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ORIGNAL ARTICLE

Prospective Study of the HCV-RNA Genotype 3a Diagnosed Patients Treated with Sofosbuvir and Peg Interferon Alpha-3

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1 Conception & Study design, Data Collection & Processing, Critical Review.
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5-7 Data Analysis and/or Interpretation.
3 Drafting of Manuscript.
4 Drafting of Manuscript, Critical Review.

Acknowledgement
We would like to acknowledge the following for their extensive support to our study:
1. Advanced Multiple Inc., 205-6660 Kennedy Rd Mississauga ON L5T2M9 Canada.
2.Rehman Lab and Diagnostics, 701-A Satellite Town, Sargodha 40100 Pakistan.
3.Arqam Laboratory, Ibn-e-Sina Hospital, Sargodha 40100 Pakistan.

Article info.
Received: April 06, 2021
Accepted: June 30, 2021

Funding Source: *Nil*
Conflict of Interest: *Nil*

Cite this article: *Nazir T, Taha N, Naveed S, Sadia H, Nazir SUR, Rehman A, Farooq M. Sultana M, Munir SS. Prospective Study of the HCV-RNA Genotype 3a Diagnosed Patients Treated with Sofosbuvir and Peg Interferon Alpha-3. RADS J Pharm Pharm Sci. 2021; 9(2):124-129.*

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ABSTRACT

Background: Hepatitis C Virus (HCV) is a global health emergency. Every year, thousands of individuals suffer from HCV. HCV if not treated, may manifest severe hepatic complications, many of which have fatal outcomes. Various therapeutic strategies are currently used to eradicate the virus from the patient's body. Treatment of the HCV patient depends largely on the genomic typing.

Objectives: The aim of the present study was to assess the comparison between Sofosbuvir and Peg-Interferon alpha in patients diagnosed with HCV RNA genotype 3a.

Methodology: A prospective case cohort study had been conducted in District Headquarter Hospital, Sargodha, Pakistan. Patients diagnosed with HCV genotype 3a were enrolled in the study and randomly divided into 2 groups. Group I was assigned Sofosbuvir 400 mg and group II Peg-Interferon alpha 3 million units. Both the groups were also administered ribavirin. The study was conducted for a period of 24 weeks and efficacy was determined by the decline in the viral RNA load.

Results: Each group had 50 patients of which majority were males. Compared to males, females had higher viral RNA load. However, the efficacy of both the treatment drugs was similar in both the genders. Comparatively, Sofosbuvir group showed better efficacy than Peg-Interferon group with significant difference in mean HCV RNA at the end of the study ($p < 0.05$).

Conclusion: Although, Sofosbuvir and PEG-Interferon both demonstrated efficacy in reducing the viral RNA load, Sofosbuvir is more efficacious and better tolerated in the management of HCV RNA genotype 3a infection.

Keywords: *Sofosbuvir, PEG Interferon alpha, HCV, genotype 3a.*

INTRODUCTION

Globally, the infections caused by Hepatitis C Virus (HCV) contributes a major portion in mortality induced by hepatic disorders [1]. HCV belonging to family Flaviviridae is a heptatropic virus having 7 distinct genotypes. With over 67 different subtypes geographically distributed variably, the treatment strategy for the HCV pathogen depends largely on the affected genotype. Owing to the variation in the nucleotide sequence of the genotypes and subtypes, each responds variably to the anti-HCV treatment [2-5].

Various studies have reported that genomic typing is beneficial in predicting the anti-viral response of the treatment. In addition, the clinical effectiveness of the anti-viral agents in HCV infection is associated with a number of factors involving both virus and host such as genotype of HCV, HCV RNA level and host IL28B genotype [6, 7].

The HCV therapy is now much more revolutionized than it was before, after the advent of Direct Acting Agents (DAAs). Previously, PEG-Interferon was the choice of agent in the management of HCV. But, the drug is associated with a number of side effects such as poor patient compliance, depression, cytopenia, etc. which limits its use in today's era of DAAs. Such adverse effects are seldom observed with the new generation of DAAs. Moreover, literature has reported that DAAs are much more efficacious than PEG-interferon based regimens in the management of HCV infection. However, the efficacy of the former in genotype 3 is not well reported. Additionally, not many direct comparisons of both the treatment options are reported in the management of HCV infection particularly of genotype 3 [8, 9].

In comparison to the other genotypes of HCV, genotype 3 is frequently associated with a higher rate of mortality and hepatic complications. Genotype 3 is more prevalent in the South East Asian countries. HCV prevalence in Pakistan is quite high. Genomic studies have revealed that HCV RNA genotype 3a is more prevalent in the HCV affected population in Pakistan [10, 11].

