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EFFECT OF DIFFERENT FACTORS;
INTERFERON ALPHA PLUS RIBAVIRIN COMBINATION THERAPY

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ABSTRACT…Objectives: To determine the effect of different factors on the efficacy of treatment in Hepatitis C patients. **Study Design:** Descriptive, analytical study. **Setting:** Shalamar hospital Lahore. **Period:** October 2010 to May 2013. **Materials and Methods:** A total of 254 Hepatitis C patients infected with different genotypes of Hepatitis C virus (HCV) were treated with Interferon alpha 2b plus Ribavirin (IFNα-2b+RBV) for 6-12 months according to viral genotype. Before starting the treatment, the presence of HCV and its quantity in the patient was done by real-time PCR. HCV Genotyping was done by multiplex PCR. **Results:** The patients with <40 years of age or had less than 2 million international units per milliliter basic viral load (<2 MIU/ml) showed better end of therapy (EOT) and sustained virological response (SVR) than ≥40 years of age or ≥2 MIU/mL basic viral load. The response of males to Interferon therapy was better than females. The patients infected with HCV genotype 1 or 4 exhibited lower response than those infected with other than 1 or 4 genotype. The affect of other variables like alcohol, diabetes, hypertension, smoking, injection brand change or missing the injection during therapy were also remarkable in the present study. **Conclusions:** With proper management of the factors mentioned in the present study efficacy of the treatment can be improved.

Key words: Hepatitis C, Interferon plus Ribavirin, affect of different factors.

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INTRODUCTION

The FDA has approved two standard combinations of Interferon plus Ribavirin therapies for the treatment of HCV patients. In first combination, recombinant Interferon alpha (IFNα) is given with Ribavirin (RBV) also known as conventional Interferon (C-IFN) therapy. In second combination Pegylated Interferon alpha (pegIFNα) the advance form of Interferon is given with RBV[1-3].

Pegylated Interferon is more effective than conventional Interferon but still the C-IFN is the drug of choice for the treatment of Hepatitis C patients in underdeveloped countries including Pakistan[4,5]. Lower treatment cost of C-IFN than pegIFNα may be the cause of its preference to treat the Hepatitis C patients. Secondly the frequent type of HCV in Pakistan and other Asian countries is genotype 3 that shows better response to conventional Interferon therapy as compared to other HCV types[5,6]. The Society of Gastroenterology and GI Endoscopy has also recommended the use of C-IFN in Pakistan for the treatment of HCV genotype 3[5,7].

Viral, immunological or host associated factors affect the treatment response and influenced the viral clearance from the patient's body[8,9]. In host related factors, race, age, gender and patient's physical condition are believed to affect the rate of treatment response. Viral factors like viral genotype, viral load, co-infection with HIV and HBV have also been associated with the response to IFN therapy[10,11].

Because of limited and expensive therapy options and their severe side effects, proper management of the therapy to increase the response rate of the patient is very important. The knowledge of host or viral related and many other factors that affect the therapy efficacy may help in therapy management and to enhance the response rate. The goal of present study was to see the host or viral related and other factors which may affect the therapy response of Hepatitis C patients treated with IFNα-2b+RBV in Pakistan.

MATERIALS AND METHODS

Patient: Naïve 254 Hepatitis C patients (Not treated before with Interferon) infected with different HCV genotypes and 10-60 years of age (Mean=35±6) were included in this study. The patients belongsed to different areas of Punjab province and were treated at Shalamar hospital, Lahore. HCV RNA, viral genotype and viral load were done in all the anti-HCV positive (by ELISA) patients before starting the therapy.

Exclusion criteria: The patients with thrombocytopenia (less than 50,000 platelets per cubic millimeter), anemia (lower than 10g of hemoglobin per deciliter in women and lower than 11g per deciliter in men) were excluded from the study. All the patients who had decompensate liver disease and serum creatinine level more than 1.5 times the upper limit of normal level or co-infected with HIV or HBV were also excluded. The patients with poorly controlled psychiatric or diabetes disease were also not enrolled in the present study.

Treatment: All the patients were treated with recombinant Interferon alpha 2b (IFNα-2b) plus Ribavirin combination therapy. The duration of treatment was associated with viral genotype (6 months for HCV genotype 2 & 3 and 12 months for genotype 1 & 4). All the patients received 3MU recombinant IFNα-2b thrice a week plus Ribavirin. The dosage of Ribavirin was 1000 mg/day for the patients under or equal to 75kg body weight and 1200 mg/day for 75kg body weight patients.

