The Professional Medical Journal
www.theprofesional.com

DOI: 10.29309/TPMJ/18.4587

ORIGINAL PROF-4587

SOFOSBUVIR AND RIBAVIRIN;

RESPONSE TO 16-WEEKS VERSUS 24-WEEKS DUAL THERAPY INCLUDING SOFOSBUVIR AND RIBAVIRIN, IN ALL CIRRHOTIC AND NON-CIRRHOTIC PATIENTS WITH HCV GENOTYPE- 3A INFECTION IN POPULATION OF KPK-PAKISTAN

Nizamuddin[1], Jamaluddin[2], Abid Shah[3], Waheed Iqbal[4]

1. MBBS, MPH, M.Phil, FCPS
Assistant Professor Pharmacology
and Consultant Physician
Khyber Medical College Peshawar.
2. MBBS, FCPS,
Associate Professor
Department of Medicine
Khyber Medical College Peshawar.
3. MBBS, FCPS (Medicine)
Assistant Professor
Department of Pharmacology
Khyber Medical College Peshawar.
4. BSc and M.Phil (Pharmacology
Chemist and Microbiologist
Khyber Medical College Peshawar.

Correspondence Address:
Dr. Nizamuddin
Apartment No. B-47, Deans Complex, Peshawar Boat.
drnizam99@yahoo.com

Article received on:
18/12/2017
Accepted for publication:
25/09/2018
Received after proof reading:
03/12/2018

ABSTRACT... Objectives: This study was conducted to evaluate the 16-weeks versus 24-weeks efficacy of sofosbuvir and ribavirin in HCV genotype-3a infection. **Study Design:** Open labeled, single center, longitudinal study. **Setting:** Khyber Medical College and Khyber Teaching Hospital, Peshawar. **Period:** The total duration of study was 6-months, starting from January 2017 to July 2017. **Methods:** Eighty patients with HCV genotype-3a infection were enrolled. Patients were assigned into 4-groups (20 patients in each group), including group-A as treatment naïve non-cirrhotic, group-B as treatment naïve with liver cirrhosis, group-C as non-cirrhotic but non-responder to peg-interferon and ribavirin and group-D as non-responder cirrhotic cases. Sofosbuvir plus ribavirin was given for 16-weeks and then extended to 24-weeks. The primary end point was end of treatment response with 16-weeks or 24-weeks therapy (EOT-16 or EOT-24), which is defined as HCV RNA level<40IU/ml after 16-weeks or 24-weeks of therapy. **Results:** Out of all 80-patients, 50% (n=40) were male and 50% (n=40) were female, with mean age of 49±2 years. In all 80 cases, 67.5% (n=54/80) of patients have responded at 16 weeks, while 82.5% (n=66/80) of patients have responded to 24-weeks of therapy. In all 40 treatment naïve patients (group A and group B), 72.5% (n=29/40) have responded at 16 weeks, while 85% (n=34/40) of patients have responded to 24-weeks of therapy. Similarly, in all 40-previously non-responder cases (group C and group D), 62.5% (n=25/40) of patients have responded at 16 weeks, while 77.5% (n=31/40) of patients have responded to 24-weeks of therapy. **Conclusion:** Results of this study confirm that dual therapy given for 24-weeks is more effective compare to 16-weeks therapy in both treatment naïve and previously non-responder cases, which may be either cirrhotic or non-cirrhotic, with chronic hepatitis-C genotype-3a infections.

Key words: Chronic Hepatitis-C, End of Treatment Response, Sofosbuvir.

Article Citation: Nizamuddin, Jamaluddin, Shah A, Iqbal W. Sofosbuvir and ribavirin; response to 16-weeks versus 24-weeks dual therapy including sofosbuvir and ribavirin, in all cirrhotic and non-cirrhotic patients with HCV genotype-3a infection in population of KPK-Pakistan. Professional Med J 2018; 25(12):1876-1881. **DOI:** 10.29309/TPMJ/18.4587

