Original Article

Effect of Triple Therapy with Sofosbuvir in Hep.-C

Outcome of 12-weeks Triple Therapy (TT), including Sofosbuvir (SOF), Ribavirin and Pegylated interferon-Alfa in all non-cirrhotic patients with chronic Hepatitis-C Genotype-3 infection

Nizamuddin[1], Ayesha Jamil[1], Muhammad Riaz[1], Waheed Iqbal[2], Fazal Rahim[1] and Hasan Raza[3]

ABSTRACT

Objective: The treatment of hepatitis C virus (HCV) infection is rapidly evolving from interferon and ribavirin which is the standard of care (SOC) for genotype 3-infection, to the most effective Triple therapy by adding Sofosbuvir to the SOC regimen. We assessed the efficacy of Sofosbuvir based triple therapy in new and previously non-responder patients with Hepatitis-C Genotype-3 infection, the most common genotype infecting Pakistani community.

Study Design: Prospective / multi-center study

Place and Duration of Study: This study was conducted at the Pharmacology Department, Khyber Girls Medical College, Peshawar Pakistan from October 2015 to April 2016.

Materials and Methods: We recruited a total of 75 patients and were assigned into three groups (Group A, B, C). Group-A as treatment naive, group-B as non-responder to conventional interferon plus Ribavirin and group-C as non-responder to peg-interferon and ribavirin. Sofosbuvir based triple therapy was given for 12-weeks. The primary end point was Sustained Virological Response12 (SVR12), which is HCV-RNA level<40IU/ml at 12weeks after completion of therapy.

Results: Among75 patients, male-female ratio was n=51and n=24respectively.Each group has25-cases. Rate of SVR12 was 100%(n=25/25) in group-A, 92%(n=23/25) in group-B and 88%(=22/25) in group-C.

Conclusion: Our findings suggest that addition of sofosbuvir to the standard therapy results in the better achievement of SVR in new and previously non-responder cases with Chronic Hepatitis-C genotype-3 infections.

Key Words: Chronic hepatitis-C, triple therapy, Sofosbuvir.

Citation of articles: Nizamuddin, Jamil A, Riaz M, Iqbal W, Rahim F, Raza H. Outcome of 12-weeks Triple Therapy (TT), including Sofosbuvir (SOF), Ribavirin and Pegylated interferon-Alfa in all non-cirrhotic patients with chronic Hepatitis-C Genotype-3 infection. Med Forum 2017;28(7):40-43.

INTRODUCTION

Infection due to hepatitis C virus is world-wide health issuewith a global prevalence of 2.2%, affecting almost 130 million people worldwide[1]. Due to implementation of extensive screening measures before blood transfusion, surgery, organs transplantation and overall improved health and hygiene practices, incidence of new cases is experiencing a downward trend in developed nations. But developing countries face different impediments, like low literacy level, paucity of health care services and poor health and hygiene practices, in achieving a similar milestones. New cases usually come to the surface when they are diagnosed during routine screening or when they present with advanced complication of cirrhosis. It has got substantial impact on morbidity, mortality and utilization of health budget[2].There are several factors that determine the success of HCV antiviral therapy and progression of the disease to complications like cirrhosis and Hepatocellular Carcinoma (HCC). Among those high base-line viral load is the most notable ones[3]. Therefore, aggressive treatment is needed to achieve Sustained Virological Response (SVR), which is the only surrogate outcome in the treatment of Chronic Hepatitis C (CHC). In these Patients, SVR shows total clearance of virus and thus decrease risk of cirrhosis and HCC[3]. In last decade, the treatment strategy for Chronic Hepatitis C (CHC) is rapidly evolving from conventional interferon plus weight based ribavirin to Pegylated-Interferon plus weight based ribavirin as dual therapy (DT) and now to highly effective Triple therapy

1. Department of Pharmacology, Khyber Girls MC, Peshawar
2. Department of Pharmacology, Khyber MC, Peshawar
3. Department of Pathology, Rehman, Medical Institute, Peshawar

Correspondence: Waheed Iqbal, Department of Pharmacology, Khyber Medical University, Peshawar.
Contact No: 0300-5909433
Email: waheediqbal22@gmail.com

Received: May 01, 2017; Accepted: June 03, 2017

(TT) including Pegylated-Interferon-Alfa, Ribavirin and Nucleotide analogue NS5B HCV RNA dependent RNA polymerase inhibitor, Sofosbuvir. The TT boasts higher efficacy, cost-effectively, shorter treatment duration and a much more agreeable adverse effects profile. However, there is still little clinical data available from other countries, especially the ones with higher hepatitis C prevalence. A simple example of discordance among different cohorts is recently reported on genotype 2 in Germany[4]. Furthermore, it is important to realize that factor such cirrhosis, age, gender, baseline viral load, viral genotype, certain IL28b SNP genotypes[5,6] seem to greatly reduce the effect of antiviral therapy.