The present study has been conducted with an aim to compare a DAAs namely Sofosbuvir with PEG-interferon alpha in hepatic infections caused by HCV RNA genotype 3a.

METHODOLOGY

Study Design

A prospective cohort case study was conducted to assess the efficacy of Sofosbuvir and PEG-Interferon alpha in patients diagnosed with HCV RNA genotype 3a. The study had been investigated at District Headquarter Hospital, Sargodha, Pakistan, while, laboratory analysis were performed at Arqam Laboratory, Ibn-e-Sina Hospital, Sargodha, Pakistan and Rehman Diagnostic Labs, Sargodha, Pakistan. A total of 691 patients were screened to be enrolled in the study. Patients having age greater than 17 years and less than 70 years, screened positive for HCV RNA 3a and not on any heparin therapy were included in the study. Patients not fulfilling the criteria were excluded from the study.

Treatment Drugs

Patients enrolled in the study were randomly divided into 2 groups namely Group I and Group II. Group I was treated with per oral Sofosbuvir 400mg, once a day along with per oral Ribavirin 500mg, two times a day. Group II was treated with subcutaneous/intramuscular PEG-Interferon alpha 3 million units, administered 3 times a week with per oral Ribavirin 400 mg in the morning and 600 mg in evening. The study duration was 24 weeks/6 months.

Study Assessment

Efficacy was determined by the reduction in the HCV RNA load (IU/ml). The patients were screened prior to the start of the therapy and then at different intervals i.e. at week 4, 12 and 24 to evaluate the efficacy of the treatment drugs. The HCV RNA load was quantitatively analyzed using Real Time PCR technique.

Statistical Analysis

All the data was statistically evaluated using SPSS Version 20.0. Comparative analysis was performed using paired student t-test. All results were considered to be significant if p-value fall below 0.05.

RESULTS

Of the total 691 patients screened to be enrolled in the study, 100 patients were found to meet the requirement of the study. These 100 patients were randomly divided in to 2 groups, each comprising 50 patients. Demographic data of the Sofosbuvir revealed 62% (n=31) and 38% (n=19) females, while, 70% (n=35) were males and 30% (n=15) were females in the PEG-Interferon alpha group.

Gender wise, high HCV RNA was observed in the females as compared to males (Figure **1a** and **1b**). However, no statistically significant difference was observed in the efficacy of the treatment drugs in both the gender groups.

Rapid decline in the HCV RNA load was observed in the both the treatment groups. However, paired t-test revealed that initially there was no significant difference in the mean viral load (IU/ml) of both the groups, but, as the treatment continued over time, the mean viral RNA load of the Sofosbuvir group was significantly lowered than that of PEG-Interferon group ($p < 0.05$) at the week 12 and 24 respectively (Figure **2**).