INTRODUCTION

The treatment strategy for chronic hepatitis-C remains the hot focus for research in last decade. There are many options available for the treatment of chronic hepatitis C. The additions of many new DAAs (Direct Acting Anti-viral) have now totally modernized the therapy in both cirrhotic and non-cirrhotic patients. Theses drugs are given for different doses and duration, which mainly depend on the genotype of virus.[1] Among these, some are specific to a single genotype while the other has pan-genotypic activities and can be given in case of all genotype infection. On of the most important drug in these DAAs is NS5B HCV RNA dependent RNA polymerase inhibitor called sofosbuvir, which is recommended in all HCV genotypes.[2]

Hepatitis-C along with hepatitis-B shares the major burden of chronic hepatitis in the whole world. This is a chronic ailment, which is considered among the leading cause of human morbidity and mortality in the whole world.[3] In a survey report by WHO, the global prevalence of CHC >3%, affecting almost 170 to 200 million people worldwide. Globally, it is one of the major reasons of chronic liver diseases and one of the leading causes of liver transplantation.[4,5]

Till now, 7-genotype of hepatitis-C virus (HCV)

are reported from different corner of the world with different incidence and prevalence. All these genotypes have different course of disease and treatment strategies. Pakistani community is mostly affected by genotype 3, especially 3a, but other genotypes are also reported from different areas of the country. HCV genotype 3, especially 3a have got a very unpredictable presentation and of course very unpredictable response to different treatment regimen.[6,7]

There are two major complication of chronic hepatitis C. One is cirrhosis and the other is hepatoma. These two conditions are considered the major causes of HCV related death. These complications are usually common and reported in those patients who have very high level of detectable HCV RNA in their serum. If this high level of viremia lead to these complication and finally death.[8]

So far, it is documented worldwide, that aggressive treatment can eradicate virus from the blood and thus can decrease the chances of cirrhosis. Therefore eradicating virus from the blood of the patients is considered the only surrogate outcome in the management of CHC. This sustained total clearance of virus from the blood or serum in these patients for 6-months after the end of therapy is termed as sustained virological response (SVR). By achieving SVR, one can decrease the risk of cirrhosis and HCC.[9]

Traditionally, Hepatitis-C genotype-3a infection was treated using Peg-interferon plus ribavirin for 24-weeks. Due to multiple adverse effects, poor outcome and availability of other effective options in the form of DAAs, this treatment is no more in use. Nowadays, highly effective oral direct acting antiviral (DAAs) are given in different combination for different duration. The combination of Sofosbuvir and Ribavirin can be given to these patients for 16-weeks and 24-weeks with different outcome in term of SVR. These drugs have got few adverse effects and very good outcomes. According to the guideline, adopted by AASLD (American association for the Study of Liver Disease) and EASL (European Association For the Study of Liver), it can be given along with ribavirin for 16 or 24 weeks to treat HCV (genotype-3a) infections in all patients with or without cirrhosis.[10,11]

There are a number of documented studies and clinical trials, which have evaluated the efficacy of Sofosbuvir and Ribavirin in different genotype of HCV infection. In this study, we have focused to compare the efficacy of this combination in HCV genotype-3a infection, if given for 16 or 24 weeks. So far, much research is available worldwide, but there is very limited data about this study in Pakistan regarding the different duration of therapy for this combination. We have conducted this study to evaluate its efficacy in Pakistani population.

MATERIALS AND METHODS

This single center, longitudinal study was conducted in the Khyber Medical College and Teaching Hospital, Peshawar. The total duration of study was 6-months, starting from January 2017 to July 2017. Sample size was calculated using WHO-online calculator. After ethical committee approval and informed consent, 80 patients having chronic hepatitis-C genotype-3a infections were enrolled. All these patients were divided into 4 groups, labeled as group-A as new non-cirrhotic cases, group-B as new cirrhotic cases, group-C as non-responders but non-cirrhotic cases and group-D as Non- responders, cirrhotic cases. The demographic and clinical information like age, sex, ethnicity, treatment strategy and other complications resulting from HCV were obtained from the patients. All patients were put on Sofosbuvir and Ribavirin therapy in recommended doses for 16-weeks and extended to 24-weeks according to their response.

Statistical Analysis

The collected information was entered into Microsoft Excel sheet. The percentage and frequencies were calculated using Microsoft Excel 2007. The remaining data was entered using Microsoft excel 2007 for further analysis. Graph pad prism 7 was used for the construction of graphs and finally all data was analyzed using SPSS version 16. Student's t-test was applied with 95% of confidence level, and significant

p-value of ≤ 0.05. Chi-square test was applied to test the association. The finding was presented in graphs and tables.