MATERIALS AND METHODS

The present study was mainly centered on patients visiting different public and private hospitals in Peshawar District of Pakistan. Total duration of study was seven months, from October 2015 to April 2016. Total 75 patients were selected, having chronic Hepatitis C genotype 3 infections. Patients were distributed into three groups (1:1:1) including group A as new, group B as non-responder to DT including Conventional interferon plus ribavirin and group C as non-responder to DT including Pegylated-interferon plus ribavirin. Patients with cirrhosis, Chronic Liver disease due to other causes and Concomitant Hepatitis B or HIV infections were excluded from the study. Due to fear of poor compliance and tolerability, patient with advanced renal, cardiac diseases and cognitive dysfunctions were excluded from the study. All these patients were put on triple therapy (TT) including Sofosbuvir, Pegylated-interferon-Alfa plus ribavirin for 12 weeks. Polymerase Chain Reaction (PCR) for HCV was done after twelve week of the completion of therapy and was labeled as SVR12. The open labeled, prospective design was used in the study.

Data Collection: Ethical approval for the study was sought from ethical committee of Khyber Teaching Hospital Peshawar, and informed consent was obtained from the patients prior to their enrollment. A total 75 patients with Chronic Hepatitis C genotype 3 infections were included in the study, according to the predefined inclusion/exclusion criteria. The demographic information of the subjects such as names, age and gender were recorded. All collected informations were recorded on pre-designed Proforma. Patients' blood samples were collected before starting the TT regimen, at 1 month and at 3-months after the start of therapy. Viral RNA was extracted and reverse transcribed to cDNA using Viral RNA extraction and cDNA synthesis kit (Qiagen; USA), respectively. HCV-RNA-PCR, genotyping and SVR12 were done with Qaigen kit, using Rotorgen 6000 Molecular System, having Lower limit of quantification (LLOQ)<40IU/ml.

Data Analysis: Data was entered in Microsoft Office Excel 2007 and analyzed, by using SPSSversion 20.0. The data was expressed as mean percentage and presented in tabulated form.

RESULTS

Out of total 75 studied patients, 68%(n=51) were male and 32%(n=24) were female, with mean age of 38±1.26 years. Age distribution among 75 patients was analyzed as n=18 (24%) patients were in age group of 21-30 years, n=21 (28%) patients were in age group of 31-40 years, n=24 (32%) patients were in age group of 41-50 years, n=9 (12%) patients were in age group of 51-60 years and n=3 (4%) patients were above 60 years of age as shown in Table1.

Status of SVR12 among 75 patients was analyzed in all three groups. In group A, n=25/25 (100%) patients have achieved SVR12, in-group B, n= 23/25 (92%) patients have achieved SVR12, while in-group C, n=22/25 (88%) patients have achieved SVR12 as shown in Table 2.

Status of response in different sub-genotype of Genotype 3 among 75 patients was analyzed in all 3 groups, which show 96.15%(n=50/52) response rate in simple genotype 3 and 86.95%(n=20/23) response rate in genotype 3a. There was no genotype 3b case in the study population. There were 2 cases with genotype 3 and 3-cases of genotype 3a, which have not responded to TT as shown in table 3.

IL28B was done in all those cases that have not responded to TT. Only n=1/5(20%) cases were with favorable CC (IL28B-rs12979860-CC) genotyping while n=4/5(80%) cases have unfavorable non-CC (IL28B-rs12979860non-CC)genotyping.

In these non-responder patients 4(80%) patients were male, 1(20%) patient was female and all of them were definitely non-cirrhotic.

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

Age	Total number of patients	Percentage
21-30 Years	18	24%
31-40 Years	21	28%
41-50 Years	24	32%
51-60 Years	09	12%
> 60 Years	03	04%
Total	75	100%

Table. No.2: SVR 12 observations in different studied groups

Groups	Observed SVR12	Percentage
Group A	25/25	100%
Group B	23/25	92%
Group C	22/25	88%

Table No.3: SVR12 status in Sub-genotype of genotype 3 in different studied groups

Groups	Genotype 3	Genotype 3a	Genotype 3b
Group A	17/17	08/08	00/00
Group B	18/19	05/06	00/00
Group C	15/16	07/09	00/00
Percentage (%)	96.15% (n=50/52)	86.95%(n =20/23)	0%

Table No.4: Sub-genotyping Status of IL28B in non-responders cases to TT

Status of IL28B	Group A	Group B	Group C	Total
IL28B-rs12979860-CC genotyping	0	0/5	01/5	20% (n=1/5)
IL28B-rs12979860non-CC genotyping	0	02/5	02/5	80% (n=4/5)

Table No.5: Over all data of responders and non-responder

Groups	No. of total cases	Genotype 3	Genotype 3a	Genotype 3b	Male	Female	No. Of responder to TT	No. Of non-responder to TT	Status of IL-28b in non-responder	
Group A	25	18	7	0	17/17	8/8	25/25	N= 00/25	CC=00	Non CC=00
Group B	25	16	9	0	11/13	12/12	23/25	N= 02/25	CC=00	Non CC=02
Group C	25	14	11	0	12/14	10/11	21/25	N= 04/25	CC=01	Non CC=02

