THERAPY SUCCESS RATE WITH PEGYLATED INTERFERON/ RIBAVIRIN TREATMENT OF RELAPSE AND NON-RESPONDER HEPATITIS C PATIENTS

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ABSTRACT

Background: The combination therapy of Interferon and ribavirin remains the first line treatment in patients with chronic hepatitis C in Pakistan. Although success rate of 24-week long treatment in treatment naïve patients' genotype 3a is high, there are a few reports on retreatment of non-responder and relapse hepatitis C patients. This study was designed to assess the sustained virological response (SVR) rates in treatment-experienced patients who had unfavorable outcome from their previous therapy.

Methodology: One hundred and thirty two (132) patients who had shown relapse (n=59) and non-response (n=73) to conventional IFN plus ribavirin were retreat-ed with Pegylated IFN plus ribavirin. Outcomes at week 12(early virological response [EVR]) and at week 24 (End of response [SVR]) were analyzed.

Results: One hundred and thirty-two patients who had relapsed (n=59; 63% genotype 3a) after previous conventional interferon plus ribavirin therapy or were non-responders (n=73; 48% genotype 3a) were analyzed. Of the re-lapsers, 78% achieved an EVR and also the SVR. Of the non-responders, 81% achieved an EVR and also the SVR. SVR rates were 27% and 15% for genotype 3a and 2a respectively. EVR and low hepatitis C viral (HCV) RNA level on re-treatment were associated with SVR. SVR rate for relapse and non-response patients was nearly equal.

Conclusion: Low baseline and at four weeks after start of therapy re-main the most crucial predictors for treatment outcome in relapse and in non-responders. Viral genotype, on the other hand doesn't seem to affect the therapy outcome significantly.

Key words: Chronic Hepatitis C, Pegylated Interferon plus ribavirin, Retreatment, Relapse, Non-responders.

This article may be cited as: **Fateen F, Yousaf MN, Khan NU, Nouman F, Iqbal W, Siraj S. Therapy success rate with pegylated interferon/ribavirin treatment of relapse and non-responder hepatitis C patients. Adv Basic Med Sci. 2017; 1(1): 11-15.**

INTRODUCTION

HCV infection is among the most life threatening problem affecting about 8.6 million Pakistanis accord-ing to WHO. WHO has rated Pakistan as 2nd country in the world having high rates of chronic infection. In the urban and rural areas of Pakistan, the main risk factor for transmission is the use of contaminated medical equipment, which is mainly due to needless use of parenteral routes of drug administration. Pakistan is among the top syringe consuming country accounting for use of 2.4 billion syringes every year[1,2].

The current recommended treatment for patients with chronic Hepatitis C is the combination of pegylat-ed interferon and ribavirin (pegIFN/RBV)[3]. Probability of achieving a sustained virological response (SVR) by this recommended therapy in treatment naïve patient is beyond 50% depending upon hepatitis C virus gen-otype and other prognostic factors which have been

reported for therapeutic success[4-6]. Patients who did not achieve SVR after prior course of interferon/ribavirin treatment need a more aggressive treatment regimen[7].

Many factors can help predict the treatment success[8]. These include different patient factors like comorbidities including metabolic disorders, hepatic or renal insufficiency, age, gender, body mass index, menopause, the state of immune system and patient interleukin 28-B (IL28B) genotype. Low baseline viral loads and certain viral genotype[9] also have significance in predicting treatment response. It has become imperative for physicians to account for as many of these factors as possible, in order to institute a more effective personalized therapy. Such considerations help determine treatment plan for both treatment-naïve and treatment-experienced patient. Antiviral arsenal of Pakistani physicians treating chronic hepatitis C still relies heavily on conventional interferon/Ribavirin combination. However, some will opt to treat the patient more aggressively with pegIFN/RBV from day zero[10]. Treatment protocol is ever shifting to include the factors that affect the therapy outcome. This equation is further complicated with the addition of directly acting antivirals (DAAs) and especially Sofosbuvir (SOF: Sovaldi). It is however, imperative for physicians to embrace these new advents in a way that it is most accessible and beneficial for the patients. For example, SOF is branded a miracle drug which offers interferon-free total eradication of hepatitis C. However, SOF along with other DAAs comes with a price tag that is not for everyone[11]. Secondly, being a new drug, SOF doesn't exactly boast a multitude of data on safety and efficacy in different genotypes and populations as opposed to conventional or pegIFN/RBV. So it is all the more crucial for the doctors to carefully triage the patients keeping all these factors under consideration.

