ORIGINAL ARTICLE

Assessment of Therapeutic Effects of Sofosbuvir plus Ribavirin in Patients Suffering from Hepatitis C Virus with Genotype 3

KHALID MAHMUD KHAN[1], TAUQEER AHMAD[2], RANA MOZAMMIL SHAMSHER KHAN[3], *ANSAR LATIF[4]*

ABSTRACT

Aim: This study was designed to assess response, safety and side effects of Sofosbuvir and Ribavirin in patients of HCV with genotype 3 infection.
Design: An open labeled study
Place and duration: Mayo Hospital Lahore and Liver clinic of Bahbood Hospital, Lahore, Department of Medicine, KMSMC, Sialkot from October 2015 to February 2017.
Method: Patients suffering from HCV infection were selected and their HCV- RNA was done by (Roche amplifier Switzerland). All patients were given Sofosbuvir 400mg daily and Ribavirin 800 -1200 mg in divided doses orally according to body weight for twenty four weeks. Followed up after 2 weeks and then at 04 interval. The patients undergoing study had baseline investigations of CBC, TSH, BSR, PCR quantitative for HCV RNA as well as genotype.
Result: Three hundred and twenty confirmed cases of chronic HCV (genotype 3) naïve patients were included.180 (56.25%)) male and 140(43.75%) female. Mean age of the patients was 45.66+ 10 years. After 2 weeks of treatment among 276 patients (86.25%) positive response i.e.; undetectable HCV-RNA a very rapid virological response (VRVR) and at 4 weeks of treatment, rapid viological response (RVR) was seen among 302 patients (94.37%). 100% patients achieved early viological response (EVR) after 12 weeks, however 4 patients developed breakthrough i.e.; PCR was positive at the end of treatment. Among 316 patients who have attained end of treatment response, 40 patients (12.65%) developed relapse after 3 month of stopping therapy, hence (SVR 12) was seen among 276 patients (87.34%). Biochemical response in the form of ALT/AST normalization was in all patients.
Conclusion: This study supports that Sofosbuvir and Ribavirine has great efficacy, well tolerated regimen with a fewer side effect and can achieve SVR in patients suffering from chronic HCV.
Keywords: Hepatitis C. Sofosbuvir Ribavirine, SVR.

INTRODUCTION

Hepatitis C is a chronic viral disease that varies in presentation from a silent disorder to a progressive inflammation of liver that may ultimately lead to cirrhosis, decompensated liver disease and hepatocellular carcinoma[1]. HCV is a major burden of the resources of health in the hospitals and its effects on the society[2]. In Pakistan the burden of this disease is increasing and is a great health problem[3]. Its prevalence is very high despite the efforts to control viral infections. In certain regions of Pakistan the prevalence is as high as 16%[4]. Hepatitis C is reported in 130 to150 millions world population[3]. In twenty percent of chronic Hepatitis C untreated patients cirrhosis may occur[4]. About 300,000 to 350,000 hepatitis c virus related deaths are being reported each year[1,5]. Therefore, it is recommended that with early treatment of Hepatitis C complications of cirrhosis and hepatic failure can be prevented. Eradication of virus may result in clinical improvement and regression of fibrosis[6,7] In Pakistan genotype 3 is common [6,7] and response to Interferons is about 70% to 80%[8] Due to Interferons side effects most of patients of chronic hepatitis C are re not willing to receive interferon based regimen. Therefore, oral treatment with Direct acting oral agents is being preferred for ch. hepatitis C[10].

