EFFECTIVENESS OF SOFOSBUVIR AND RIBAVIRIN IN CHRONIC HEPATITIS C GENOTYPE 2 AND 3 PATIENTS

Jawad Khan, Muhammad Imranullah, Saira Nasr Malik, Noor Ul Amin, Muhammad Daud

ABSTRACT

Objective: To determine the effecctiveness of Sofosbuvir and Ribavirin in chronic hepatitis C genotype 2 and 3 patients.

Study Design: Retrospective study

Place and Duration: January 15th 2015 and November 19th 2016, DHQ hospital Swabi

Materials and Methods: A total of 150 cases of Chronic hepatitis Cwere taken who attended the hospital between January 15th 2015 to November 19th 2016 were included in this study and their PCR done at 4 and 12 weeks for genotype 2,4 and 24 weeks for genotype 3, and 3months after the completion of treatment. It comprises of both treatment naive (those who had not been treated previously for Hepatitis C) and treatment experienced (those who had previous treatment failure for hepatitis C or relapse, either due to the drug intolerance, drug resistance and/or other factors). SPSS v21 was used to analyze the data.

Results: The total number of patients was 150, number of male patients was 80 and females were 70 in both genotypes, the number of patient with genotype 2 was 55 and with genotype 3 were 95. Number of male patients was 80 and female were 90. ETR in both genotype were 90.33% while SVR was 88%, SVR for genotype 2 was 96.36% and for genotype 3 was 85%.

Conclusion: Drug Combination's (Sofosbuvir and Ribavirin) effectiveness was demonstrated in chronic hepatitis C patients in genotype 2 and 3.SVR for genotype 2 was more than 90% while for genotype 3 it was more than 80%. It is very effective if it is compared to older interferon based therapy. Although this requires further studies to confirm the findings our study emphasize that this therapy should be made readily available.

Keywords: Sofosbuvir, Ribavirin, Chronic hepatitis C, Genotype, End Treatment Response, Sustained Virological Remission.

INTRODUCTION

There are six main genotypes of the hepatitis C virus (HCV), genotypes 2 and 3 account for approximately 30% of chronic infections worldwide and the most common genotype in Pakistan is genotype 3(71%) followed by genotype 2(24%)[1]. Although these two genotypes have historically been grouped together in treatment guidelines and clinical trials,[2] recent evidence suggests that there are important clinical differences between them.[1,3] HCV genotype 3 infection is associated with a higher rates of complication in terms of fibrosis, cirrhosis, decompensation and hepatocellular carcinoma.[4] Moreover, genotype 3 patients response very less to interferon based therapy as compared to genotype 2.[5]

Hepatitis C has been named 'the silent storm' based on its propensity to cause cirrhosis and liver cancer and other complication like GI bleeding and ascites.

Department of Gastroenterology MTI HMC Peshawar

Address for correspondence:
Dr Jawad Khan
Department of Gastroenterology MTI HMC Peshawar
Email: rudeelf@hotmail.com
Cell No: 0333-9109091

The routes of transmission of hepatitis c are via blood-to-blood contact, vertical transmissions from mother to the fetus and through unprotected intercourse. The intravenous drug abusers are at maximum risk, as well as people exposed to unsafe blood transfusions, unsterilized needles, equipment's, shaving or surgical and dental instruments as well.The Natural course of Hepatitis C is not well understood and it remains asymptomatic for many years even sometime more than 20 years.[6] Two third of patients become chronic carriers and develop chronic hepatitis and complications leading tojaundice, cirrhosis, liver failure and sometimeshepatocellular carcinoma.[7] 130–150 million people globally have chronic hepatitis C infection.[8] One third ofchronic hepatitis C patients eventually develop cirrhosiswithin 20years.[9] As a result,500,000 people die each yearfrom hepatitis C-related complicated diseases.Pakistan has the second highest prevalence rate for Hepatitis C, ranging between 4.5 and 8 percent, compared to the global average of 2.2 percent.Still, in some areas of Pakistan like KPK and Punjab rural areas and Sindh the prevalence of hepatitis C is as high as 30 to 40%.[6] A Research conducted inAyub medical college Abbottabad in 2001demonstrated that Interferon plus Ribavirintreatment regimen has efficacy of 71%.Another research conducted in Aga khan university Karachi in

