been infected by hepatitis C virus.[1] The infected individual may progress to chronic hepatitis C to severe cirrhosis and hepatocellular carcinoma (HCC) and eventually death.[2] In Pakistan its infection varies, depending on region and various factors are contributing in increasing rate of HCV infection, although in developed countries its infection rate has been decreased[3,4]

HCV has been classified into six major types and more than 64 distinct subtypes. [5] Its distribution varies among different geographical regions. HCV genotypes 1 and 3 have worldwide distribution. While in Pakistan and Khyber Pakhtunkhwa , the prevalent genotype is 3.[6,7]

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To treat HCV infection, various strategies have been adopted since its discovery. In early days the first treatment option was Interferon, a cytokine helping in inhibiting viral replication, followed by introduction of Ribavirin, a nucleoside inhibitor. The response rate in this treatment option was as low as 40-60%.[8, 9, 10] Later on in 2001; Pegylated IFN (Peg IFN) in combination with Ribavirin was introduced. This enhanced the response rate to 60-80%.[11] But still there was need of greater improvement in response. Both of these treatment regimes were also associated with severe side effects and sometimes treatment discontinuation may happened.

Now with the development of new direct acting antiviral (DAA) drugs, HCV management has been greatly revolutionized. NS5B polymerase inhibitor, responsible for HCV replication has greater improved the virological response. This regime is effective in all genotypes and has equal importance in all gender.[12] The first drug available in Pakistan market is Sofosbuvir.

Efficacy and response of antiviral drugs has been noted worldwide and has been proved to be the best of antiviral. But still no extensive study has been done in Pakistan and especially in Khyber Pakhtunkhwa to reflect its efficacy and treatment response. Although in our province many studies have explored the prevalence, rate of active HCV infection, HCV genotype distribution and conventional IFN response in chronic HCV patients.[7, 13, 14] But studies regarding direct acting antiviral drugs effectiveness are very rare. This time we are presenting the efficacy of Sofosbuvir in combina-

tion with Ribavirin in terms of end therapy response in chronic HCV patients in KPK.

MATERIAL AND METHODS

This is a prospective observational study and was conducted in Kuwait teaching hospital Peshawar, Pakistan. Patients along with informed consent were enrolled from July 2016 to august 2017. A total of 180 patients were included. Among these, 160 were treatment naïve and 20 (15 non responders and 05 relapsers) were treatment experienced patients. Subjects with decompensated liver cirrhosis were excluded from our study.

All of the enrolled patients were administered Sofosbuvir 400 mg once daily and Ribavirin 800-1200 mg in a divided weight dependent dose for six month period. Biochemical profile was done throughout the length of treatment while PCR was repeated after six months therapy.

The end point of the study is ETR (end therapy response) which is defined as absence of HCV RNA at the end of six months therapy.

RESULTS

A total of 180 patients were included in this study. Among these 85 (47.22%) were male and 95 (52.8%) were female. Mean age was 37±11 with range of 18-78 (Table.1) Treatment naïve and experienced patients were 160 (88.8%) and 20 (12.2%) respectively. After six months completion of therapy, ETR was noted among the enrolled patients. Among 160 (88.8%) naïve subjects, 159 (99.3%) subjects showed positive ETR that is at the end of six months therapy their PCR was negative while only one (0.625%) patient had positive PCR and was non responder. Among 20 treatment experienced patients, 19 (95%) patients were negative for HCV RNA while only 1 (5%) patient had positive HCV RNA and this was among the non responders to previous IFN based therapy (table. 2).

ALT level was high among the most of the patients 165 (91.1%) prior to therapy while it was low at end of therapy in 159 (87.7%) patients. In contrast to ALT, hemoglobin (HB) level was normal in156 (86.6%) patients prior to therapy while suboptimum in 68 (37.7% at the end of therapy (table.1).

