

# **Viral Load & Genotype are the Major Determinants of SVR in Chronic Hepatitis C Patients of Azad Kashmir, Pakistan**

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## **ABSTRACT**

This study was carried out to assess predictive power of some additional factors prevailing in our population taking conventional interferon. So that we can decrease the relapse rate and hence improve SVR. This was observational study carried out at Department of Medicine, DHQ Teaching Hospital Mirpur, Azad Jammu & Kashmir from July 2009 to July 2011. The gender, abnormal Alanine Aminotransferase (ALT) at start of treatment, HCV genotype, achievement of End Treatment Response (ETR) and achievement of Sustained Viral Response (SVR) were the qualitative variables while age, quantity of ALT at start of treatment and HCV viral load were quantitative variables. Out of 235 patients, 75.3% patients achieved ETR while amongst them only 76.8% achieved SVR. ETR and SVR were statistically correlated with age of patients, gender, ALT, Viral Load and HCV Genotype. The ETR was found 76% among male gender as compared to 75% among females. SVR was 2.158 times more among females as compared to males and ETR was 2.98 times more among younger patients with age below 40 years. ETR was found 75% among the patients with abnormal initial ALT and SVR was found 54% among the patients with abnormal initial ALT. ETR was found 76% among the patients with low viral load and SVR was 24.29 times more among patients with low viral load, and the association was statistically significant ( $p=0.000$ ). The patients with HCV Genotype 3a, 2a, 3b, 2b and untypable had ETR 77%, 72%, 81%, 75% and 68% respectively and the association was statistically insignificant ( $p=0.856$ ), while with Genotype 3a, 2a, 3b, 2b and untypable had SVR 58%, 54%, 64.5%, 65% and 21% respectively and the association was statistically significant ( $p=0.025$ ). The overall SVR with standard interferon and Ribavirin treatment was low in patients of Azad Kashmir, Pakistan and more dependent on the significant drop-out of the patients after they attained ETR, otherwise SVR was 76.8% in those who came for follow-up.

**Keywords:** Chronic hepatitis C virus (HCV), HCV Viral Load, HCV Genotype, End of Treatment.

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## **INTRODUCTION**

Hepatitis C is caused by infection with the hepatitis C virus (HCV)<sup>1</sup>. 3% of the world's population<sup>2</sup> while 6% Pakistani population<sup>3</sup> is infected with it, and the genotype 3 is the most prevalent virus<sup>4,5</sup>. Pegylated interferon is the better option than the usual conventional interferon as treatment of chronic hepatitis C and is now considered as the standard of care for these infected patients. Due to marked difference in cost, standard interferon-ribavirin combination therapy is still the preferred regimen for genotype 2 & 3, especially in developing countries<sup>6</sup>.

Undetectable virus at the end of either a 24-week or 48-week course of therapy is referred as an End of Treatment Response (ETR). The Sustained Virological Response (SVR) is defined as the absence of HCV RNA (ribonucleic acid) from serum

after 24 weeks of therapy is Non-responder. Relapse is defined as reappearance of HCV RNA in serum after therapy is discontinued. Therefore, HCV testing should be performed annually for at least 2 years after completion of therapy to see the relapse<sup>7</sup>. If patient relapses or is non responder to conventional interferon, then re-treatment with pegylated interferon is required<sup>8,9,10</sup>.

A large number of relapsers and non responder patients to conventional interferon and ribavirin therapy require expensive retreatment with pegylated interferon. Even after the large expenditures bearded by the patients, response rate will be only up to 20%<sup>11</sup> in comparison to 93% for treating naïve patients with it<sup>12</sup>.

The known factors, predictive of response to treatment in chronic hepatitis C include low serum HCV RNA level, non genotype 1, absence of cirrhosis, age younger than 40 years, lack of steatosis or obesity, mode of acquisition of infection and white race<sup>13,14</sup>. A body mass index higher than 30 has been associated with poor response to

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therapy. Weight reduction, in turn, leads to improved outcome<sup>15</sup>.

This study was carried out to assess predictive power of some additional factors prevailing in our population taking conventional interferon. So that we can decrease the relapse rate and hence improve SVR. National consensus can be suggested to treat these patients with conventional interferon or Pegylated interferon as initial therapy on the basis of these factors predictive of response and therefore, the health resources can be saved as it is not possible to provide pegylated interferon to all pts.