DISCUSSION

Chronic Hepatitis C is a global problem and the paradigm shift of treatment from interferon based therapy to direct acting anti-viral therapy has totally changed the direction of research around the globe. One of the option in current guidelines, adopted by European Association for the Study of Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) for the treatment of Chronic HCV genotype 3 infection is 12 weeks triple therapy, including Sofosbuvir, peg-interferon Alfa and ribavirin[7]. These new weapon in the therapeutic armamentarium against Hepatitis C has given new option to the clinician to use it liberally and at the same time, a pleasant and affordable choice for both cirrhotic and non-cirrhotic patients". In our present study, "100% patients response rate has been observed to TT in case of newly diagnosed cases, 92% response rate in case of previously non-responder to conventional interferon plus ribavirin, while 84% response rate in case of previously non-responder to peg-interferon and ribavirin". These finding are close to the finding of many clinical trials by Gilead Sciences, which show 100% SVR12 and SVR24 in all new cases with genotype 3, treated with triple therapy including Sofosbuvir, pegylated-interferon and ribavirin for 8 weeks[8,9].

Triple therapy is for short time and can be considered safe, tolerable and effective both in cirrhotic and non-cirrhotic patients. This has been confirmed by LONESTAR-2 trials using a small cohort and show, that SVR12 rate in new patients treated with triple therapy was 83%.They also concluded, that there is no difference in the response rate in both cirrhotic and non-cirrhotic patients.[10]

Present findings of our study are generally consistent with another prior study conducted by " by Graham R. Foster et al[11]. They reported that in patients with HCV-genotype 3 infection, SVR12 rate is 93% in those who received Sofosbuvir, pegylated-interferon and ribavirin for 12 weeks." Other shared findings include role of IL28B non-rs12979860-CC genotyping, male sex and cirrhosis in treatment response to Sofosbuvir based regimen. However small sample size is a limitation of the present study.

The most common adverse effect observed in our study were, aches and pains, flue like symptoms and insomnia, but due to short period of therapy and mild nature of all these adverse effects, none of the patient discontinue the treatment".

And finally, it is now accepted world wide with many trials, "that short term treatment with TT is a new hope for all hepatitis C genotype 3 infected patients and should be considered the first choice in all eligible cases". However, large trial is needed to address role of age, sex, genotype 3-subgroup, initial viral load and IL28B status in the response rate of HCV genotype 3 infections to TT.

CONCLUSION

Triple therapy is the most effective treatment in both new and previously non-responder cases with Chronic Hepatitis C genotype 3 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 3 infection.

Author's Contribution:

Concept & Design of Study:	Nizamuddin
Drafting:	Hasan Raza
Data Analysis:	Ayesha Jamil Muhammad Riaz
Revisiting Critically:	Waheed Iqbal
Final Approval of version:	Nizamuddin

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

REFERENCES

1. Ward J. The hidden epidemic of hepatitis C virus infection in the United States: occult transmission and burden of disease. Topics Antiviral Med 2012;21(1):15-9.
2. Vietri J, Prajapati G, El Khoury AC. The burden of hepatitis C in Europe from the patients' perspective: a survey in 5 countries. BMC gastroenterol 2013;13:16.
3. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461(7262):399-401.
4. Tacke F, Gunther R, Buggisch P, Klinker H, Schober A, John C, et al. Treatment of HCV genotype 2 with sofosbuvir and ribavirin results in lower SVR rates in real life than expected from clinical trials. Liver Int 2017; 37(2).
5. Esposito I, Trinks J, Soriano V. Hepatitis C virus resistance to the new direct-acting antivirals. Expert opinion on drug metabolism & toxicology 2016;12(10):1-13.
6. Aqel BA, Pungpapong S, Leise M, Werner KT, Chervenak AE, Watt KD, et al. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 in patients with cirrhosis. Hepatol 2015;62(4): 1004-12.
7. Gutierrez JA, Lawitz EJ, Poordad F. Interferon-free, direct-acting antiviral therapy for chronic hepatitis C. J viral hepatitis. 2015;22(11): 861-70.
8. Lawitz E, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, et al. Sofosbuvir in combination with pegylated-interferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. Lancet Infec Dis 2013;13(5):401-8.
9. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3. New Eng J Med 2014;370(21):1993-2001.
10. Lawitz E, Poordad F, Brainard DM, Hyland RH, An D, Dvory-Sobol H, et al. Sofosbuvir with pegylated-interferon Alfa and ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. Hepatol 2015;61(3):769-75.
11. Foster GR, Pianko S, Brown A, Forton D, Nahass RG, George J, et al. Efficacy of sofosbuvir plus ribavirin with or without pegylated-interferon-Alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. Gastroenterol 2015; 149(6): 1462-70