Original Article

Efficacy of Sofosbuvir and Ribavirin in HCV

Treatment outcome in patients with HCV Genotype-3a Infection, Treated with 24-Weeks Dual Therapy (Sofosbuvir and Ribavirin)

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ABSTRACT

Objective: This study was mainly conducted to evaluate the efficacy of sofosbuvir and ribavirin in HCV genotype-3a infection, which is the most common genotype, infecting Pakistani community.
Study Design: Open labeled, single center, longitudinal study.
Place and Duration of Study: This study was conducted at the Institute of Basic Medical sciences (IBMS), Khyber Medical University, Peshawar from June 2016 to November 2016.
Materials and Methods: Total of 80 patients with HCV genotype-3a infection were enrolled. Patients were assigned into four groups including group-A as treatment naïve non-cirrhotic, group-B who were treatment naïve but cirrhotic, group-C as non-cirrhotic cases who were non-responder to peg-interferon and ribavirin and group-D as non-responder cirrhotic cases. Sofosbuvir plus ribavirin was given for 24-weeks. The primary end point was end of treatment (EOT-24) response with 24-weeks therapy, which is defined as HCV RNA level<40IU/ml after 24-weeks of therapy.
Results: Among 80 patients, male-female ratio was 56.25%(n=45) and 43.75%(n=35) respectively. Each group has 20 cases. Rate of EOT-24 was 90% (n=18/20) in group-A, 80%(n=16/20) in group-B, 85%(=17/20) in group-C and 75%(n=15/20) in group-D. The EOT-24 was 85%(n=34/40) in all treatment Naïve cases, while 77.5%(n=31/40) was observed in all non-responder cases. The overall response was 82.5%(n=66/80).
Conclusion: Results of this study confirm strong efficacy of dual 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, Cirrhotic, dual therapy, End of Treatment response, Sofosbuvir.

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INTRODUCTION

Treatment of chronic hepatitis-C is rapidly evolving in last decade. The additions of new DAAs (Direct Acting Anti-viral) have now totally revolutionized the therapy in both cirrhotic and non-cirrhotic patients. The most important drug in DAAs is NS5B HCV RNA dependent RNA polymerase inhibitor called sofosbuvir, which is now recommended in all HCV genotypes and is considered as one of the most important weapon in the therapeutic armamentarium against hepatitis C virus.[1] Hepatitis-C is a chronic ailment, which affects human in almost every corner of the world and thus sharing a huge part in death rate of the world population. Globally, CHC is considered as emerging public health problem, which is considered the most significant single cause of liver diseases and liver transplantation.

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Hepatitis-C virus (HCV) is considered as one of the leading cause of post transfusion non-A and non-B hepatitis[2,3]. It is now documented world wide that together chronic hepatitis-C and hepatitis–B affect >75% cases of all chronic liver disease (CLD). In a survey report by WHO, the global prevalence of CHC >3%, affecting almost 170 to 200 million people worldwide[4]. Majority of these people are at highest risk to develop cirrhosis and finally hepatocellular carcinoma (HCC), which are considered as the most important complications and causes of death in patients with Hepatitis-C infection. WHO states in a report, that about 4% of HCV infection leads to HCC worldwide and this complication is usually common in those patients having, high level of detectable HCV RNA in their serum for longer period[5]. Therefore in all patients aggressive treatment is needed to completely eradicate virus from the serum, which is the only surrogate outcome in the management of CHC. This total clearance of virus from the blood or serum of these patients is termed as sustained virological response (SVR). By achieving SVR, one can decrease the risk of cirrhosis and HCC[6].

So far, 7-genotype of hepatitis-C virus (HCV) are discovered having different prevalence in different countries. Pakistani community is mostly affected by

genotype 3, especially 3a, which have got unpredictable response to different treatment regimen.