Treatment success rate of genotype 3a in Pakistan, vary between 68-85% in different reports[12]. This means that there is a considerable chunk of patients either relapsing or not responding to the standard antiviral treatment. There are but a few reports on the use of pegIFN/RBV for retreatment of patients who relapsed and/nonresponse after previous treatment with standard interferon plus ribavirin[13-15]. In the present study, we aim to report the efficacy of retreatment with pegIFNa-2a plus ribavirin in patients who had failed to respond to a first course of standard interferon plus ribavirin based treatment and to identify the factors associated with SVR in retreatment.

METHOD

Study design: This is a retrospective study conducted at Mufti Mahmood teaching hospital, Dera Ismail Khan. Patients' data was retrieved from the registry available at the offices of Hepatitis Control Program. Patients were registered during the years 2011 and 2012.

Inclusion and Exclusion Criteria: Patients who were not responsive or relapsed as reported on the basis of polymerase chains reaction (PCR) results, were included in the study. Patients above 50 years of age, having body mass index less than 18.5 & above 30, with hepatic cirrhosis, with underlying conditions that could alter disease presentation including metabolic disorders like thyroid dysfunction, diabetes mellitus, hepatic dysfunction and renal failure, were excluded from this study. Also the patients not complying with the standard anti-viral therapy for any reason and co-infected with HBV/HIV and/ or with alcohol consumption were excluded from the study. A total of 132 patients fit our designated criteria and were enrolled in the study.

Viral Genotyping: Extraction of RNA was done using Qiagen kit (Invitrogen, Corp., California; USA). Viral genotyping was done by means of the method used by Ohno et al16.

Quantification of HCV RNA: Blood samples (3 mL venous blood) were collected at pretreatment, at week 12 during treatment, and at week 24 of follow-up. The concentration of HCV RNA was determined using a quantitative RT-PCR assay (Cepheid SmartCycler® Realtime PCR). The assay was performed according to the manufacturer's instructions. The lower detection limit of the qualitative assay is 100 copies/mL. An early virological response (EVR) at week 12 was defined as undetectable HCV RNA by qualitative PCR, or a 2-log10 or greater reduction in HCV RNA relative to the baseline value by quantitative PCR. SVR was defined as undetectable HCV RNA (less than50 IU/mL) by qualitative PCR 24 weeks after administration of the last dose of pegIFNa-2a.

RESULTS

A total of 132 patients were recruited in the study and retreated with pegylated interferon alpha plus ribavirin. 72 patients were non-responders while 60 patients were with the previous history of relapse to standard interferon plus ribavirin treatment. The base line demographic characteristics of these patients are presented in Tables 1 and 2.

Patients with previous relapse to standard treatment: Overall, an EVR was achieved in 46 of 59 patients (78%). All patients achieve SVR. Responders of the previously relapse patients mostly were of geno-

Table 1: Association of Gender and response

	Previous Non-responders	Previous Relapse	Total no. of Patients	After Treatment Non-Responder group		After Treatment Relapse group	
				SVR +ve	SVR -ve	SVR +ve	SVR -ve
Male	50	45	95	41	9	35	10
Female	22	15	37	18	4	14	1
Total	72	60	132	59(82%)	14(18%)	46(82%)	13(18%)

Table 2: Relationship between age group and response

Age	Non-responders (27)	Responders (105)	Total no. of patients
19-29	6	20	26
30-40	6	32	38
41-50	15	53	68

Table 3: Re-treatment of previously Relapse patients

Genotype	Responders (46)	Non-Responders (13)	Total no. of Patients
1a	1/46(2.1%)	1/13(8%)	2/59(3.3%)
2a	6/46(15.2%)	2/13(15.3%)	8/59(13.5%)
3a	30/46(65%)	7/13(54%)	37/59(63%)
3b	8/46(17%)	3/13(23%)	11/59(18.6%)
Non-typable	-	-	-

Table 4: Retreatment of previously non-response Patients

Genotype	Responders	Non-responders	Total no. of patients
1a	4/59(6.7%)	1/14(7.1%)	5/73(6.8%)
2a	18/59(30%)	4/14(28.5%)	22/73(30%)
3a	29/59(49%)	6/14(43%)	35/73(48%)
3b	7/59(12%)	2/14(14%)	9/73(12%)
Non-typable	1/59(1.6%)	1/14(7%)	2/73(2.7%)

Table 5: Relationship between genotype and response

Genotype	Total Number	RVR%	EVR%	ETR%	SVR%
1a	7	-	3.7%	3.7%	3.7%
2a	30	-	15%	15%	15%
3a	72	-	27%	27%	27%
3b	20	-	7.5%	7.5%	7.5%
Un-typable	2	-	0.75%	0.75%	0.75%

