EFFICACY AND SENSITIVITY OF THE PEG INTERFERON ALPHA-3 MILLION UNITS AGAINST HCV-RNA GENOTYPE 3A GIVEN TO THE CONFIRMED OF NEW AND RELAPSED HUMAN PATIENTS.

Nida Taha[1], Taha Nazir[2], Safila Naveed[3], Halima Sadia[4], Misbah Sultana[5], Saeed Ur Rashid Nazir[6], Abdul Rehman[7], Rahat shamim[8]

ABSTRACT

Introduction: PEG-Interferon and ribavirin had been the mainstay for the treatment of infections caused by HCV. The use of them in the era of Direct Acting Agents might have been lessened but their efficacy in achieving a sustained virological response in clinical practice cannot be doubted. Objective: The goal of the present investigation is to evaluate the effectiveness and sensitivity of PEG-interferon alpha with ribavirin in naïve and relapsed cases of HCV infection with genotype 3a. **Methods:** A total of 50 HCV cases had been evaluated of which 64% (n=32) were treatment naïve cases while the remaining 36% (n=18) were relapsed cases. Both the cases were treated with 3 million units of PEG-Interferon alpha thrice per week administered subcutaneously/intramuscularly along with ribavirin 400 mg in the morning and 60 mg in the evening for a period of 6 months. **Results:** Efficacy and sensitivity of the treatment was analyzed by the decrease in viral load and virological response of the drug at different intervals i.e. week 4, 12 and 24 respectively. The mean viral load of all the enrolled cases significantly lowered at the end of therapy i.e. 708796.64 IU/ml to 69481.02 IU/ml. However, there was a significant difference ($p<0.05$) in the mean HCV RNA load at the end of therapy in both the cases. **Conclusion:** Due to unavailability and inappropriateness of the use of current therapies in the management of HCV infection, treatment regimens comprising PEG-interferon alpha could serve as a possible alternative with efficacy and sensitivity at the same time.

Keywords: Efficacy, Sensitivity, Peg Interferon, Alpha-3 Million, HCV-RNA Genotype 3a

How to cite this article: Taha N[1], Nazir T[2], Naveed S [3], Sadia H[4], Sultana M [5], Nazir S R[6], Rehman A[7], Shamim R[8.] **EFFICACY AND SENSITIVITY OF THE PEG INTERFERON ALPHA-3 MILLION UNITS AGAINST HCV-RNA GENOTYPE 3A GIVEN TO THE CONFIRMED OF NEW AND RELAPSED HUMAN PATIENTS.** JPUMHS 2020;10:04;23-26.

DOI: http://doi.org/10.46536/jpumhs/2020/10.02.252

1. Scientific Executive, Microbiology and Molecular Biology Research Group, Advanced Multiple Incorporation, Mississauga, ON, Canada.
2. C.E.O, Microbiology and Molecular Biology Research Group, Advanced Multiple Incorporation, Mississauga, ON, Canada.
3. Professor, Department of Pharmacy Practice, Jinnah University for Women, Karachi 74600 Pakistan.
4. Lecturer, Department of Pharmacy Practice, Jinnah University for Women, Karachi 74600 Pakistan.
5. Associate Professor, University College of Pharmacy, University of the Punjab, Lahore, Pakista
6. Assistant Professor, College of Pharmacy, University of Sargodha, Sargodha 40100 Pakistan.
7. Professor, Sargodha Medical College, University of Sargodha, Sargodha 40100 Pakistan.
8. Assistant Professor, University College of Pharmacy, University of the Punjab, Lahore, Pakistan

Corresponding Author: Halima Sadia**,** Faculty of Pharmacy, Jinnah University for Women, 5C Nazimabad, Karachi 74600 Pakistan.**.** halimasadia093@gmail.com

INTRODUCTION

Hepatitis C virus (HCV) is a leading cause of liver disease induced mortality worldwide. The progression of HCV virus to cirrhosis, chronic hepatitis and hepatocellular carcinoma eventually contributes to its high mortality [1, 2]. Despite of the numerous efforts to decrease the global incidence of HCV, mortality associated with HCV infection is expected to increase over the next twenty years [3].

The global rise in the cases of HCV infection is attributed to the variability in the genomic sequence of the pathogen. 7 genotypes with more than 60 subtypes have been discovered responsible for causing the pathologic sequeale of the HCV infection [4].

The primary goal for the management of HCV infection is complete eradication of virus from the host body which is achieved by the sustained virologic response (SVR). The desirable SVR is usually achieved in a time span of 3 to 6 months. The efficacy of pharmacological agents is attributed by a number of factors involving both host and virus such as host IL28B genotype, genotype of HCV and HCV RNA level. The combination use of PEG-Interferon alpha 2a along with ribavirin has been a long stay of the HCV infection treatment. However, with the advent of Direct Acting Agents (DAAs), the therapy of HCV infection has been revolutionized[5-7].