Previously, the treatment strategy for Hepatitis-C genotype 3a infection was using Peg-interferon plus ribavirin (PEG-IFN+RBV) for 24-weeks. But this therapy has multiple adverse effects and poor outcome in term of SVR. Nowadays, highly effective oral direct acting antiviral (DAAs) like Sofosbuvir and Ribavirin can be given to these patients with few adverse effects and very good outcomes. According to AASLD and EASL guideline[7], it can be given along with ribavirin for 24 weeks to treat HCV (genotype-3a) infections in all patients with or without cirrhosis[8]. Being used extensively worldwide with very good response, clinical score improvement and minimal adverse effects, it's still needs further studies at national level in both patients (cirrhotic and non-cirrhotic), including all treatment naive and old non-responder cases for further validation of its efficacy in our Pakistani community.

MATERIALS AND METHODS

This single center, longitudinal study was conducted in the Institute of Basic Medical sciences (IBMS), Khyber Medical University Peshawar. The total duration of study was 6-months, starting from June 2016 to November 2016.The samples of this study were collected from Medical Training Institute (MTI), Hayatabad Medical Complex Peshawar. After ethical committee approval and informed consent, 80 patients having chronic hepatitis-C genotype 3a infections were enrolled in this study applying strict inclusion and exclusion criteria. Sample was collected using non-probability and purposive sampling technique, sample size for the study was calculated using WHO-online sample size calculator, on MS Excel. All these patients were divided into 4 groups, labeled as A (new non-cirrhotic cases), B (new cirrhotic cases), C (non-responders, non-cirrhotic cases) and D as (Non-responders, cirrhotic) cases. The non-responders were those cases, who have not responded to peg-interferon and ribavirin based therapy, being given previously for good 24 weeks. The demographic and clinical information like age, sex, ethnicity, treatment strategy and other complications resulting from HCV were obtained from the patients. The personal information of all patients was kept confidential.

Statistical analysis: All collected information was entered into Microsoft Excel sheet. All the percentage and frequencies of different patients group with and without cirrhosis were calculated using Microsoft Excel 2010. The rest of the data was entered using Microsoft excel 2007 and graph pad prism for construction of graphs and thus analyzed by using SPSS version7. Student's t-test is used 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 tables.

RESULTS

Out of total 80 studied patients, 56.25%(n=45) were male and 43.75%(n=35) were female, having mean age of 51±2 years.

Age distribution among 80 patients was analyzed as n=01(1.25%) patients were in age-group of 21-30 years, n=09(11.25%) patients were falling in age group of 31-40 years, n=29(36.25%) patients were falling in age group of 41-50 years, n=24(30%) patients were falling in age group of 51-60 years and n=17(21.25%) patients were above 60 years of age as shown in Table 1.

In 80 patients of all four groups, over all status of response in the form of undetectable HCV-RNA from the serum at 24-weeks was analyzed. In case of both treatment-naïve and previously non-responder cases with or without cirrhosis of all 4-group, 82.5% (n=66/80) of patients have responded to 24-weeks of therapy. In all 40-treatment naïve cases of group A and B, status of response at 24-weeks was analyzed. Among all 40-treatment naïve patients, 85% (n=34/40) of patients have responded. In all 40-non-responder cases of group C and D, status of response at 24-weeks was analyzed. Among all 40-previously non-responder cases, 77.5% (n=31/40) of patients have responded to 24-weeks of therapy, as shown in table 2.

Table No.1: Age distribution of different patient with CHC genotype 3 infection

Age	Total number of patients	Percentage
21-30 Years	01	1.25%
31-40 Years	09	11.25%
41-50 Years	29	36.25%
51-60 Years	24	30%
> 60 Years	17	21.25%
Total	80	100%

Table No.2. Response in all treatment Naïve and all non-responder cases, at 24 weeks.

Clinical status	Number of cases	Number of cases response at 24 week	%age
Treatment Naïve A+B)	40	34/40	85%
Non-responder (C+D)	40	31/40	77.5%

Table No.3: Response in all 4-groups at 24 weeks.