Table 6: Relationship between viral load and response

HCV RNA viral load	No. of Patients	SVR%
<600,000	105(79%)	105(79%)
>800,000	20(15%)	-
600,000-800,000	7(5.3%)	-

type 3a. (Table 3, 5)

Patients with previous non-response to standard treatment: Overall, an EVR was achieved in 59 of 73 patients (81%).All of the patients with EVR achieved SVR. Responders of the previously non-response patients were mostly of genotype 3a. (Table 4, 5)

DISCUSSION

Although this study is retrospective in nature, the results of our analysis suggest that retreatment of chronic HCV patients with pegIFNa-2a plus ribavirin may be of worth in selected group of patients who have failed previous standard treatment of interfer-on plus ribavirin. The results show that the nature of the response to previous IFN-based therapy is very im-portant in predicting the outcome of retreatment. The results also identify groups in which retreatment with Pegylated IFN and ribavirin therapy may be of value and those in which it is not.

We analyzed that response rate of previous non-re-sponders patients were nearly equal to responders of relapse patients which conflicts the previous studies showing high number of responders in previously re-lapse patients (17-19).

In relapsers and non-responders, genotype did not appear to influence the likelihood of achieving SVR. It may be that after being exposed to the selection pressure of Pegylated IFN plus ribavirin therapy, this group responds more similarly than a diverse collec-tion of treatment-naive patients with a similar geno-type composition. This may be especially true of pre-vious non-responders. For example, a genotype 2 or 3 non-responder may be similar to a genotype 1 non-re-sponder (i.e., difficult to treat). If this hypothesis is correct, it suggests that genotype should not greatly influence the decision to retreat a non-responder to previous standard IFN plus ribavirin therapy.

In this study, we have determined the basal viral load regarding number of patients achieving SVR. On the basis of specified levels, we categorized viral load into three classes i.e. low level (< 600,000 IU/ml), intermediate level (600,000-800,000 IU/ml) and high level (> 800,000 IU/ml). We have observed that the vi-ral load in 79% patients was less than 600, 000 IU/mL, while it was between 600,000-800,000 IU/ mL in 5.3% patients and 15% patients had more than 800, 000 IU/ mL viral load (Table 6). It is already established that under therapeutic considerations sustained virological response (SVR) can be easily attained in genotype 3 HCV patients with low viral load (<600,000-800,000 IU/ml) when compared with patients having high viral load (>600000-800000 IU/mL) (20, 21). Our study veri-fies that the patients who achieved EVR are more likely to have SVR than those who did not. There are reports which suggest that the pegIFN/RBV therapy should be discontinued in patients without EVR at week 12 (11). However, assessment of EVR is most helpful in patients infected with genotype 1. Testing for EVR can signifi-cantly reduce the cost of therapy for these patients. However, EVR testing is of little benefit in patients with genotypes 2 and 3 because almost all can achieve EVR, SVR occurs in most cases, and there is no cost saving. Our results corroborate the NIH recommended utilization of quantitative HCV RNA testing to assess EVR (22). Further studies are needed to include fac-tors like IL28-B genotype to assess their effect on the retreatment of relapsers and non-responders.

CONCLUSION

Patients achieving EVR in their previous therapy present with a better chance of clearing virus in their second round of antiviral treatment. Viral genotype, however, doesn't have any significant effect on treat-ment outcome in relapsers and non-responders.

REFERENCES

1. Mühlberger N, Schwarzer R, Lettmeier B, Sroczynski G, Zeuzem S, Siebert U. HCV-related burden of disease in Europe: a systematic assessment of incidence, preva-lence, morbidity, and mortality. BMC Public Health. 2009;9(1):34.

2. Re VL, Kostman J. Management of chronic hepatitis C. Postgraduate medical journal. 2005;81(956):376-82.

3. Sherman M, Shafran S, Burak K, Doucette K, Wong W, Girgrah N, et al. Management of chronic hepatitis B: consensus guidelines. Canadian Journal of gastroenter-ology. 2007;21(Suppl C):5C.

4. Zeuzem S, Buti M, Ferenci P, Sperl J, Horsmans Y, Cianci-ara J, et al. Efficacy of 24 weeks treatment with pegin-terferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreat-ment viremia. Journal of hepatology. 2006;44(1):97-103.

5. Yu M-L, Dai C-Y, Huang J-F, Hou N-J, Lee L-P, Hsieh M-Y, et al. A randomised study of peginterferon and ribavi-rin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut. 2007;56(4):553-9.