RESULT

All 80 patients in this study were analyzed. Out of all 80 patients, 50% (n=40) were male and 50% (n=40) were female, mean age of 49±2 years.

The age distribution among 80 patients was analyzed as n=05(6.25%) patients were in age-group of 15-30 years, n=30(37.5%) patients were falling in age group of 31-45 years, n=40(50%) patients were falling in age group of 46-60 years, n=04(5%) patients were falling in age group of 61-75 years and n=01(1.25%) patients were above 75 years of age as shown in Table-I.

In all 80 patients in four groups, individual status of response in the form of undetectable HCV RNA from the serum at 16-weeks and 24-weeks was analyzed. In all 20-treatment naïve non-cirrhotic cases of group-A, 80% (n=16/20) of patients have responded at 16-weeks, while 90% (n=18/20) of patients have responded to 24-weeks of therapy. In all 20-cases of group-B having treatment naïve cirrhotic cases, 65% (n=13/20) of patients have responded at 16-weeks, while 80% (n=16/20) of patients have responded to 24-weeks of therapy. In all 20-cases 0f group-C, having previously non-responder and non-cirrhotic cases, 70% (n=14/20) of patients have responded at 16-weeks, while 85% (n=17/20) of patients have responded to 24-weeks of therapy. In all 20-cases of group-D having previously non-responder and cirrhotic cases, 55% (n=11/20) of patients have responded at 16-weeks, while 75% (n=15/20) of patients have responded to 24-weeks of therapy, as shown in Figure-1&2 and presented in Table-II.

Associations of response rate in HCV-genotype 3a infection to dual therapy with sofosbuvir plus ribavirin given for 16-weeks and 24-weeks were further analyzed. The significant p-value of 0.02 shows that 24-weeks of dual therapy is superior to16-weeks dual therapy for the optimal treatment as shown in Table-III.

Further associations of response rate in HCV-genotype-3a infection to dual therapy with sofosbuvir plus ribavirin given for 16-weeks and 24-weeks in all four groups were further analyzed. The significant p-value of 0.02 shows that 24-weeks therapy is superior to16-weeks therapy in all treatment Naïve and previously non-responder cases as shown in Table-IV.

Age	Total Number of Patients	Percentage
15-30 Years	05	6.25%
31-45 Years	30	37.5%
46-60 Years	40	50%
61-75 Years	04	5%
> 76 Years	01	1.25%
Total	80	100%

Table-I. Age distribution of different patient with CHC genotype-3 infection

Groups	Number of Cases	Number of Cases Response at 16 Week	Percentage	Number of Cases Response at 24 Week	Percentage
Group A	20	16/20	80%	18/20	90%
Group B	20	13/20	65%	16/20	80%
Group C	20	14/20	70%	17/20	85%
Group D	20	11/20	55%	15/20	75%
Total	80	54/80	67.5%	66/80	82.5%

Table-II. Response in all 4-groups, at 16 and 24 weeks

	Responders	Non-Responder	Total	χ^2	P-value
At 16 weeks' treatment	54	26	80	4.80	0.02
At 24 weeks' treatment	66	14	80		

Table-III. Test for association (Chi-square)

Groups	Success at 16 Weeks	Failure at 16 Weeks	Success at 24 Weeks	Failure at 24 Weeks	Value of "r"	95% CI	P-value
NCNC	16	4	18	2	0.99	0.6732 to 0.9998	0.007
NCC	13	7	16	4			
NRNC	14	6	17	3			
NRC	11	9	15	5			
Total	54	26	66	14			