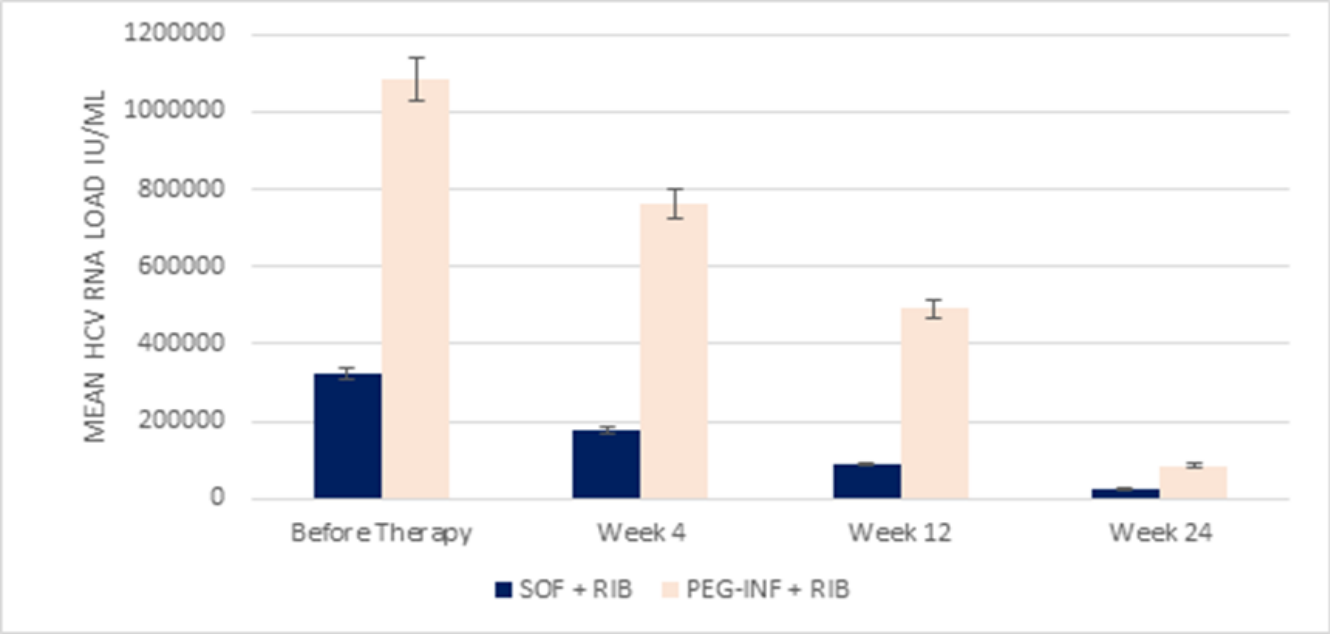

Figure 1a. Efficacy of the treatment drugs in female patients.

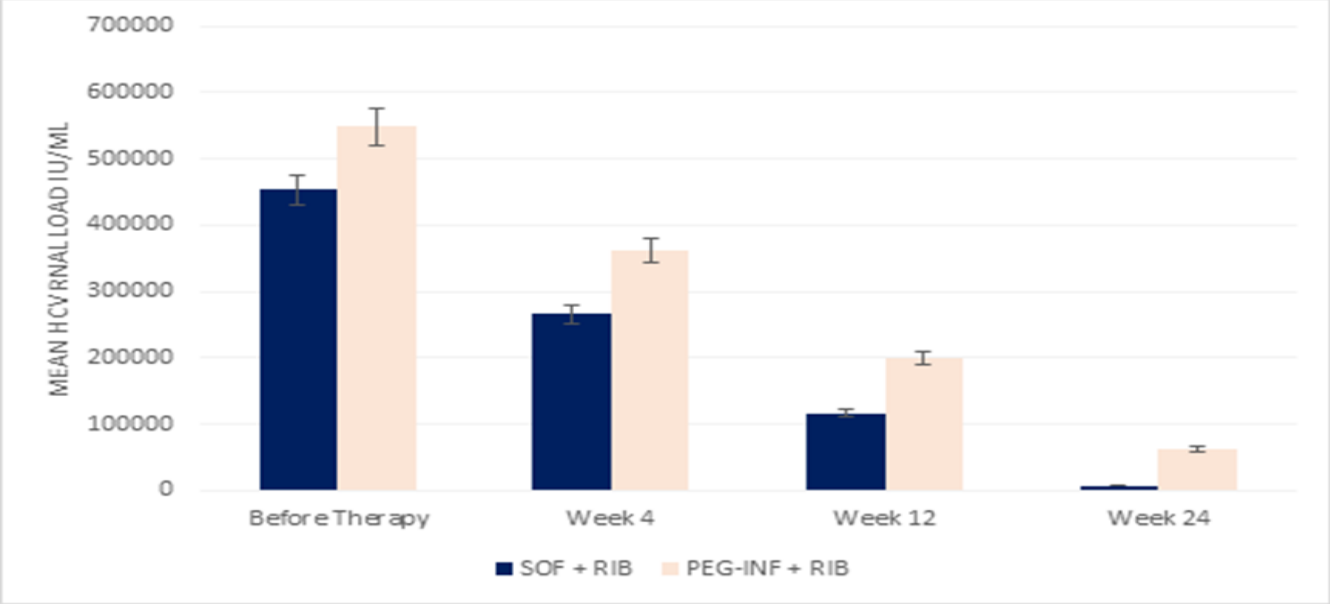

Figure 1b. Efficacy of treatment drugs in male patients.