6. Ferreira SdC, Carneiro MdV, Souza FF, Teixeira AC, Villa-nova MG, Figueiredo JFdC, et al. Long-term follow-up of patients with chronic hepatitis C with sustained virolog-ic response to interferon. Brazilian Journal of Infectious

Diseases. 2010;14(4):330-4.

(b) Patel K, Muir AJ, McHutchison JG. Diagnosis and treatment of chronic hepatitis C infection. Bmj. 2006;332(7548):1013-7.

(c) Lindh M, Arnholm B, Eilard A, Farkkila M, Hellstrand K, Lagging M, et al. Hepatitis C treatment response kinet-ics and impact of baseline predictors. Journal of viral hepatitis. 2011;18(6):400-7.

(d) Cariani E, Villa E, Rota C, Critelli R, Trenti T. Translating pharmacogenetics into clinical practice: interleukin (IL)28B and inosine triphosphatase (ITPA) polymophisms in hepatitis C virus (HCV) infection. Clinical chemistry and laboratory medicine : CCLM / FESCC. 2011;49(8):1247-56.

(e) Qureshi MS, Iqbal M, Nomani AZ, Rasheed K. Time for change: conventional interferon regimes should not be the standard of care for management of Pakistani genotype-3 in chronic hepatitis C. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2014;24(1):70-2.

(f) D'Souza R, Main J, Crossey M, Rosenberg W, Murray-Ly-on IM, Hayward C, et al. Discontinuation of pegylated interferon plus ribavirin in patients who are not re-sponding to therapy -- patients' views of early cessation of therapy. Alimentary pharmacology & therapeutics. 2005;21(1):43-7.

(g) Umar M, Bilal M. Hepatitis C, A Mega Menace: A Pakistani Perspective. Journal of Pakistan Medical Students. 2012;2(2).

(h) Jacobson IM, Gonzalez SA, Ahmed F, Lebovics E, Min AD, Bodenheimer HC, et al. A randomized trial of pegylat-ed interferon α-2b plus ribavirin in the retreatment of chronic hepatitis C. The American journal of gastroen-terology. 2005;100(11):2453-62.

(i) Oze T, Hiramatsu N, Mita E, Akuta N, Sakamoto N, Naga-no H, et al. A multicenter survey of re-treatment with pegylated interferon plus ribavirin combination therapy for patients with chronic hepatitis C in Japan. Hepatolo-gy research : the official journal of the Japan Society of Hepatology. 2013;43(1):35-43.

6. Lagging M, Rembeck K, Rauning Buhl M, Christensen P, Dalgard O, Farkkila M, et al. Retreatment with peg-interferon and ribavirin in patients with chronic hepatitis C virus genotype 2 or 3 infection with prior relapse. Scan-dinavian journal of gastroenterology. 2013;48(7):839-47.

7. Ohno O, Mizokami M, Wu R-R, Saleh MG, Ohba K-i, Orito E, et al. New hepatitis C virus (HCV) genotyping system that allows for identification of HCV genotypes 1a, 1b, 2a, 2b, 3a, 3b, 4, 5a, and 6a. Journal of clinical micro-biology. 1997;35(1):201-7.

8. Yoshida EM, Sherman M, Bain VG, Cooper CL, Deschenes M, Marotta PJ, et al. Retreatment with pegylated in-terferon alpha-2a and ribavirin in patients with chronic hepatitis C who have relapsed or not responded to a first course of pegylated interferon-based therapy. Canadian Journal of Gastroenterology. 2009;23(3):180.

9. Morris Sherman M, Cooper CL, Mel Krajden M, MD10 RJB. Retreatment with pegylated interferon alpha-2a and ribavirin in patients with chronic hepatitis C who have relapsed or not responded to a first course of pe-gylated interferon-based therapy. Can J Gastroenterol. 2009;23(3).

10. Pessoa MG, Cheinquer H, Almeida PR, Silva GF, Lima MPJ, Paraná R, et al. R e-treatment of previous non-re-sponders and relapsers to interferon plus ribavirin with peginterferon alfa-2a (40KD), ribavirin±amantadine in patients with chronic hepatitis C: randomized multi-centre clinical trial. Ann Hepatol. 2012;11:52-61.

11. Dalgard O, Bjøro K, Hellum KB, Myrvang B, Ritland S, Skaug K, et al. Treatment with pegylated interferon and ribavarin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. Hepatology. 2004;40(6):1260-5.

12. Niederau C, Mauss S, Schober A, Stoehr A, Zimmermann T, Waizmann M, et al. Predictive Factors for Sustained Virological Response after Treatment with Pegylated Interferon α-2a and Ribavirin in Patients Infected with HCV Genotypes 2 and 3. PloS one. 2014;9(9):e107592.

13. 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.