Detection of HCV RNA and viral genotype

Qualitative and quantitative detection of HCV RNA in the Hepatitis C patient's blood was done by Real-time PCR technique. HCV RNA Real-time amplification kit (Robogene® HCV RNA qualitative and quantification kit: AJ ROBOSCREEN Germany) was used for the detection and quantification of the Hepatitis C virus. The detection limit of the kit was <100 IU/ml or <200 copies/ml. Before the amplification, HCV RNA was isolated from the patient's blood sample by column based, Roboscreen RNA isolation kit (Instant virus RNA kit: AJ Roboscreen Germany). HCV genotype was detected by multiplex PCR using the primers and protocol of previous study[12].

RESULTS

The patients with < 40 years of age had better end of therapy response (EOT) and sustained virological response (SVR) (EOT=77.97% and SVR=92.03%) than those with ≥40 years of age (EOT=61.04% and SVR=82.98%). Males had better EOT than females (75.81% Vs. 69.30%) but the SVR in males was lower than females (87.07% Vs. 90%). The patients infected with 1 or 4 HCV genotype had lower EOT and SVR than those infected with other than 1 or 4 HCV genotype (39.29% and 36.36% Vs. 73.23% and 83.45%). All the patients with <2 MIU/ml basic viral load showed better response (EOT=81.34% and SVR=91.74%) than those who had ≥2 MIU/mL basic viral load (EOT=64.17% and SVR=80.52%) (Table-I).

The percentage of non responders in both males and females was almost same who had previous diabetes, tuberculosis treatment or hypertension history i.e. 70.32%, 45.57%, and 50.65% in males and 75.23%, 50.26%, and 55.12% in females respectively. Almost the same situation was noted in alcoholic and smoker patients. Effect of incomplete rest during therapy was little bit higher in male non responders as compared to female, while the season effect was noted higher on treatment response in females than males i.e. 55.89% females and 45% males remained non responders who were treated in the winter. The patients who completed their therapy in winter or spring season showed better response than those who completed their therapy in winter season. Effect of injection brand change and delaying or missing the injection more than three times during the therapy was also associated with in both the genders.

Variables	EOT	SVR
Age(years) **<40** **≥40**	**77.97% (138/177)** **61.04% (47/77)**	**92.03% (127/138)** **82.98% (39/47)**
Gender Males Females	 75.81% (116/153) 69.30% (70/101)	 87.07% (101/116) 90% (63/70)
HCV genotypes Genotype 1 or 4 Other than 1 or 4 Genotype	 39.29% (22/56) 73.23% (145/198)	 36.36% (8/22) 83.45% (121/145)
Basic Viral load ≥2MIU/mL <2MIU/Ml	 64.17% (77/120) 81.34% (109/134)	 80.52% (62/77) 91.74% (100/109)

Table-I. Affect of different variables on virological response (n=254)

Variables	Percentage of non responders	
	Females	Males
Diabetic (Under control with medication)	75.23%	70.32%
Previous TB treatment history	50.26%	45.57%
Hypertension history (but under control with medication)	55.12%	50.65%
Alcoholic history (One year previous)	55.43%	45%
Smokers	42%	40.43%
Incomplete rest during therapy	50%	58.87%
Therapy in summer	55.89%	45%
Therapy in winter or spring	35.09%	30%
Injection brand change during the therapy	56.65%	58.08%
Dropped or delayed injection (more than three times)	59.03%.	64.60%

Table-II. Affect of host and environment variables on treatment response.

DISCUSSION

These days the standard treatment for Hepatitis C patient is the combination of Interferon (IFN) or Pegylated Interferon (PEG-IFN) plus Ribavirin. However, the success rate of this treatment is 40-80%[13]. Furthermore, the treatment is expensive and has massive financial burden for the patient. The rate of treatment success depends upon a number of virological (viral genotype, viral load), host (age, gender, race, physical condition of the patient) and other factors[11].

The patients infected with HCV genotype 2 or 3 demonstrated better response to Interferon therapy than those infected with genotype 1 or 4. Interestingly, in Pakistan most of the population is infected with HCV genotype 3[14,15]. As HCV genotypes 2 and 3 are more sensitive to Interferon therapy, with proper management we can reduce the disease burden in our region.

The impact of basic viral load on treatment response was significant in the present study. The patients with lower basic HCV viral load (<2 MIU/mL) revealed the better response than those who had ≥2 MIU/mL viral load. The relation of baseline viral load with Interferon therapy response has also been reported in several previous studies where the patients with lower baseline viral load were also more sensitive to Interferon therapy than patients with higher baseline viral load[17-22]. This indicates that viral load plays an imperative role in the treatment response and may also be used as treatment response predictor.