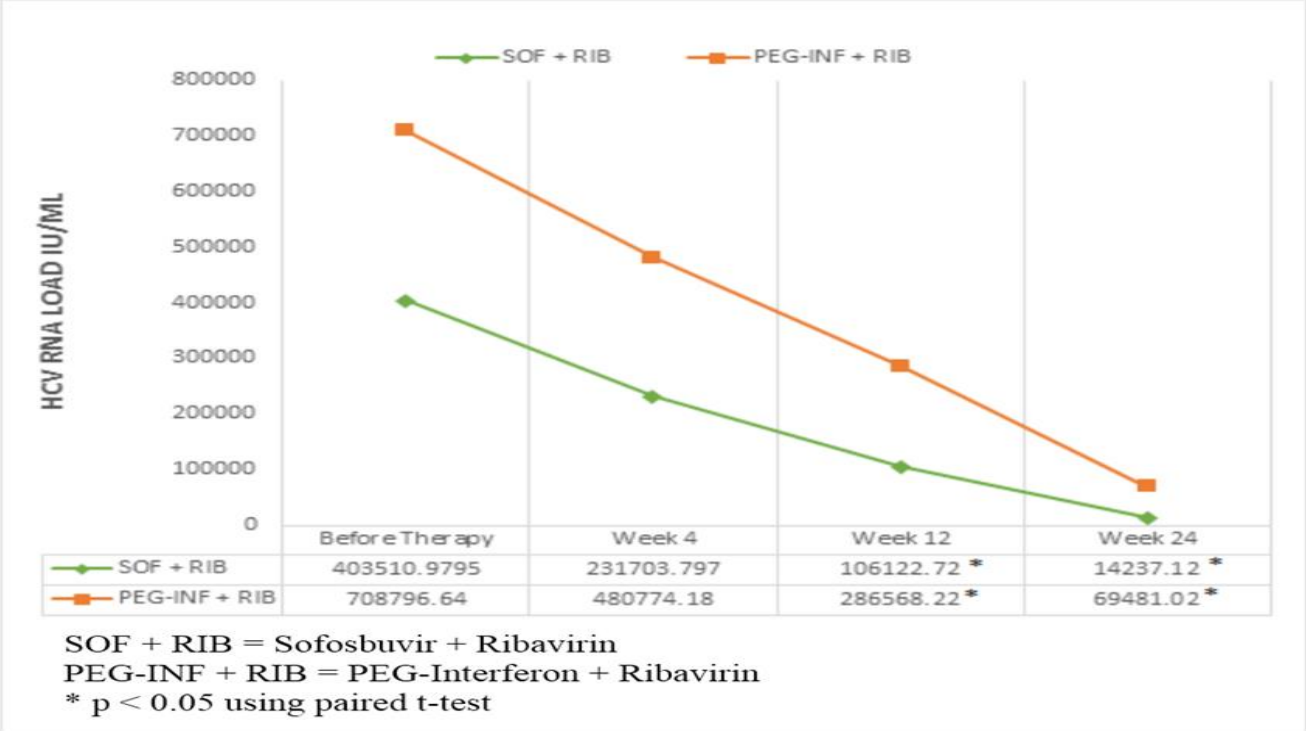

Figure 2. Efficacy of SOF+RIB and PEG-INF+RIB IN HCV RNA genotype 3a.

DISCUSSION

More than 170 million individuals are infected by the HCV globally. The disease commonly manifests as an acute infection, which, in majority of the cases progress to chronic infection leading to a variety of hepatic complications including hepatocellular carcinoma. Currently, HCV accounts for the major reason behind the hepatic transplantation around the globe [12, 13].

Various therapeutic strategies have been evolved since the discovery of the HCV in 1989. Treatment regimens having improved efficacy in terms of excellent SVR and less side effects are the main stay for the HCV infection treatment.

Initially, interferon based regimens were the first agents of choice in the management of the infection. These regimens exerts its anti-HCV action by suppressing the RNA cycle of the HCV directly as well as indirectly having spectrum of activity in all the HCV genotypes. The approved use of PEG-Interferon alpha was a major breakthrough in the advancement of HCV management at the start of the millennium. The compliant dosing guidelines and better efficacy than the non-pegylated interferon based regimens, made it a drug of choice for the pharmacotherapy of HCV infection. The PEG-Interferon based regimens ruled until the advent of DAAs in the early 2011 [9].

Regimens comprising of DAAs are highly effective treatment option for HCV infection owing to few side effects, shorter duration of therapy as well as low pill burden in compared to the previously used regimens. One such DAAs, Sofosbuvir has similar spectrum of efficacy to that of PEG-interferon but with fewer side effects and improved patient compliance. The drug acts by inhibiting HCV NS5B polymerase. Moreover, it offers the advantage of high barrier to resistance and excellent safety profile.

Seo *et.al*, 2017 has reported the comparative efficacy of Sofosbuvir/ribavirin to PEG-interferon/ribavirin in HCV infection of genotype 2. The study was conducted for a period of 3 months and efficacy was determined by sustained virological response and decline in the hepatic markers for hepatic complications. Sofosbuvir/ribavirin in comparison to PEG-interferon significantly achieved a good SVR. Additionally, improvement in hepatic function was also observed in the Sofosbuvir treated group [14].