Sofosbuvir is a direct-acting nucleotide polymerase inhibitor which has revolutionized the management of chronic hepatitis C. It has less adverse effects than Interferons[11,12]. Sofosbuvir is an active nucleotide analogue and targets the HCV-specificNS5B polymerase. It acts as a non obligate chain terminator and this effect is independent of the viral genotype.[13] Lalezari J, et al. showed positive SVR (24) in 92 percent of genotype 2 or 3 patients (23 of 25 patients) after treatment with Sofosbuvir and Ribavirin[14]. Edward J. Gane et al, conducted study in 50 HCV patients of untreated genotype 2 or 3 Hepatitis C patients, Sofosbuvir and Ribavirin for 12 weeks had an undetectable level of serum HCV RNA at 2,4,8,12,24, and 48 weeks[15]. HCV Genotype 3 has

[1]Associate Professor Medicine
[2]Assistant Professor Medicine,
[3]Associate Professor Psychiatry & Behavioural Sciences,
[4]Associate Professor, Head of Department of Surgery,
Khawaja Muhammad Safdar Medical College, Sialkot.
Correspondence to Dr. Tauqeer Ahmad. Email: drahmadtauqeer@gmail.com Cell. 0300-6118046

less rates of SVR and few drugs are effective in treatment of genotype 3[16]. Response rate for patients who have genotype 3infectiontaking oral treatment is 80-85%, much less as compared to genotype 1 or 2[17].

There are very few studies reported from Pakistan indicating the efficacy and side effects of Sofosbuvir and Ribavarin treatment. The objective of this study was to assess the efficacy of the Sofosbuvir based treatment in patients of HCV genotype 3 in Punjab, Pakistan.

MATERIAL AND METHODS

An open labeled multicentre study conducted at Liver clinic / South Medical Ward Mayo Hospital Lahore, Bahbood Hospital, Lahore and department of medicine at KMSMC, Sialkot conducted from October 2015 to February 2017.

One hundred and sixty patients, 90 male and 70 female between the age of 40-60 years were included. Information was given to all patients about events of the treatment, its side effects and outcome of treatment after informed written consent. Pregnant ladies, renal compromised patients, cardiac patients, patients of CCF and stroke or any major co-morbid condition were not included in this study. Hemoglobin of less than10 g/dl, platelet count of 50,000/mm3 or less, ALT, AST and ALP 10 times or more and bilirubin level more than the upper normal limit, and creatinine clearance of less than 30ml/min was used as an exclusion criteria. Patient who were suffering from HCV infection were selected and their HCV-RNA was done by (Roche reverse transcriptase) with lower limit of detection of 15 IU/ml were included after informed consent. Before starting therapy all baseline investigations CBC, LFT, serum Albumen, Urea, Creatinine, FBS, Lipid profile, Prothrombin Time (PT), APTT, TSH, and Genotype were done. An ultrasound of abdomen was done to see the evidence of cirrhosis on ultrasound abdomen.

All the patients with genotype 3 who fulfill inclusion criteria were enrolled in the study. Sofosbuvir was given 400 mg per oral daily along with Ribavirin 800-1200mg according to body weight. Ribavirin was given orally (800mg daily in patients with a body weight of <65 kg, 1000 mg daily in patients with a body weight of <75 kg, and 1200 mg daily in patients with a body weight of ≥75 kg). Initially patients were reviewed fortnightly and then every month. Treatment was continued for 24 weeks.

Patients followed up with CBC, LFTs t and RFTs. PCR for HCV-RNA was performed at week 2, 4, 12 weeks during the course of therapy. At the end of therapy PCR for HCV-RNA Qualitative was done to assess the end of treatment response (ETR). PCR for HCV-RNA Qualitative was done after 12 weeks of stopping treatment again to assess sustained virological response (SVR12). Patients with negative HCV RNA at the end of treatment and 12 weeks later were considered to achieve sustained viral response (SVR12), those with positive HCV RNA at the end of treatment were labeled as non-responders whereas those with negative PCR at the end of treatment but positive PCR after 12 weeks were labeled as relapsers. Data was analyzed by SPPS v 21.