Despite of superior efficacy, adverse effects such as hematological adverse events, hypersensitivity reactions reported by telaprevir etc. and high costs associated with the DAAs therapy makes them unavailable where they are required the most. The availability of PEG-Interferon alpha

along with a good SVR property makes it a reliable option for the pharmacotherapy of infections caused by HCV[5].

Additionally, in long term outcomes, PEG-Interferon alpha based regimens have established efficacy with low incidence of hepatic complications. They are preferred agents in scenarios where there is difficult to treat genotype 3 and in population where safety of DAAs have not been validated yet[8, 9].

The present investigation is aimed to characterize the efficacy and sensitivity of PEG-Interferon alpha in combination with ribavirin against naive and relapsed cases of HCV-3a, administered for a period of 24 weeks in routine clinical practice.

METHODOLOGY

A prospective case control study was conducted at District Headquarter Hospital, Sargodha, Pakistan to assess the effectiveness and sensitivity of PEG-Interferon alpha in patient affected by HCV genotype 3a. Cases were enrolled in the study on the basis of the criteria laid in table 1. Cases meeting the criteria were then segregated into treatment naïve and relapsed cases. Both the cases were treated with 3 million units of PEG-Interferon alpha thrice per week administered subcutaneously/intramuscularly along with ribavirin 400 mg in the morning and 60 mg in the evening. The cases were treated for a period of 6 months. Cases were initially screened for HCV RNA load prior to the therapy and then were subsequently screened at week 4, week 12 and at the end of therapy. Screening was performed by the Real Time PCR technique.

The data obtained from the cases was statistically interpreted using SPSS Version 20.0. One-way ANOVA was employed to assess the variability in means of new and relapsed cases. Results were considered to be significant if p-value was found to be less than 0.05.

Table 1: Requirements for enrollment in the study

Age greater than 17 years and less than 70 years
HCV RNA positive with genotype 3a
Previously treated or not treated with PEG-Interferon alpha therapy. Patients with no treatment were classified as new or naïve cases while those who were treated with the treatment drug, but again become infected were termed as relapsed cases
No active heparin therapy

RESULTS

Of the 50 patients analyzed, 64% (n=32) were treatment naïve cases while the remaining 36% (n=18) were relapsed cases. Demographically, 30% (n=15) were females and 70% (n=35) were males.

Our results revealed that compared to males, females have significantly higher viral RNA load (Figure 1). The viral RNA significantly decreased in both the genders with no noteworthy difference in the decline pattern.

Efficacy and sensitivity of the treatment was analyzed by the decrease in viral load and virological response of the drug at different intervals i.e. week 4, 12 and 24 respectively in both the cases. The drug significantly reduced the viral load in both the cases. However, the efficacy and sensitivity of the drug was found to more pronounce in the naïve cases as compared to the relapsed cases (Table 2).

In treatment naïve cases, rapid virological response assessed at week 4 was achieved with a reduction in 35% of the viral RNA load. Over the course of time, more than 65% and 94% viral RNA was found to be reduced at week 12 and week 24 respectively. On the contrary, despite of reduction in viral RNA in relapsed cases, 85% reduction was observed at the end of the therapy in relapsed cases.