## MATERIAL AND METHODS

This was observational study carried out at Department of Medicine, DHQ Teaching Hospital Mirpur, Azad Jammu & Kashmir from July 2009 to July 2011. A total 317 patients were treated with conventional interferon and ribavirin during this period. Out of these, 235 patients who had completed the treatment with regular visits were recruited. The gender, abnormal Alanine Aminotransferase (ALT) at start of treatment, HCV genotype, achievement of ETR and achievement of SVR were the qualitative variables while age, quantity of ALT at start of treatment and HCV viral load were quantitative variables. The whole data was interpreted in negative or positive values. Frequencies and ranges were computed for presentation of qualitative variables and means and standard deviations were calculated for quantitative variables. The available data was evaluated retrospectively on SPSS version 15.

## RESULTS

Two hundred and thirty five patients of chronic viral hepatitis C who received interferon therapy along with ribavirin were enrolled, 28.5% were males and 71.5% females. The mean age (years) of patients was  $38.43 \pm SD$  of 10.27, the mean ALT (IU/L) was  $74.54 \pm SD$  of 54.22 and the mean Viral load (IU/ml) was  $2716778 \pm SD$  of 1732056.663. The majority of the patients had genotype 3a (47.2%), while 23% patients had genotype 2a, 13.2% had genotype 3b, 8.5% had genotype 2b and 8.1% patients had untypable genotype. Only 7(3%) patients had their ALT within normal limit at the start of interferon therapy, while 228(97%) patients had abnormal ALT (Tables 1, 2).

Out of 235 patients, 177 patients (75.3%) achieved End Treatment Response (ETR) while amongst them only 135 patients (76.7%) achieved Sustained Viral Response (SVR). Out of 235 patients, 177(75.3%) achieved End Treatment Response (ETR) while amongst them only 136 patients (76.8%) achieved Sustained Viral Response

(SVR). The ETR and SVR were statistically correlated with age of patients, gender, ALT (IU/L), Viral Load (IU/ml) and HCV Genotype. The ETR was found 76% (51 out of 67) among male gender as compared to 75% (126 out of 168) among females and the association was not statistically significant ( $p=1.000$ ). The SVR was found 52% (35 out of 67) among male gender as compared to 60% (101 out of 168) among females. The SVR was 2.158 times more among females as compared to males, however this association was also not statistically significant ( $p=0.149$ ).

The ETR was found 76% (99 out of 131) among patients of age below 40 years as compared to 75 % (78 out of 104) among patients of age 40 years or above and the association was not statistically significant ( $p=1.000$ ). The SVR was found 62.5% (82 out of 131) among patients of age below 40 years as compared to 52% (54 out of 104) among patients of age 40 years or above. The SVR was 2.98 times more among younger patients with age below 40 years as compared to patients of age 40 years or above, however this association was also not statistically significant ( $p=0.088$ ).

The ETR was found 75% (172 out of 228) among the patients with abnormal initial ALT and 71 % (5 out of 7) among the patients with normal ALT and the association was not statistically significant ( $p=0.683$ ). The SVR was found 54% (124 out of 228) among the patients with abnormal initial ALT and 86 % (6 out of 7) among the patients with normal ALT. The SVR was 3.054 times more among patients with normal ALT as compared to patients of abnormal ALT, however this association was also not statistically significant ( $p=0.134$ ).

The viral load  $\geq 400,000$  IU/mL was labeled as High Viral load and the Viral load  $< 400,000$  IU/mL was labeled as Low Viral load. The ETR was found 75% (78 out of 104) among the patients with high viral load and 76 % (99 out of 131) among the patients with low viral load and the association was not statistically significant ( $p=1.000$ ). The SVR was found 37.5% (39 out of 104) among the patients with high viral load and 69.5 % (91 out of 131) among the patients with low viral load. The SVR was 24.29 times more among patients with low viral load as compared to patients of high viral load and the association was statistically significant ( $p=0.000$ ).

The patients with HCV Genotype 3a, 2a, 3b, 2b and untypable had ETR 77%,72%, 81%,75% and 68% respectively and the association was statistically insignificant ( $p=0.856$ ), while the patients with HCV Genotype 3a, 2a, 3b, 2b and untypable had SVR 58%,54%, 64.5%,65% and 21% respectively and the association was statistically significant ( $p=0.025$ ). The untypable genotype was unfavourable for SVR.