RESULTS

Three hundred and twenty confirmed cases of chronic Hepatitis C were included in this study, 180 male (56.25%)) and female 140(43.75%) between the age 40-60 years. Patients showed good compliance. However, majority of patients had some decline in hemoglobin level, however 60 patients showed hemoglobin below 10 gm/dl . A drop of more than 3 g/dl seen and managed with Ribavirin dose adjustment, injection erythropoietin and iron supplementation, when required. Forty two patients showed rise in uric acid level. However 198 patients (61.87%) felt mild weakness and fatigue, 74 patients (23.13%) patients suffered from headache, 56 patients (17.5%) felt myalgia and arthralgia and cough was observed among 8.75% patients. 8 patient developed urticaria. Mild anxiety and depression was seen in 20 pts. All these abnormalities are shown in table- 1.

.Table 1. Adverse Effects of Treatment

Symptoms	**n**
Fatigue and weakness	198(61.87%)
Headache	74(23.13%)
Myalgia and arthralgia	56(17.5%)
Epigastric discomfort	52(16.25%)
Cough	42(13.13%)
Depression	36(11.25%)
Decrease appetite	28(8.75%)
Insomnia	20(6.87%)
Hb<10gm%	60(18.75%)
Leukopnia (WBc<4000)	50(15.60%)
Throbocytopnia (pit,100,000)	44(13.75%)
Hyperurecemia	42(13.13%)

Response to therapy was seen after 2 weeks of treatment as recorded undetectable HCV-RNA a very rapid viological response (VRVR) among 276 patients (86.25%) and at 4 weeks of treatment, rapid viological response (RVR) was seen among 302 patients (94.37%). 100% patients achieved (EVR) after 12 weeks,, however 4 patients who showed VRVR, RVR, and EVR developed breakthrough i.e., PCR was positive at weeks 24. Among 316 patients who have attained end of treatment response, 40

patients (12.65%) developed relapse after 3 month of stopping therapy, hence (SVR 12) was seen among 276 patients (87.34%) as shown in table 2.

Table 2: Response to therapy

Investigation	n
HCV-RNA Not detected at week 2	276(86.25%)
HCV-RNA Not detected at week 4	302(94.37%)
HCV-RNA Not detected at week 12	320(100%)
HCV-RNA Not detected at week 24	316(81.25%)
Breakthrough HCV-RNA detected at week 24	4(2.64%)
Sustained virological response 12 week post treatment	275/316 (87.34%)
ALT normalization	300(100%)

DISCUSSION

Hepatitis C is a common cause of CLD in Pakistan and throughout the world and it is expected to increase many folds in next coming years due to its chronicity and mode of transmission. HCV infection has multiple risk factors and mostly the patients of HCV have non-specific symptoms..In different studies patients with genotype 2 and 3 of HCV have SVR rates at 4 weeks ranging from 88 to 100%.[12] In this study naïve patients of Chronic HCV and genotype 3 were treated and had early decline in HCV RNA levels. VRVR was seen in 86.25% patients, RVR among 94.37 % patients and at the end of 12 weeks of treatment HCV RNA levels were not detected in all (100%)patients. This response was seen even at the end of treatment in all except 4 patients who developed breakthrough i.e.; PCR was positive after the end of treatment. and SVR 12 was observed among 87.34%. These results are comparable to other published studies.

Study done by Sarwer S and Khan AA showed SVR12 86.2% (119/138) with Sofosbuvir / Ribavirin therapy in treatment naïve patients however it was 79.4% (54/68) in treatment experienced patients and difference was insignificant (p value 0.19).[18] Edward J. Gene et All conducted a study in 50 naive patients with HCV genotype 2 or 3 infection. All patients were treated with Sofosbuvir and Ribavirin for duration of 12 weeks and undetectable level of serum HCV RNA at 2 4,8,12,24 and then at 48 weeks was seen. All patients had a positive SVR after 24 weeks of treatment[15].