Groups	Number of cases	Number of cases response at 24 week	%age
Group A	20	18/20	90%
Group B	20	16/20	80%
Group C	20	17/20	85%
Group D	20	15/20	75%
Total	80	66/80	82.5%

Table No.4: Association between cirrhotic and non-cirrhotic

	Cirrhotic	Non-Cirrhotic	χ^2	p-value
Treatment Success	31	35	1.38	0.23
Treatment failure	09	05		
Total	40	40		

Table No.5: Association between treatment Naïve and Old non-responders

	Treatment Naïve	Old non-responders	Total	χ^2	p-value
Treatment Success	34	32	66	0.34	0.5
Treatment failure	06	08	14		
Total	40	40	80		

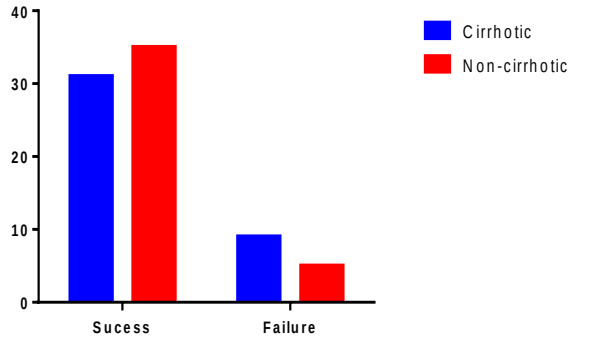

Figure No.1: Association between cirrhotic and non-cirrhotic

Figure No.2: Association between treatment Naïve and old non-responder cases

In all four groups, individual status of response in the form of undetectable HCV RNA from the serum at 24-weeks was analyzed. In all 20-treatment naïve non-cirrhotic cases of group-A, 90% (n=18/20) of patients have responded while in all 20-cases of group-B having treatment naïve cirrhotic cases, 80% (n=16/20) of patients have responded to 24-weeks of therapy. Similarly, in all 20-cases 0f group-C, having previously non-responder and non-cirrhotic cases, 85% (n=17/20) of patients have responded while in all 20-cases of group-D having previously non-responder and cirrhotic cases, 75% (n=15/20) of patients have responded to 24-weeks of therapy (Table 3).

Associations of response rate in case HCV-genotype-3a infection to dual therapy with sofosbuvir+ribavirin given for 24-weeks was further analyzed in all cirrhotic (both new and old cases) and non-cirrhotic (both new and old cases). The non-significant p-value of 0.23 shows that 24-weeks therapy is equally effective in both cirrhotic and non-cirrhotic cases as shown in figure no 1 and presented in table 4.

Associations of response rate in HCV-genotype-3a infection to the same dual therapy, given for 24-weeks was further analyzed in all treatment naïve (both having cirrhosis and those without cirrhosis) and old non-responder (both having cirrhosis and without cirrhosis). The non-significant p-value of 0.5 shows that 24-weeks therapy is equally effective in both treatment naïve and old non-responder cases as shown in figure 2 and presented in table 5.

DISCUSSION

As chronic hepatitis-C is a global problem and the paradigm shift in the treatment combination from interferon-based therapy to direct acting anti-viral therapy has totally changed the direction of research around the globe. The new DAAs have really revolutionized the treatment strategy in all HCV genotypes. One of the option in current guidelines adopted by AASLD (American Association for the Study of Liver Diseases), IDSA (Infectious Diseases Society of America)[9] and EASL (European Association for the Study of Liver)[10], for the optimal treatment of Chronic HCV genotype-3 infection is sofosbuvir with or without peg-interferon. This is also recommended along with ribavirin for 24-weeks in both cirrhotic and non-cirrhotic cases of HCV genotype-3 infection.

In our present study, 90%(n=18/20) response rate has been observed to dual therapy in case of newly diagnosed non-cirrhotic cases with HCV-genotype-3a infection, while 80%(n=16/20) response rate has been observed in case of treatment naive but cirrhotic patients with HCV-genotype-3a, being managed for 24-weeks with sofosbuvir plus ribavirin. On the other hand, 85%(n=17/20) response rate has been observed in old non-responder but non-cirrhotic cases, while 75%(n=15/20) response rate has been observed in old non-responder but cirrhotic patients with HCV genotype-3a, being treated for 24-weeks with sofosbuvir and ribavirin.

Total response observed in our study in all non-cirrhotic patients was 87.5%(n=35/40), while response observed in cirrhotic cases was 77.5%(n=31/40). The association of response rate in both non-cirrhotic and cirrhotic was further analyzed with an insignificant p-value of 0.23, which show that 24-weeks therapy is equally superior in both non-cirrhotic and cirrhotic cases and must be given judicially for 24 weeks to achieve optimal results.