Table-IV. Pearson correlation test between 16-weeks and 24-weeks of treatment

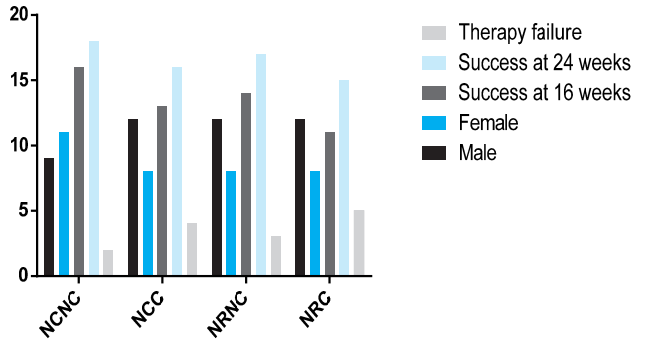

Figure-1. Therapy success at 16 weeks vs. 24 weeks

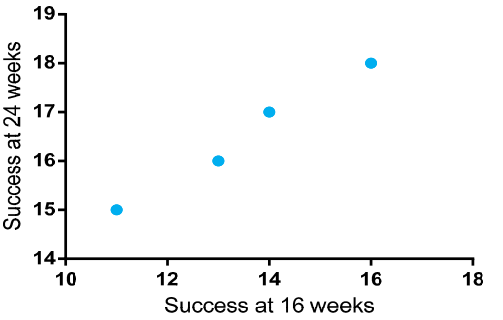

Figure-2. Therapy success at 16 weeks' vs. 24 weeks

DISCUSSION

Chronic hepatitis-C is a global problem and the most attractive topic for research worldwide. Their treatment regimen is also changing very rapidly over the last decade. Timely treatment can prevent cirrhosis and hepatoma in these patients.[9,12] According to the current guidelines adopted by AASLD (American Association for the Study of Liver Diseases), IDSA (Infectious Diseases Society of America)[10] and EASL (European Association for the Study of Liver)[11], oral DAAs including Sofosbuvir can be given in different combination for 12-24 weeks. There are a number of documented studies and clinical trials, which have evaluated the efficacy of Sofosbuvir and Ribavirin in different HCV-genotype infection for 16 or 24 weeks.

In our present study, the overall status of response in the form of undetectable HCV-RNA from the serum in all patients was 67.5% (n=54/80) and 82.5% (n=66/80), being treated for 16 and 24-weeks respectively. The significant p-value of 0.02 show that 24-weeks therapy is superior to16-weeks therapy in all treatment Naïve and previously non-responder patients.

In our study, HCV-RNA-PCR was undetectable in 67.5% (n=54/80) of cases at 16 weeks of therapy with a P-value of .007. These finding are close to the finding of a study, conducted by Graham R. Foster et all, which show that 71% of patients with HCV genotype-3 infection have responded to16-weeks therapy with sofosbuvir and ribavirin, while 84% have responded to 24-weeks therapy of this combination. This shows that 24-weeks therapy is statistically superior to 16-weeks therapy with a P= 002.[13]

The finding of our study is close to the finding of BOSON trials which was conducted in patients with HCV-genotype-2 and 3 infection, with or without cirrhosis. In this randomized controlled trials, three treatment regimens were used including sofosbuvir and ribavirin for 16-weeks and 24-weeks. In all new patients with HCV-genotype-3 infections, 77% patient have responded to 16-weeks while 88% have responded to 24-weeks of sofosbuvir and ribavirin based regimen. Similarly, in non-responder patients with HCV-genotype-3 infections, who have not responded previously to peg-interferon and ribavirin treatment, 64% have responded to 16-weeks and 80% to 24-weeks of sofosbuvir plus ribavirin based therapy.[13]

The finding of our study is also closed to the finding of another trial named FUSION, which was basically evaluating the effectiveness of sofosbuvir and ribavirin therapy in treatment-experienced patients with genotype-2 or 3 HCV infection, being treated for 12-weeks and 16-weeks. In this trial, treatment-experienced patient with HCV-genotype-3 infections, 30% (n=19/64) responded to 12-weeks therapy, while 62% (n=39/63) have responded to 16-weeks therapy of sofosbuvir plus ribavirin. This result was further analyzed in cirrhotic patients and there was 19% with 12-weeks therapy, while 61% of the patients have responded to 16-weeks therapy. These results confirm, that giving 12 and 16-weeks therapy of sofosbuvir plus ribavirin is not absolutely sufficient for the treatment of both cirrhotic and non-cirrhotic patients with HCV genotype-3 infection, and treatment must be tailored to 24-weeks.[14]