DISCUSSION

Hepatitis C is the biggest problem of the developing countries amongst the infectious diseases. In Pakistan its prevalence is about 3-4%. In KPK province of Pakistan, due to lack of awareness of the routes of transmission, proper diagnostic procedures and therapeutic strategies, HCV burden in common population is increasing day by day and has reached endemic status in some of the regions of the province.[4,13]

Table 1: Demographics of patients

Characteristics	Number (%)
Age (Years)	
Mean SD	45 ± 11
Range	18-81
Gender	
Male	85
Female	95
ALT, IU/L	
At the start of therapy	165 individuals having high level
At the end of therapy	159 individuals having normal level
HB Level	
At the start of therapy	156 individuals having normal level
At the end of therapy	68 individuals having sub optimum level

Table 2: End of Treatment Response in HCV patients

Response	N (%)
Naïve patients	159/160, (99.3%)
Non responder	4/5, (80%)
Relapse	15/15, (100%)

HCV has been treated with different antiviral regimes since its discovery, like conventional IFN, Peg IFN and now the latest development DAA. It has been used worldwide with encouraging reports. Even in Pakistan, it has been tried with different trials with successful results.

In this study involving previous untreated and treated patients, infected with either HCV genotype. HCV RNA level was dramatically declined rapidly after imitation of treatment and this was maintained till the end of treatment. By six months of treatment 98.8% of patients had an undetectable HCV RNA (lower than 10 IU/ml) [Table.2]. Uniform response is notable as the enrolled patients' population was of diverse groups who had an HCV infection with either of HCV genotypes 1, 2, or 3 and those who had not receive previous treatment against HCV infection and those who had not responded to prior treatment with Interferon and Ribavirin.

Overall ETR was 98.8% among the enrolled patients. Among 160 (88.8%) naïve subjects, 159 (99.3%) subjects showed positive ETR that is at the end of six months therapy their PCR was negative while only one (0.625%) patient had positive PCR and was non responder. Among 20 treatment experienced patients, 19 (95%) patients were negative for HCV RNA while only 1 (5%) patient had positive HCV RNA and this was among the non responders to previous IFN based

therapy [Table.2].

Response rate in the current study (98.8%) in comparison with standard Peg IFN and Ribavirin combination regimes is much higher. In one study conducted in adolescent population of Pakistan, treated with Peg IFN and Ribavirin combination therapy, the virological response was only 86%.[15] IN KPK, different studies were conducted and response rates were much lower than the current study.[14, 16]

In comparison to DAA in combination with, Ribavirin the response of the current study is almost in agreement with other studies. Like a study conducted by Lawitz E, et al. who had taken different patients groups and various doses of Sofosbuvir, the response rate was in the range of 90-98%.[17] According to another study, conducted by Gane EJ, et al. the response rate was in the range of 92-100% .[18] Beside these, other studies too conducted nationally as well as internationally support the highest response of DAA in chronic HCV patients.[19,20,21]

Data about the effectiveness and response of Sofosbuvir and Ribavirin combination therapy in Pakistan is very rare. The high response rates endorsed the results of the current study. Open labeled uncontrolled trials are under way in other parts of the world to evaluate the effectiveness of the newer drugs in treating HCV patients. These drugs may include trial of Sofosbuvir and daclatasvir and Sofosbuvir and Ledipasvir. Conclusion of these drugs may further help in establishing the role of newer antiviral regimes in treating HCV patients.[22, 23]

ALT level as the biochemical parameter was more significantly influenced by this therapy [Table.1]. As the ALT is a biochemical marker of virus-induced hepatocytolysis, its normalization is associated with reduction or disappearance of viral particles. Similarly as the viral particles are constituent part of the cryo- precipitating immune complexes, the formation of such complexes are clearly affected with the reduction of viral particle or viral particles no more exist following administration of DAA.

Looking on to the HB level [Table. 1], HB level was more in most of the patients (86.6%) prior to therapy but during and at the end of therapy there was depression in HB level (47.5%). Such correlation has been shown by other studies too in which there was a great regression in HB level. This might be possible side effects of DAA or any of the antiviral drugs.[17]

The absence of viral breakthrough in any of the patient during treatment confirms that Sofosbuvir has a higher barrier to resistance. S282T, the only mutation that has been identified in vitro as having reduced susceptibility to nucleotide inhibitors like, Sofosbuvir has very poor replicative fitness, as is indicated by its absence in untreated patients infected with HCV.[24, 25]

CONCLUSION

In conclusion, Sofosbuvir in combination with, Ribavirin was associated with highest ETR in all previously untreated chronic HCV patients having either of the HCV genotypes. These early results may pay attention to the practitioners for short duration of treatment in treating HCV patients. Moreover pan genotypic efficacy and response of DAA in combination with Ribavirin support continued investigation of Sofosbuvir in combination with Ribavirin alone or in combination with other DAA agents in various populations of HCV patients.

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