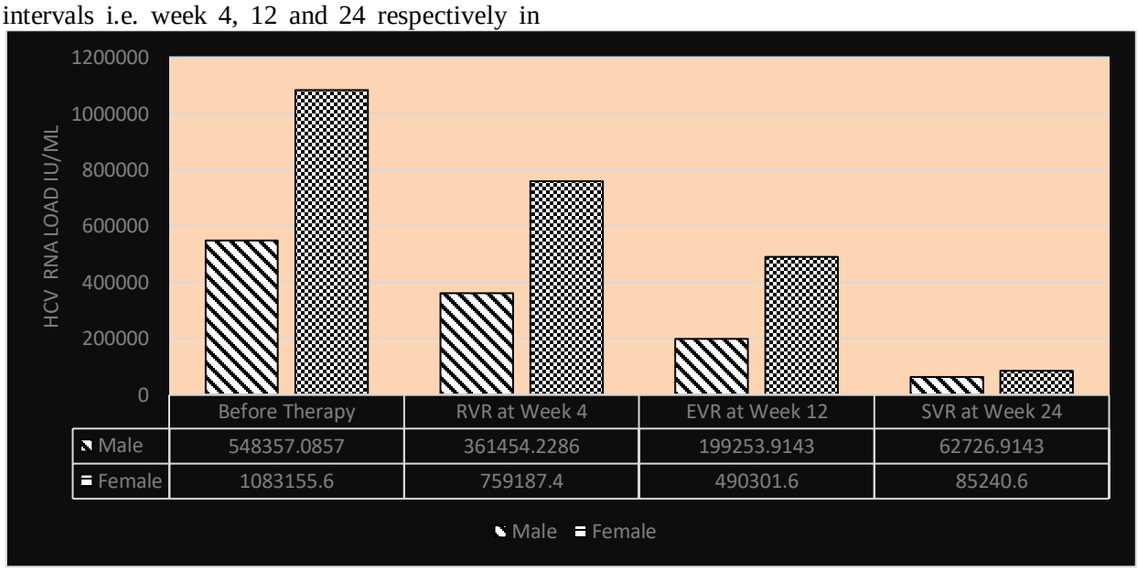

Figure 1: Efficacy and Sensitivity of PEG-Interferon in HCV RNA Genotype 3

Table 2: Efficacy and Sensitivity of PEG-Interferon alpha in new/naïve and relapsed cases of HCV RNA genotype 3a

HCV RNA Load IU/ml	Cases	
	New/Naïve cases (n=32)	Relapsed Cases (n=18)
Before Therapy	577499.53 ± 38776.90	942213.72 ± 379820.39
RVR at Week-4	359386.50 ± 35251.96	696574.50 ± 264423.49
EVR at Week-12	186988.96 ± 28273.95	463598.00 ± 188980.90
DVR at Week-24	31122.03 ± 17280.06 *	137674.77 ± 43026.02*

* $p < 0.05$ using one-way ANOVA
# Results are expressed as Mean ± Standard Error

DISCUSSION

It has been more than 30 years since the HCV has been discovered. Various studies have reported that majority of the acute HCV infections proceed to chronic infection, eventually posing the suffered individual at an increased risk of chronic liver complication including hepatocellular carcinoma which may lead to fatal outcomes[10] (). Infections due to HCV are a global health problem. The emergence of new efficacious treatment options such as Direct Acting Agents (DAAs) for HCV has led the cure of HCV much easier to achieve than it was in the past.

However, despite of the improved efficacy of the DAAs in providing high Sustained Virological Response (SVR) and a shorter course of treatment, the cost associated with these agents confer a significant economic burden on the patient. For example, Sofosbuvir, which is a DAAs exerting its anti-viral action by inhibiting nucleotide NS5B polymerase, a 12-week course of therapy costs around 84000 USD. A number of countries especially developing countries have constrained financial health care resources. The availability of these efficacious anti-HCV agents remains a big question to the suffered population [11, 12].

PEG-Interferon alpha in comparison to DAAs is a patient-pocket friendly option and at the same time efficacious. Zeuzem et.al has reported the efficacy of PEG-Interferon alpha 2b and ribavirin in HCV with genotype 1. The study was conducted for a time period of 24 weeks. Participants of the study were given 1.5 µg/kg of PEG-Interferon alpha 2b along with ribavirin 800-1200 mg. The results revealed that the viral RNA became negative at week 4 of the treatment while at the end of therapy i.e. 24 weeks, good SVR was observed [13].

Another study by Santantonio et.al reveals the effectiveness of PEG-Interferon alpha 2b in the management of acute HCV. Undetectable HCV RNA was found in majority of the patients at the end of 6 months therapy [14]

A comparative analysis of PEG-interferon alpha 2b with interferon alpha 2b also revealed the superior efficacy of PEG-interferon alpha 2b in terms of increased life expectancy, reduced hepatic complications and a cost-effective therapy in the initial management of HCV [15].

Yan et.al has reported the effectiveness of PEG-interferon alpha 2a plus ribavirin in the management of chronic HCV. The PEG interferon alpha 2a was treated at the dose 90µg/week for 6 months. The anti-HCV effect was equivalent to the 180µg/week dose of PEG-interferon alpha 2a. High early treatment response and good SVR was observed at the end of treatment [16].

Another study has reported that PEG-Interferon alpha 2a along with ribavirin significantly achieved SVR in more than 60% of the enrolled cases in a clinical setting. The study also reported that high SVR was observed in genotype 2 and 3. Moreover genome wide studies have validated that genotypes are strong predictors of the high SVR in PEG-Interferon based therapy. Asian populations have dominant IL28B genotype particularly in the South East Asian population which favors the high virological response in them when treated with PEG-Interferon based therapy[17-19].

In Pakistan, the prevalence of HCV infection is very high. Around 10,000,000 people had been affected by HCV by the start of 21st century where, the frail system of healthcare in Pakistan is one of the major reasons behind such a high number. Variable genomic studies have revealed high prevalence of genotype 3a in the HCV affected population in Pakistan[20].