Similarly, total response observed in our study in all treatment naive patients was 85%(n=34/40), while response observed in all old non-responder cases was 80%(n=32/40). The association of response rate in both treatment naïve and old non-responder was further analyzed with an insignificant p-value of 0.5, which show that 24-weeks therapy is equally superior in both treatment naïve and old non-responder cases and must be given judicially for 24-weeks to achieve good results.

Our finding are also closed to the finding of another study, conducted in Europe by Stefan Zeuzemet all, on Sofosbuvir and Ribavirin in HCV-genotypes-2 and 3 infection. Data was collected from more than 77 centers in Europe. Among 250 patients with HCV genotype-3 infections that have received 24 weeks of sofosbuvir plus ribavirin, 213(85%) patients had achieved EOT and SVR12 after the cessation of treatment[11].

Another study conducted by Michael charlton et al, on dual therapy, including sofosbuvir and ribavirin for the treatment of recurrent hepatitis-C virus infection in patients after liver transplantation. In this study, forty patients with HCV-infection were enrolled and treated. EOT and SVR12 were observed in 70%(n=28/40) patients treated with 24-weeks therapy of sofosbuvir and ribavirin. This finding show, that the recommended 24-weeks therapy is also very much effective in the treatment of HCV-infection even in patients having transplanted liver[12].

Another study conducted by Mark S. Sulkowski et al, on sofosbuvir and ribavirin containing dual therapy for the treatment of Hepatitis-C in most challenging patients with HIV-co-infection. They have enrolled patients with different genotypes and all of them were given sofosbuvir along with ribavirin for 24-weeks. EOT and SVR12 were observed in 67%(n=28/42) patients with HCV-genotype-3 infections. These finding show that good result can seen in HCV-genotype-3 and HIV co-infected patients, if they are treated with the same dual therapy of sofosbuvir and ribavirin for good 24-weeks[13].

This combination is not only associated with superior EOT and SVR rate, but also with improved quality of life and minimal adverse effects. In our study the most common adverse effects observed with this combination are insomnia, fatigue, weight loss and anxiety. This is confirmed by Younossi, ZmM. et al, in a study, showing the minimal impact of sofosbuvir and ribavirin on routine activity and health related quality of life in chronic hepatitis-C. At the same time, there was significant improvement in HRQL score in these patients with treatment and minimal adverse effects were observed[14].

Small sample size, lack of data on potential confounders, poor elaboration and investigation regarding cirrhosis, effects of the level of cirrhosis on response rate, initial immune response of hepatocyte, role of IL28B on response rate, identification of S282T variant of the NS5B protein region which is the first identified sofosbuvir resistant variant (RAV) and drug level monitoring in non-responder regarding compliance are considered as the main limitations of this study.

And finally, it is now accepted worldwide with many trials, that sofosbuvir plus ribavirin is considered as a new hope for all hepatitis-C genotype-a infection, which was once considered as the most difficult to treat sub-genotype in this group. This is the only therapy, which can be given to all patients, with normal liver or patients with an advanced cirrhotic liver. Due to ideal response rate, acceptable adverse effects profile and cost effectiveness, it is now clear that sofosbuvir should be considered the first choice in all eligible cases, infected by HCV genotype-3 and its sub-types. However, large trial is needed to address role of age, sex, and genotype 3-subgroup, initial viral load and IL28B status in the response rate of HCV genotype 3a infections to Sofosbuvir based therapy.

CONCLUSION

It is now concluded that dual therapy including sofosbuvir and weight based ribavirin can be considered as an effective treatment in both treatment Naïve patients and all previously non-responder cases with chronic hepatitis-C genotype-3a infections in Pakistani population. Further study is suggested, both at national and international level for further confirmation and specification of this regimen for HCV genotype 3a infection.

Author's Contribution:

Concept & Design of Study:	Nizamuddin
Drafting:	Shafiq Ahmad Tariq
Data Analysis:	Sami Siraj, Waheed Iqbal
Revisiting Critically:	Shafiq Ahmad Tariq, Waheed Iqbal
Final Approval of version:	Nizamuddin

Conflict of Interest: The study has no conflict of interest to declare by any author.

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