According to Haroon Yousaf and colleagues reported 100% (847/847) response to Sofosbuvir and Ribavirin at the end of treatment (ETR) and 99.17% (840/847) SVR at 12 weeks of therapy. The rate of SVR was higher in previously treated patients (99.34%) as compared to naïve patients (97.80%)[19]. In previously untreated patients of HCV Infection, resistance to protease and non nucleoside inhibitors are reported in more than 5% cases due to mutations in NS3 and NS5B regions[21]. It is possible that in some cases relapses may occur after some time as Hepatitis C virus in lymphocytes, hepatocytes, macrophages remain undetectable. Some studies have supported that eradication of virus from the hepatocytes may results in to HCV-RNA undetectable up to 12 years.[22]. In another cohort patients after the end of therapy were followed for 18 years. HCV-RNA remained undetectable in serum but was detectable in biopsies of liver.[23] In our study Relapse rate was among 12.66 % patients with SVR 12 of 87.34% and results were comparable to other published studies[18,20].

This study shows the adverse affect profile of antiviral therapy was comparable with previous studies[5,19,24]. Fatigue, headache, arthralgia, Epigastric discomfort, Cough, depression and insomnia were the most frequent adverse effects. Mild anxiety and depression and irritable behavior along with insomnia were also observed among significant number of patients. Hematological abnormalities seen were Hb<10gm% (n=37) 23.13%, Leucocytes count <4000 (n=105) 62.6% and Platelet count < 100,000 (n=28) 17.5%. Adverse effects were mild to moderate, clinically manageable and all patients tolerated the side effects easily.

CONCLUSION

This study supports that Sofosbuvir and Ribavirin has greater efficacy, well tolerated regimen with a fewer side effect and can achieve SVR in majority of patients suffering from Chronic Hep C Infection with genotype 3. Moreover, this study favors that Hepatitis C can be eliminated with this treatment from Pakistan.

Disclosure of interests: The authors declare no conflicts of interest.

Source of funding: No funding was received for this study.

REFERENCES

1- Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus Sofosbuvir, with or without Ribavirine, to treat chronic infection with hepatitis C virus genotype 1 in non responders to pegylated interferon and Ribavirin and treatment-naive patients: The COSMOS randomized study. Lancet. 14;384(9956):1756-1765. doi: 10.1016/ S0140-6736(14)61036-9

2- Zare F, Fattahi MR, Sepehrimanesh M, Safarpour AR.Economic Burden of Hepatitis C Virus Infection in Different Stages of Disease: A Report From Southern Iran. Hepat Mon. 2016;16(4):e32654.

3- Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect. 2011;17(2):107-115. doi: 10.1111/j.1469-0691.2010.03432.

4- Ahmed N, Asgher M, Shafique M, Qureshi JA. An evidence of high prevalence of hepatitis C virus in Faisalabad, Pakistan. Saudi Med J 2007; 28: 390-395

5- Zahid Azam, Muhammad Shoaib, Masood Javed, Muhammad Adnan Sarwar, Hafeezullah Shaikh, Nasir Khokhar. Initial results of efficacy and safety of Sofosbuvir among Pakistani Population: A real life trial. Hepatitis Eradication Accuracy Trial of Sofosbuvir (HEATS). Pak J Med Sci 2017 Vol. 33 No. 1. 48-52. doi: https://doi.org/10.12669/pjms.331.12352.

6- Waheed Y, Shafi T, Safi SZ, Qadri I. Hepatitis C virus in Pakistan: a systematic review of prevalence, genotypes and risk factors. World J Gastroenterol. 2009; 15(45):5647-5653. doi: 10.3748/wjg.15.5647

7- Khan N, Akmal M, Hayat M, Umar M, Ullah A, Ahmed I, et al. Geographic distribution of hepatitis C virus genotypes in Pakistan. Hepat Mon. 2014;14(10):e20299. doi: 10.5812/ hepatmon.20299.