The response of Hepatitis C patients to therapy is not only viral factors dependent but also on host factors like age, gender and diseases like diabetes and depression[23-25]. In present study the affect of age and gender was significant. The patients under forty years of age exhibited better end of therapy (EOT) and sustained virological response (SVR) than those with equal to or above forty. That indicates that the treatment in younger patients gives better results than old age patients[23,24]. Regarding patients gender, the males were more sensitive to Interferon therapy than females. The impact of age and gender on treatment response may be because of weak immunity in aged groups that may not help them to wash out the virus from their body and the low potential to tolerate the Interferon therapy. In previous studies it has been indicated that the tolerance of Interferon therapy in male and younger patients is better than old and female patients[7,26,27].

The percentage of female non responders was

little higher than males who had previous diabetic, tuberculosis, and hypertension history. Nearly the same situation was noted in alcoholic and smoker patients. The similar findings were also reported in other studies[11,28]. During therapy the diabetes and hypertension were kept under control in all the patients with additional specific medication. Alcohol drinkers and smokers were under observation and counseling was done with them on a regular basis. In addition storage condition of IFN may also be less favorable in summer.

In previous studies mostly the virological, host and treatment related factors like viral load, genotype, age, gender and the effect of different antiviral drugs were commonly addressed as treatment response predictors. The effect of incomplete rest, season, injection brand change, and delay in injection on treatment efficacy was not highlighted previously. The effect of season on treatment response was noted high in the present study. Those who completed their therapy in winter or spring season were better responders than those who were treated in summer season. Season effect may be because in our study region the summer season is very hot and the temperature reached to 52^0C and it makes difficult to tolerate the treatment which has its own side effects. Hot season may also affect the immune system which may not work properly against the viral clearance from the patient's body in such unpleasant conditions.

Effect of injection brand change on treatment efficacy as noted in the present study may because of the concentration change in Interferon of different brands, which may affect the proper standard dosage. The effect of delaying or missing the injection more than three times during the therapy was also noted which may be because of re-increase of viral load in the patient's body during that period, as HCV replicates at an estimated rate 10^{12} virions per day[29,30].

CONCLUSIONS

Although some host and viral related factors like age and gender of the host; viral load and genotype of the virus are unchangeable, other factors like proper diet, complete rest during therapy, missing or delaying of the injection or changing the injection brand during therapy can be controlled. Moreover, proper control of hypertension, diabetes and abstinence from alcohol and smoking can also be controlled and modified to increase response rate with the modification of lifestyle. With proper management of these factors better response to interferon therapy could be achieved.

REFFRENCES

1. Sarasin-Filipowicz, J. Edward. Oakeley, H. T. Francois. Duong, V. Christen, L. Terracciano, W. Filipowicz, and M. H. Heim. 2008. **Interferon signaling and treatment outcome in chronic Hepatitis C.** PNAS. 105(19): 7034-39.

2. Hadziyannis SJ, Sette HJ, Morgan TR, Balan V, Diago M, Ackrill AM 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;140:346-55.

3. Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. **Early virologic response to treatment with pegInterferon alfa-2b plus Ribavirin in patients with chronic Hepatitis C.** Hepatology. 2003;38(3):645-52.

4. Hadziyannis SJ, Cheinquer H, Morgan T. **Peg Interferon alpha-2a (40 KD) in combination with Ribavirin efficacy and safety results from phase 3, randomized double blind, multicenter study examining effect of duration and Ribavirin dose.** J Hepatol. 2002;36(1): 3-14.

5. Karayiannis P. **The Hepatitis C virus NS3/4A protease complex interferes with pathways of the innate immune response.** J Hepatol. 2005;43:743-45.

6. Zuberi FB, Zuberi FF, Memon AS, Qureshi MH, Sheikh AZ, Salahuddin A. **Sustained virological response based on rapid virological response in genotype-3 chronic Hepatitis C treated with standard Interferon in the Pakistani population.** World J Gastroenterol. 2008;14(14): 2218-21.

7. Idrees M, Riazuddin S. 2009. **A study of best positive predictors for sustained virologic response to Interferon alpha plus Ribavirin therapy in naive chronic Hepatitis C patients.** BMC Gastroenterol. 9: 5-14.

8. de Careaga BO. **Hepatology Predictive factors for**

response to treatment of chronic Hepatitis C. Ann Hepatol. 2006;5(1):24-28.

9. Imran M, Manzoor S, Ashraf J, Khalid M, Tariq M, Khaliq HM, Azam S. **Role of viral and host factors in interferon based therapy of hepatitis C virus infection.** Virolo J. 2013;10:299.