## ORIGINAL ARTICLE

Table 1: Quantitative Factors associated with SVR in chronic hepatitis C patients of Azad Kashmir (n=235)

Quantitative variables	Minimum	Maximum	p-value
Age of patients (years)	20	60	0.013
ALT (IU/L)	45	86	0.393
Viral Load (millions IU/ml)	1.6	10.5	0.003

Table 2: Qualitative Factors associated with ETR in chronic hepatitis C patients of Azad Kashmir (n=235)

Qualitative variables	ETR achieved (n=177)	ETR not-achieved (n=58)	Likelihood Ratio	p-value
Male	51 (76%)	16 (24%)	0.032	1.000
Female	126 (75%)	42(15%)	0.010	1.000
<40 yrs of age	99 (76%)	32 (24%)	0.010	1.000
≥40 yrs of age	78 (75%)	26 (25%)		
ALT(IU/L) abnormal	172(75%)	56(25%)	0.057	0.683
ALT (IU/L) normal	5(71%)	2(29%)		
Viral load(IU/ml) high	78(75%)	26(25%)	0.010	1.000
Viral load(IU/ml) low	99(76%)	32(24%)		
HCV genotype a	85(77%)	26(23%)	1.327	0.856
HCV genotype a	39(72%)	15(28%)		
HCV genotype b	25(81%)	6(19%)		
HCV genotype a	15(75%)	5(25%)		
Untypable	13(68%)	6(32%)		

Table 3: Qualitative Factors associated with SVR in chronic hepatitis C patients of Azad Kashmir (n=235)

Qualitative variables	SVR achieved (n=136)	SVR not-achieved (n=99)	Likelihood ratio	p-value
Male	35(52%)	32 (48%)	2.158	0.149
Female	101(60%)	67 (40%)		
<40 yrs of age	82 (60%)	52 (40%)	2.98	0.088
≥40 yrs of age	54 (49%)	53 (51%)		
ALT(IU/L) abnormal	130 (57%)	98 (43%)	3.054	0.134
ALT (IU/L) normal	6 (86%)	1 (14%)		
Viral load(IU/ml) high	42 (40.4%)	62 (59.6%)	24.29	0.000
Viral load(IU/ml) low	94 (71.7%)	37 (28.3%)	11.15	0.025
HCV genotype a	64 (58%)	47 (42%)		
HCV genotype a	29 (54%)	25 (46%)		
HCV genotype b	20 (64.5%)	11 (35.5%)		
HCV genotype a	13 (65%)	5 (35%)		
Untypable	4 (21%)	15 (79%)		

## DISCUSSION

Pakistan is a state with high burden of hepatitis C patients. Role of predictive factors to reduce the treatment failure rate in these hepatitis C patients is very important. The optimal way to direct antiviral therapy in these patients would be to treat only those patients who will become sustained responders. However, positive prediction of sustained virologic response is still not easy, although different baseline predictors have been described: genotype 2 or 3, a baseline viral load less than 2 to 3.5 million copies/mL (581,000-1,017,000 IU/mL), no or only portal fibrosis, female gender, and age younger than 40 years<sup>16,17</sup>. In our retrospective analysis of chronic hepatitis C patients receiving interferon therapy, the ETR was 75.3%, but SVR was only 76.8%. Poynard et al<sup>17</sup> found that in the most favorable population with all positive prediction characteristics, the rates of sustained virologic response with standard

combination therapy IFN- plus ribavirin was 79%. It means that if we consider positive predictors while treating hepatitis C patients, SVR can be improved. Retrospectively in our study, we found that SVR was 24.29 times more among patients with low viral load as compared to patients of high viral load ( $p=0.000$ ), and the untypable genotype was unfavorable for SVR ( $p=0.025$ ).

In 2004, Ferenci<sup>18</sup> found that sustained viral response was 1.5 times greater in hepatitis c patients with low viral load (<2 million copies per milliliter;800 IU/mL) than in patients with high viral load.

In the prospective study of Muto et al.,<sup>19</sup> patients with viral loads greater than 2,000,000 copies per milliliter or 800,000 IU/ IU/mL have the worst responses. The Tokyo Chiba Hepatitis Research Group<sup>20,21</sup> found that HCV virus eradication rate in patients with serotype 2 was higher than in those with serotype 1.

In our study, the overall SVR is 57.9%. It means that remaining 52.1% non responders/re-lapsers will seek pegylated interferon for their retreatment and it will benefit only up to 20% cases<sup>11</sup> in comparison to 93%<sup>12</sup> for treatment naïve patients. Our study revealed better treatment response in patients with low viral load and genotype 3 b. So whole scenario suggest us that the conventional interferon may not be used in Azad Kashmir, Pakistan, as it not only increasing the relapse rate but also produces resistance to re-treatment as well. If it is not practicable due to cost, then national consensus should be made on the basis of predictive factors to group the patients into two categories: one who may be provided conventional interferon and others who should never be treated with it to decrease non-responders and relapse rate and in this way SVR could be improved and the resistant pool to re-treatment can be decreased.