Our findings are also closed to the finding of another study, conducted in Russia by Konstantin Zhdanov et al, on sofosbuvir plus ribavirin. It was basically given to the patients, having chronic HCV genotype-1 or 3 Infection. In this study, sofosbuvir and ribavirin has resulted with good response to16 or 24-weeks of treatment in treatment-naive patients with HCV-genotype-3 infection. In non-cirrhotic patients, 88% (n=21/24) and 96% (n=25/26) response was observed with 16 and 24 weeks therapy respectively. In case of cirrhotic patients, 83% (n=5/6) and 60% (n=3/5) have responded to16 and 24 weeks of therapy respectively.[15]

Finally, it is now accepted worldwide with many trials, that all DAAs are very effective and safe in the treatment of HCV infection. Their duration of treatment may be different for different genotypes and different population. Keeping the end result of above trails including our study, Sofosbuvir plus ribavirin combination is still considered superior in hepatitis-C genotype-3a infection, if it is given for good 24-weeks.

The main limitations of this study was the small sample size, lack of data on potential confounders, poor evaluation of the level of cirrhosis, role of IL28B on response rate, effect of viral load on final response, drug level monitoring for compliance and identification of S282T variant of the NS5B protein region which is the first identified sofosbuvir resistant variant (RAV).

CONCLUSION

It is obviously concluded from above study that 24 weeks dual therapy including sofosbuvir plus weight based ribavirin therapy is superior to 16 weeks therapy in both treatment Naïve and previously non-responder patients with HCV genotype-3a infections in Pakistani population. Further study is suggested for further confirmation and specification of this regimen given for 24 weeks in HCV genotype 3a infection.

REFRENCES

1. Noell BC, Besur SV. **Changing the face of hepatitis C management–the design and development of sofosbuvir.** Drug design, development and therapy. 2015;9:2367.

2. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. **Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options.** New England Journal of medicine. 2013;368(20):1867-77.

3. Razavi H, ElKhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, et al. **Chronic hepatitis C virus (HCV) disease burden and cost in the United States.** Hepatology. 2013;57(6):2164-70.

4. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. **Global epidemiology of hepatitis C virus infection: New estimates of age□specific antibody to HCV seroprevalence.** Hepatology. 2013;57(4):1333-42.

5. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al. **Global distribution and prevalence of hepatitis C virus genotypes.** Hepatology. 2015;61(1):77-87.

6. Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, *et al.* **Expanded classification of hepatitis-C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource.** Hepatology. 2014;59(1):318-27.

7. Umer M, Iqbal M. **Hepatitis C virus prevalence and genotype distribution in Pakistan: Comprehensive review of recent data.** World journal of gastroenterology. 2016;22(4):1684.

8. Li DK, Chung RT. **Impact of hepatitis C virus eradication on hepatocellular carcinogenesis.** Cancer. 2015;121(17):2874-82.

9. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. **Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies.** Annals of internal medicine. 2013;158(5_Part_1):329-37.

10. Diseases AAftSoL, America IDSo. **HCV guidance: recommendations for testing, managing, and treating hepatitis C.** AASLD, IDSA; 2015.

11. Flamm SL. **Advances in the Treatment of Hepatitis C Virus Infection From EASL 2015.** Gastroenterology & Hepatology. 2015;11(6 Supplement 3).

12. Van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour J-F, Lammert F, et al. **Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis.** Jama. 2012;308(24):2584-93.

13. 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):1462-70.

14. Nelson D, Feld J, Kowdley K, Al-Assi M, Lin M, Mo H, et al. **Oral therapy with sofosbuvir+ ribavirin for 12 or 16 weeks in treatment experienced gt2/3 hcv-infected patients: Results of the phase 3 fusion trial.** Journal of Hepatology. 2013;58:S3-S4.

15. Zhdanov K, Isakov V, Kersey K, Zhu Y, Svarovskaia E, Massetto B, et al., editors. **Sofosbuvir plus ribavirin for the treatment of Russian patients with chronic HCV genotype 1 or 3 infection.** 24th Conference of the Asian Pacific Association for the Study for the Liver, Brisbane-Australia; 2014.

In order to succeed,
We must first believe that we can.

– Nikos Kazantzakis –

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Nizamuddin	Study design, Drafting and critical analysis.	
2	Jamaluddin	Study planning, Script writing and final proofing.	
3	Abid Shah	Co-author and Critical Analysis.	
4	Waheed Iqbal	Data collection/analysis.	