2010 also showed 74% efficacy.[10]

Sofosbuvir is a new drug that was approved for the treatment of HCV in 2014, since December 2013 it has been available in Pakistan for the treatment of HCV. Sofosbuvir is an oral nucleotide analogue inhibitor of the HCV NS5B polymerase that is effective against HCV genotypes 2 and 3 when it is administered in combination with ribavirin.[11] fortunately; genotypes 3 and 2 are the commonest types in Pakistan.

So a shortened and relatively drug course via Sofosbuvir has the potential of being more effective and more feasible compared to its alternative: The Pegylated Interferon which is very expensive, has lower efficacy in terms of SVR and more side effects.[12] Considering that 10 million Pakistanis (6% to 8% of the population) are infected with Hepatitis C and are vulnerable to developing fatal complications of advanced liver disease, introduction of newer drugs like Sofosbuvir is greatly needed. The objective of this study was to determine the efficacy of Sofosbuvir and Ribavirin combination in terms of ETR and SVR, after three months of finishing treatment.

MATERIALS AND METHODS

It is a retrospective study, conducted in the time period between January 15th, 2015 and November 19th, 2016. It was a clinical record based study and done at DHQ hospital Swabi KPK Pakistan. Cases with CHC genotype 2 and 3 treated with sofosbuvir and ribavirin were included in this study during this times period. Those patients whose complete data was found missing (they may be the dropped out cases) were excluded. As this was a retrospective study, there was nodirect contact between the patient and researchers however ethical approval was taken from the head of the hospital and hospital ethical committee.

Sample size was calculated by using WHO sample size calculator which was approximately 150 with confidence interval (CL) of 95%, anticipated population proportion (P) of 7 and absolute precision (d) of .15. Patients included in this study were diagnosed cases of chronic hepatitis C, treated with Sofosbuvir 400mg once a day and Ribavirin 400mg twice a day for 6 months for genotype 3 and 3 months for genotype 2.

Chronic Hepatitis C was defined as persistence of HCV RNA in blood for at least 6 months after onset of initial infection.[2] PCR negative is defined as viral load < 50 IU/mL or undetectable via PCR.ETR is defined as negative PCR at the end of treatment. SVR is defined as negative PCR after 3 months of end of treatment.[13, 14] All the data was collected and analyzed using SPSS v.21

RESULTS

In our study there were N=150 cases in whom-80patients (57.3%) were males and 70 patients (53.7%) were females. Mean age of the subjects was 46 with ST+_29.5 years. 86 patients (57%) subjects fell in the age group of 20-49 years and the other 64 patients (43%) fell in age group of 50-79 years. SVR in genotype 2 with 12 week treatment is 96.36%(n=53),and SVR in genotype 3 is 85% (n=81).out of the total ,70 males(87.5%) and 62 (88.5%)of the females responded to the above mentioned therapy and achieved SVR and their significance test was found out to be insignificant ($p > .05$).

Over all SVR after 12 weeks for both genotypes is 88%. Data was taken for weeks 12 for genotype 2 which is end treatment response and 3 months after ETR which is sustained virological response, while for genotype 3, data was taken at 24 weeks which is end treatment response and 3 months after ETR which is sustained virological response. The treatment response at different weeks is shown in table I, II and III respectively. Effect of the treatment regimen in genotypes 1 and 2 is shown in table IV. Following are the diagrammatic illustrations.

DISCUSSION

Sofosbuvir is a game changer in the treatment of

Table 1: End Treatment Response in Males and Females.

Gender	Total	Responded to treatment	Percentage responded
Male	80	74	92.5
Female	70	66	94.2

Table 2: End Treatment Response for genotype 2 and 3.