## CONCLUSION

The overall Sustained Viral Response (SVR) to standard interferon and Ribavirin treatment was low in patients of Azad Kashmir, Pakistan and it was more dependent on the significant drop-out of the patients after they attained ETR, otherwise SVR was 76.8% in those who came for follow-up . The assessment of predictors of response, like viral load and genotype may help in individualizing the treatment, patient selection and decrease in an ever expanding pool of non-responders and re-lapsers.

## REFERENCES

- Houghton M. Hepatitis C viruses. In: Fields BN, Knipe DM, Howley PM, eds. *Fields Virology*, 3<sup>rd</sup> ed. Philadelphia, Lippincott - Raven, 1996:1035-1058.
- World Health Organization. Initiative for vaccine research: hepatitis C virus [Internet]. [Updated 2010]. Available from: [http://www.who.int/vaccine\\_research/diseases/viral\\_cancers/en/index2.html](http://www.who.int/vaccine_research/diseases/viral_cancers/en/index2.html).
- Ali, S.A., Donahue, R.M., Qureshi, H., Vermont, S.H.(2009). Hepatitis B and hepatitis C in Pakistan: prevalence and risk factors. *Int. J. Infect. Dis.*, 13, 9.
- Jafri, W., Subhan, A. (2008). Hepatitis C in Pakistan: magnitude, genotype, disease characteristics and therapeutic response. *Trop. Gastroenterol.*, 29,194-201.
- Idrees, M., Butt, S., Awan, Z., Aftab, M., Khubaib, B., Rehman, I.U., et al. ( 2009). Nucleotide identity and variability among different Pakistani hepatitis C virus isolates. *Virology*, 24,130.
- Hamid, S., Umar, M., Alam, A., Siddiqui, A., Qureshi, H., Butt, J. (2003). Pakistan Society of Gastroenterology (PSG) consensus statement on management of hepatitis C virus infection. *J Pak Med Assoc.*, 54,146-50.
- Ghany, M., Strader, D., Thomas, D., Seef, L. (2009). Diagnosis, Management, and Treatment of Hepatitis C:An update. *Hepatology*. 49,1341.
- Jacobson, I.M., Gonzalez, S.A., Ahmed, F., et al. (2005). A randomized trial of pegylated interferon alpha-2b plus ribavirin in the retreatment of chronic hepatitis C. *Am J Gastroenterol*. 100, 2453-62.
- Shiffman, M.L., Di, Bisceglie, A.M., Lindsay, K.L., et al. (2004). Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology*, 126, 1015-23.
- Taliani, G., Gemignani, G., Ferrari, C., et al. (2006). Pegylated interferon alfa-2b plus ribavirin in the retreatment of interferon-ribavirin nonresponder patients. *Gastroenterology*, 130, 1098-106.
- Cheng, S.J., Bonis, P.A., Lau, J., et al. (2001). Interferon and ribavirin for patients with chronic hepatitis C who did not respond to previous interferon therapy: A meta-analysis of controlled and uncontrolled trials. *Hepatology*, 33, 231.
- Zeuzem, S., Hultcrantz, R., Bourliere, M., et al. (2004). Peginteron alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotype 2 or 3. *Hepatology*, 40, 993.
- Strader, D.B., Wright, T.L., Thomas, D.L., (2004). Diagnosis, management and treatment of hepatitis C: A.A.S.L.D. practice guideline. *Hepatology*, 39, 1147.
- Alberti, A., Bevegno, L. (2003). Management of hepatitis C. *J. Hepatol*, 38, 104.
- McCullough, A.J.(2003). Obesity and its nurturing effect on hepatitis C. *Hepatology*. 38, 557.
- Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, Bain V, et al. Randomized trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *International Hepatitis Interventional Therapy Group (IHIT). Lancet* 1998;352:1426- 1432.
- Poynard T, McHutchison J, Goodman Z, Ling MH, Albrecht J. Is an "a la carte" combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? The ALGOVIRC Project Group. *HEPATOLOGY* 2000;31:211-218.
- Ferenci P. Predictors of response to therapy in chronic hepatitis c. *Semin Liver Dis* 2004;21(2):25-31.
- Muto H, et al. Types of human leukocyte antigen and decrease in HCV core antigen in serum predicting efficacy of interferon in patients with chronic hepatitis C. Analysis by a prospective study. *J Gastroenterol* 2004;39(7): 674-80.
- Shiratori, et al. Predictors of the efficacy of the interferon therapy in chronic hepatitis C virus Infection. Tokyo Chiba Hepatitis Research Group. *Gastroenterology* 1997;113(2);558-66.
- Careaga B. Predictive factors for response to treatment of chronic hepatitis C. *Annals of Hepatology* 2006;5(1): 24-28.