10. Lehmann M, Meyer MF, Monazahian M, Tillmann HL, Manns MP, Wedemeyer H. **High rate of spontaneous clearance of acute Hepatitis C virus genotype 3 infection.** J Med Virol. 2004;73(3):387-91.

11. Asselah T, Estrabaud E, Bieche I, Lapalus M, Muynck SD, Marcellin P. **Hepatitis C: viral and host factors associated with non-response to pegylated Interferon plus Ribavirin.** Liver International. 2010;1:1259-69.

12. Ohno T, Mizokami M, WU RR, Saleh MG, Ohba K, Orito E, Mukaide M, Williams R, Lau JN. **New Hepatitis C virus (HCV) genotyping system that allows for identification of HCV genotypes 1a, 1b, 2a, 2b, 3a, 3b, 4, 5a, and 6a.** J Clin Micro. 1997;35(1):201-7.

13. Iqbal S, Dogar KR, Bashir MZ, Akhtar MS. **Sustained biochemical and virological response of different HCV genotypes to Interferon-alpha plus Ribavirin combination therapy.** Pharmacologyonline. 2010;2:161-69.

14. Iqbal S, Ahmad R, Yousaf MH, Mumtaz A, Amine D, Rasool G, Manzoor A. **Assessment of major genotypes and subtypes of Hepatitis C virus.** Prof Med J. 2007;14(2):266-71.

15. Idrees M, Riazuddin S. **Frequency distribution of Hepatitis C virus genotypes in different geographical regions of Pakistan and their possible routes of transmission.** BMC Infect Dis. 2008;8: 69-73.

16. Jensen DM, Morgan TR, Marcellin P, et al. **Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy.** Hepatology. 2006;43: 954-60.

17. Zeuzem S, Buti M, Ferenci P, 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.** J Hepatol 2006;44:97-103.

18. von Wagner M, Huber M, Berg T, et al. **Peginterferonalpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic Hepatitis C.** Gastroenterology. 2005; 129: 522-27.

19. Berg T, Sarrazin C, Herrmann E, et al. **Prediction of treatment outcome in patients with chronic Hepatitis C: significance of baseline parameters and viral dynamics during therapy.** Hepatology. 2003; 37: 600-9.

20. Martinot-Peignoux M, Boyer N, Pouteau M, et al. **Predictors of sustained response to alpha interferon therapy in chronic Hepatitis C.** J Hepatol 1998;29: 214-23.

21. Martinot-Peignoux M, Marcellin P, Pouteau M, et al. **Pretreatment serum Hepatitis C virus RNA levels and Hepatitis C virus genotype are the main and independent prognostic factors of sustained response to interferon alfa therapy in chronic Hepatitis C.** Hepatology 1995;22:1050-56.

22. Marcellin P, PouteauM,Martinot-PeignouxM, et al. **Lack of benefit of escalating dosage of interferon alfa in patients with chronic hepatitis C.** Gastroenterology 1995; 109:156-65.

23. Asselah T, Rubbia-Brandt L, Marcellin P, et al. **Steatosis in chronic Hepatitis C: why does it really matter?** Gut 2006; 55:123-30.

24. Moucari R, Asselah T, Cazals-Hatem D, et al. **Insulin resistance in chronic Hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis.** Gastroenterology 2008; 134:416-23.

25. Alvarez-Uria G, Day JN, Nasir AJ, et al. **Factors associated with treatment failure of patients with psychiatric diseases and injecting drug users in the treatment of genotype 2 or 3 Hepatitis C chronic infection.** Liver Int 2009;29:1051-55.

26. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, Goodman ZD. **Interferon alfa-2b alone or in combination with Ribavirin as initial treatment for chronic Hepatitis C.** Hepatitis Interventional Therapy Group. N Engl J Med. 1998;339:1485-92.

27. Poynard T. **Randomized trial of Interferon alpha-2b plus Ribavirin for 48 weeks versus Interferon alpha-2b plus Placebo for 48 weeks for the treatment of chronic Hepatitis-C.** Lancet. 1998;351:1426.

28. Franciscus A. **HCV Diagnostic Tools: Genotype and Quasispecies.** HCSP Fact Sheet. 2008;2 (2):1-3.

29. Herrmann E, Zeuzem S. **The kinetics of Hepatitis C virus.** Eur Gastroenterol Hepatol. 2006;18:339-42.

30. Tong X, Guo Z, Wright-Minogue J, Xia E, Prongay A, Madison V, Qiu PN, Venkatraman S, Velazquez F, Njoroge FG, Malcolm BA. **Impact of naturally occurring variants of HCV protease on the binding of different classes of protease inhibitors.** Biochemistry. 2006;7:1353-61.