The current investigation is based on analyzing the efficacy and sensitivity of PEG-Interferonalpha in HCV infection detected with the genotype 3a. Previous studies have reported the efficacy of PEG-Interferonalpha in achieving SVR by decreasing the viral RNA load. The findings of our investigation were consistent with the previous findings. PEG-Interferon alpha 3 million units significantly lowered the HCV RNA load. The sensitivity of the drug could be analyzed by the decline in the viral RNA from the 1st month of the therapy. Moreover, substantial decline in the HCVRNA over the course of therapy was observed pointing towards the efficacy and sensitivity of PEG-Interferon alpha in achieving a significant delayed viral response after 6 months of the therapy.

CONCLUSION

Current therapies in the management of HCV may be sometime inappropriate or unavailable for the patient. PEG-Interferon alpha had been an efficacious agent in the management of HCV. On the basis of our findings, PEG-Interferon alpha could serve as a possible substitute with efficacy

and sensitivity at the same time. Variable therapeutic strategies and regimens can successfully help to eradicate HCV associated morbidity and mortality in a real world setting.

ETHICS APPROVAL: The ERC gave ethical review approval

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin

FUNDING: The work was not financially supported by any organization. The entire expense was taken by the authors

ACKNOWLEDGEMENTS: We would like to thank the all contributors and staff and other persons for providing useful information.

AUTHORS' CONTRIBUTIONS: All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST: No competing interest declared.

REFERENCES

1. El-Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. Hepatology. 2002;36(5B):s74-s83.
2. Lauer GM, Walker BD. Hepatitis C virus infection. New England journal of medicine. 2001;345(1):41-52.
3. Ghany MG, Strader DB, Thomas DL, Seeff LB, Diseases AAftSoL. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology (Baltimore, Md). 2009;49(4):1335.
4. 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.
5. Mangia A, Foster GR, Berg CP, Curescu M, De Ledinghen V, Habersetzer F, et al. Efficacy and safety profile of boceprevir-or telaprevir-based triple therapy or dual peginterferon alfa-2a or alfa-2b plus ribavirin therapy in chronic hepatitis C: the real-world PegBase observational study. Annals of gastroenterology. 2017;30(3):327.
6. Omata M, Kanda T, Wei L, Yu M-L, Chuang W-L, Ibrahim A, et al. APASL consensus statements and recommendation on treatment of hepatitis C. Hepatology international. 2016;10(5):702-26.
7. Organization WH. Guidelines for the screening, care and treatment of persons with hepatitis C infection: World health organization; 2014.
8. Huang Y, Li M-H, Hou M, Xie Y. Peginterferon alfa-2a for the treatment of chronic hepatitis C in the era of direct-acting antivirals. Hepatobiliary & Pancreatic Diseases International. 2017 2017/10/15/;16(5):470-9.
9. Feuerstadt P, Bunim AL, Garcia H, Karlitz JJ, Massoumi H, Thosani AJ, et al. Effectiveness of hepatitis C treatment with pegylated interferon and ribavirin in urban minority patients. Hepatology. 2010;51(4):1137-43.
10. Lavanchy D. Evolving epidemiology of hepatitis C virus. Clinical Microbiology and Infection. 2011;17(2):107-15.
11. Andrieux-Meyer I, Cohn J, de Araújo ESA, Hamid SS. Disparity in market prices for hepatitis C virus direct-acting drugs. The Lancet Global Health. 2015;3(11):e676-e7.
12. Burstow NJ, Mohamed Z, Gomaa AI, Sonderup MW, Cook NA, Waked I, et al. Hepatitis C treatment: where are we now? International journal of general medicine. 2017;10:39.
13. Zeuzem S, Buti M, Ferenci P, Sperl J, Horsmans Y, Cianciara J, et al. Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. Journal of hepatology. 2006 2006/01/01/;44(1):97-103.
14. Santantonio T, Fasano M, Sinisi E, Guastadisegni A, Casalino C, Mazzola M, et al. Efficacy of a 24-week course of PEG-interferon α-2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance. Journal of hepatology. 2005;42(3):329-33.
15. Siebert U, Sroczynski G, Rossol S, Wasem J, Ravens-Sieberer U, Kurth B, et al. Cost effectiveness of peginterferon α-2b plus ribavirin versus interferon α-2b plus ribavirin for initial treatment of chronic hepatitis C. Gut. 2003;52(3):425-32.
16. Yan Z, Fan K, Wang X, Mao Q, Deng G, Wang Y. Efficacy and Safety of Low-Dose Peginterferon Alpha-2a Plus Ribavirin on Chronic Hepatitis C. Gastroenterology Research and Practice. 2012 2012/12/03;2012:302093.
17. 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.
18. Hadziyannis SJ, Sette H, Jr., Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med. 2004 Mar 2;140(5):346-55.
19. 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.
20. Akhtar S, Moatter T, Azam S, Rahbar M, Adil S. Prevalence and risk factors for intrafamilial transmission of hepatitis C virus in Karachi, Pakistan. Journal of Viral Hepatitis. 2002;9(4):309-14.