8- Khalid Mahmud Khan, Inayat Baloch, Farook Dedhi, Shazia Sibghtullah, Nadia . Assessment of Therapeutic Effects on Sustained Viral Response with Conventional Interferon and Ribavirin Therapy in Patients of Chronic Hepatitis C Virus. pakistan Journal of Medical and Health Sciences.Vol. 7, Issue 2, APR – JUN 2013 Website: www.pjmhsonline.com

9- Chung RT. A watershed moment inthe treatment of hepatitis C. N Engl J Med 2012;366:273-5.

10- Younossi ZM, Stepanova M, Nader F, Lam B, Hunt S. The patient's journey with chronic hepatitis C from interferon plus ribavirin to interferon- and ribavirin-free regimens: a study of health-related quality of life. Aliment Pharmacol Ther. 2015;42(3):286-295.

11- McQuaid T, Savini C, Seyedkazemi S. Sofosbuvir, aSignificant Paradigm Change in HCV Treatment. J Clin Transl Hepatol. 2015;3(1):27-35.

12- Satsangi S, Mehta M, Duseja A, Taneja S, Dhiman RK,Chawla Y. Dual treatment with sofosbuvir plus ribavirin is as effective as triple therapy with pegylated interferon plussofosbuvir plus ribavirin in predominant genotype 3 patients with chronic hepatitis C. J Gastroenterol Hepatol.2016 Sep 14. doi: 10.1111/jgh.13595.

13- Sofia MJ, Bao D, Chang W, et al. Discovery of a β-d-2'-deoxy-2′-α-fluoro-2′-β-C-methyluridine nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus. J Med Chem 2010;53:7202-18.

14- Lalezari J, Lawitz E, Rodriguez-Torres M, et al. Once daily PSI-7977 plus pegylated IFN/ribavirin in Phase 2B trial: rapid virologic suppression in treatment naive patients with HCV GT2/GT3. J Hepatol

15- Edward J. Gane, M.D., Catherine A. Stedman, M.B., Ch.B., Ph.D.,Robert H. Hyland, D.Phil., Xiao Ding, Ph.D., Evguenia Svarovskaia, Ph.D.,William T. Symonds, Pharm.D., Robert G. Hindes, M.D., and M. Michelle Berrey, M.D., M.P.Hall Nucleotide Polymerase Inhibitor Sofosbuvir plus Ribavirin for Hepatitis C. N Engl J Med 2013;368:34-44. DOI: 10.1056/NEJMoa1208953

16- Feld JJ, Foster GR. Second generation direct-acting antivirals-Do we expect major improvements? Hepatol. 2016;65(1Suppl):S130-S142.

17- Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370(21):1993-2001.

18- Sarwar S, Khan AA. Sofosbuvir based therapy in Hepatitis C patients with and without cirrhosis: Is there difference? Pak J Med Sci.2017;33(1):37-41. doi: https://doi.org/10.12669/pjms.331.12163

19- Muhammad haroon Yousaf, Muhammad Iftikhar Yousaf, Sajid Iqbal. Dramatic response of hepatitis C patients chronically infected with HCV genotype 3 to sofosbuvir based therapies in Punjab. Pakistan. Hepatol Int (2017) 11 uppl 1):S1–S1093 S27.

20- Foster GR, Pianko S, Brown A, Forton D, Nahass RG,George J, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection.Gastroenterology. 2015;149(6):1462-1270.

21- Kuntzen T, Timm J, Berical A, et al. Naturally occurring dominant resistance mutations to hepatitis C virus protease and polymerase inhibitors in treatment-na.ve patients. Hepatology 2008;48:1769-78.

22- Camma C, Guinta M, Pinzello G, Morabito A, Verderio P, Pagliaro L. Chronic hepatitis C and interferon alpha: Conventional and Cumulative meta-analysis of randomized controlled trials. Am J Gastrienterol 1999; 94: 581-94

23- Maylin S, Martinol-Peignoux M, Maccari R, et al. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. Gastroenterology. 2008; 135: 821-9

24- Gane EJ, Stedman CA, Hyland RH, Ding X, SvarovskaiaE, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med.2013;368(1):34-44. doi: 10.1056/NEJMoa1208953