Another study has reported the comparative analysis of interferon free regimens with that of PEG-Interferon based regimens. Pearlman et.al reports that a regimen of Sofosbuvir with Simeprevir is more efficacious than PEG-interferon, Ribavirin and Sofosbuvir in a 4 month study. Higher SVR and tolerability was achieved with the former, while side effects and low quality of life scores were observed with the latter. The study was conducted in HCV patients with genotype 1a [15].

Lawtiz *et.al*, 2013 reports the efficacy of the combination regime of Sofosbuvir plus Peg-Interferon in treatment naïve patients for a period of 3 months. The study was peformed in HCV patients having genotypes 1, 4, 5 and 6, with predominantly genotype 1. The study demonstrated a good SVR of more than 90% was observed at the end of the therapy. The study also reports a non-inferiority trial in which patients were randomly assigned to either Sofosbuvir regimen for a 3 month period or a Peg-Interferon regime for a 6 month period having HCV RNA 2 or 3. The results of the inferiority trial revealed that Sofosbuvir was better tolerated than Peg-Interferon. However, similar SVR was observed with both the treatment regimens [16].

The results of our investigation were consistent with the previous findings. Though reduction in viral RNA load was evident in both the groups, Sofosbuvir comparatively was found to be more efficacious in reducing the viral RNA load. More than 96% reduction was observed in the viral RNA load in Sofosbuvir treated patients compared to patients treated with PEG-Interferon alpha where 90% reduction was observed.

CONCLUSION

Not much comparative studies between Sofosbuvir and PEG-Interferon have been reported. Few comparative studies have been reported the comparative management of HCV infection predominantly of the genotype 1 and 2 by both the drugs. The findings of our investigation suggest that PEG-Interferon alpha and Sofosbuvir, along with ribavirin are efficient in reducing the viral RNA load in HCV management of the genotype 3a when administered for a period of 6 months. However, in comparison to PEG-Interferon, Sofosbuvir is more effective and better tolerated.

REFERENCES

1. Lauer GM, Walker BD. Hepatitis C virus infection. New England journal of medicine. 2001;345(1):41-52.
2. Raza A, Ovais M, Aziz H, Anwar A, Irfan J, Ahmad I, *et al*. Evaluation of Temporal Virological Responses to Interferon-α-2b plus Ribavirin among Genotype 3a Hepatitis C Virus-Infected Patients. Intervirology. 2017;60(3):75-81.
3. 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.
4. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. Journal of hepatology. 2014;61(1):S45-S57.
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. Shahnazarian V, Ramai D, Reddy M, Mohanty S. Hepatitis C virus genotype 3: clinical features, current and emerging viral inhibitors, future challenges. Annals of gastroenterology. 2018;31(5):541.
7. Sarin SK, Kumar CK. Treatment of patients with genotype 3 chronic hepatitis C-current and future therapies. Liver International. 2012;32:141-5.
8. Berden FA, Aaldering BR, Groenewoud H, IntHout J, Kievit W, Drenth JP. Identification of the best direct-acting antiviral regimen for patients with hepatitis C virus genotype 3 infection: a systematic review and network meta-analysis. Clinical Gastroenterology and Hepatology. 2017;15(3):349-59.
9. Panel A-IHG. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2018;67(10):1477.
10. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'hUigin C, *et al*. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009;461(7265):798-801.
11. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales Jr FL, *et al*. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. New England journal of medicine. 2002;347(13):975-82.

12. Cortez KJ, Kottilil S. Beyond interferon: rationale and prospects for newer treatment paradigms for chronic hepatitis C. Ther Adv Chronic Dis. 2015;6(1):4-14.
13. Salmon-Ceron D, Rosenthal E, Lewden C, Bouteloup V, May T, Burty C, *et al*. Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV-infected patients: The French national Mortalite 2005 study. Journal of hepatology. 2009;50(4):736-45.
14. Seo K, Kim SK, Kim SR, Ohtani A, Kobayashi M, Kato A, *et al*. Comparison of Sofosbuvir Plus Ribavirin Treatment with Pegylated Interferon Plus Ribavirin Treatment for Chronic Hepatitis C Genotype 2. Dig Dis. 2017;35(6):541-7.
15. Pearlman BL, Ehleben C, Perrys M. The Combination of Simeprevir and Sofosbuvir Is More Effective Than That of Peginterferon, Ribavirin, and Sofosbuvir for Patients With Hepatitis C–Related Child's Class A Cirrhosis. Gastroenterology. 2015;148(4):762-70.e2.
16. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, *et al*. Sofosbuvir for previously untreated chronic hepatitis C infection. New England journal of medicine. 2013;368(20):1878-87.