Treatment status	Patient number	Percentage
PCR negative	140	93.33
PCR positive	10	6.66

Table 3: Sustained Virological Response at 3 months after treatment.

Treatment status	Patient number	Percentage
PCR negative	132	88%
PCR positive	18	12%

Table 4: Sustained Virological Response in various genotypes.

Genotype	SVR	SVR
	PCR negative	PCR positive
2	53 (96.36%)	2 (3.7%)
3	81 (85%)	9 (15%)

chronic hepatitis C.it is the first pan genotypic oral drug for hepatitis C introduced in 2014. It has rapidly become the main constituent of all the modern treatment regimens approved.[15] This drug is extremely effective due to its high antiviral activity, ability to be used against all genotypes and negligible risk of viral resistance[21,15]. Therefore we conducted this research among the hepatitis C patients of Peshawar to investigate its efficacy against viral genotypes 2 and 3 patients.

In this study 150 patients participated and overall SVR was 88% in which SVR for genotype 2 was 96.36% and for genotype 3 was 85%. In case of genotype 3, considered to be the most difficult to treat, our end treatment responses were considerably higher than expected as compared to previous studies, this may because multiple reasons like lower BMI, difference in metabolism and different resistant pattern and different sub genotypes of HCV. In an international Study conducted in the United States by lewitz et al in 2013, 66% of the treatment naïve patients with genotype 3 showed successful end therapy response with this treatment regimen.[16] In another International study by Foster GR et al, successful end treatment response was achieved in 76% of genotype 3 cases treated with the aforementioned combination.[17] While in our study successful end therapy response could be seen in 85% of the patients having genotype 3.

In another study conducted in VALENCE trial, SVR in patient with genotype 2 was 93% and in genotype 3 was 85%.[17] Side effects including nausea, headache, malaise, diarrhea and irritability.[18] these findings provide further confirmationof important differences in response to treatment between HCV genotype 2 and genotype 3 and the need for a longer treatment duration with Sofosbuvir–ribavirin in patients with HCV genotype 3 infection. The biologic bases and the host or viral factors that account for the differences in treatment responsiveness between the two genotypesare not well understood.

Sofosbuvir was the first oral drug in combination with ribavirin for HCVtreatment that has more that has better efficacy than interferon based therapies. After sofosbuvir, different other drugs like Ledisprevir, Vikera Pak, Daltasavir, Simeprevir and recently Velpetsavir based therapies with or without ribvirin has also been approved for treatment for HCV with better SVR rates than Sofosbuvir alone therapies. Ledisprevir is also been recently registered in Pakistan but it is not recommended for genotype 2 and 3. Recently approved Velpetsavir based therapy has the best SVR rate among all genotpe more than 95% and will be soon registered with the Govt. At the moment, Sofosbuvir and ribavirin is the only registered drug in Pakistan for HCV with easily availability and subsidized rate.

Limitations of the study include insufficient data about the side effects of this drug combination therapy and the stage of liver damage among the patients like early fibrosis, advanced fibrosis compensated cirrhosis. The study wasRetrospective in nature and the availability of cases was limited due to recent introduction of Sofusbuvir and lack of awareness among health care providers about it.Second, given that few liver biopsy specimens were available for the study population, questions regarding the extent of liver disease, including steatosis, fibrosis and its associationWith relapse among patients with genotype 3 infection, cannot be adequately addressed Therefore further Research about this drug is needed in the future to broaden our understanding.

CONCLUSION

In conclusion, the oral Sofosbuvir–ribavirin regimen resulted in high rates of sustained virologic response both in patients with HCV genotype 2 infections and in those with genotype 3 infection as compared to interferon based therapies. This treatment offers an alternative to a peg interferon-based regimen and may make possible treatment of a substantial number of patients with HCV infection who are ineligible to receive interferon because of absolute or relative contraindications like advance cirrhosis or who are non-responder or relapse to previous therapies..

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