

The Role of Nitazoxanide in Combination with Interferon and Ribavirin in the Treatment of Genotype 3 Hepatitis C among patients with Type 2 Diabetes Mellitus

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ABSTRACT

Aim: To study the effect of nitazoxanide with interferon alpha and ribavirin on the SVR rate among genotype 3 chronic hepatitis C type 2 diabetic patients.

Study design: A randomized clinical trial.

Place and study duration: Department of Endocrinology & Metabolism, Services Hospital Lahore from March 2011 to June 2013.

Methodology: A randomized clinical trial was conducted in which genotype 3 chronic hepatitis C patients with type 2 diabetes and HCV(PCR) positive tests were randomized into two groups; Group A received treatment with conventional interferon alpha and ribavirin, while group B received triple therapy, nitazoxanide along with interferon and ribavirin for 24 weeks. HCV (PCR) RNA and alanine amino transaminase levels (ALT) was monitored every 4 week for 24 weeks, and then at 48 weeks.

Results: The response to treatment among Group A and B was compared using virological response rates; RVR= 46% vs 45%, EVR=30% vs 47%, ETR=27% vs 50% and SVR rate were 37% vs 16%, respectively.

Conclusion: The results showed that nitazoxanide along with conventional interferon and ribavirin was comparable to and did not show an added benefit over interferon and ribavirin in chronic hepatitis C type 2 diabetic patients.

Keywords: Chronic Hepatitis C, Rapid Viral Response: RVR, End of Treatment Response: ETR

INTRODUCTION

Chronic hepatitis C infects 130-150 million people worldwide, each year about 350,000 infected people die of HCV related liver disease¹. The prevalence of HCV infection in Pakistan, according to an estimate is approximately 10 million with predominance of genotype 3 and average prevalence rate is 6%². HCV infection is the major cause of more than 60% of patients suffering of CLD and HCC in the country^{3,4,5,6}. Diabetes mellitus, has fast become an important public health problem in Pakistan, with a prevalence rate expected to rise to 13.8% by the year 2030, making Pakistan fourth in rank amongst those with diabetic patients age ranging 20-79⁷.

The relation between HCV infection and diabetes has been studied extensively in the past^{8,9,10,11,12}. Studies done in Pakistan also support a strong correlation between these two chronic conditions, especially high prevalence of HCV sero-conversion seen in elderly male patients of longer duration of poorly controlled type 2 diabetes¹³.

The high prevalence of these diseases and suboptimal response to the standard therapy has led

to a constant quest for new novel treatments. Nitazoxanide, an anti-parasite used to treat *Cryptosporidium parvum* and *Giardiasis lamblia* also showed a decline in alanine amino transaminase levels (ALT) in patients, which led to study their use in HCV infection. An enhanced effect of interferon therapy was seen amongst patients pretreated with this drug. Nitazoxanide induces double stranded RNA –activated protein kinase (PKR) phosphorylation, which improves host cell defenses against viral infection^{14,15}.

The previously conducted trials done using Nitazoxanide to treat hepatitis C patients have shown mixed reviews. It is also worth mentioning here that in all the earlier trials only genotype 1 or 4 were studied and good quality evidence regarding the efficacy of this drug in treatment of hepatitis C genotype 3 is lacking. The rationale of study was to combine nitazoxanide, an easily available drug at low cost, to the conventional treatment in hope of achieving a better SVR in a low income country. Thus, in our opinion the issue of role of nitazoxanide in HCV is still unclear. All these factors constitute a sufficient rationale in addition to a very real & practical need for exploring every low cost therapy for this disease in developing countries.

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METHODOLOGY

A randomized clinical trial was conducted at Department of Endocrinology & Metabolism, Services Hospital Lahore. The recruitment of patients started in March 2011 and was completed in June 2013. A written consent from the participants was taken. The trial protocol was approved by the Institutional Review Board of Services Hospital Lahore. The trial was registered at the website "clinical trial.gov".

The sample size was calculated using the software Epi-Info 3.5.1 with Confidence level of 95% and power of study 80%. Calculated sample size was 66 i.e. 33 in each group. Adding attrition rate sample size is 80 patients' i.e. 40 patients in each group.

Eligible patients were well controlled type 2 diabetic adults of 30-55 years of age who had genotype 3 chronic hepatitis C infection and detectable HCV-PCR for more than 6 months with three times raised alanine amino transaminase levels. Previously treated, pregnant females, and those with signs of hepatic decompensation due to diseases other than hepatitis C were excluded.

A randomized controlled clinical trial was performed. A total of 153 HCV-PCR-(RNA) positive diabetic patients were screened. HCV-(PCR)-RNA test was done using HCV RNA Real Time Quantification kit. Eighty patients were finally recruited in the trial after the initial screening and were randomly divided into two equal groups; A & B. A follow up period of every 4 weeks for 24 weeks was observed. On each visit and at 48 weeks the patient underwent tests done at baseline and HCV-PCR tests to assess the response. Patients in group A received conventional interferon 3 MIU thrice weekly along with ribavirin 800-1200 mg per day according to body weight while Group B patients in addition received oral nitazoxanide 500 mg tablets twice daily with meals.

Baseline laboratory tests like complete blood picture, liver function tests, HbA1c and ultrasound abdomen to assess the splenic index and presence of ascites were performed.

SVR (sustained viral response) is defined as; a negative PCR (RNA) HCV 24 weeks after the completion of treatment.

RVR (rapid viral response); HCV- PCR below the detectable limits at 4 weeks after initiation of treatment. EVR (early viral response); HCV- PCR below the detectable limits at 12 weeks after initiation of treatment. ETR (end of treatment response); HCV-PCR below the detectable limits at 24 weeks after initiation of treatment

The results were analyzed using SPSS ver 13. Categorical variables were compared using the Pearson Chi square, while continuous variables were

compared using a t-test. P-values <0.05 were considered as significant.

Outcome variables like RVR, ETR and SVR were presented as percentages. While continuous variable such as age will be presented by mean and standard deviation.

A multivariate binary logistic regression analysis was performed to determine the risk factors associated with the achievement of SVR. The outcome variable was achievement of SVR. The independent variables included in the model were age, gender, body mass index (BMI), HbA1c, RVR, alanine amino transaminase (ALT). The Relative Risk of achieving SVR was calculated with 95% Confidence Intervals (95% CI) for each of the independent variable. P-value < 0.05 was considered as statistically significant.

RESULTS

A sum of 80 cases were enrolled in this study which was later divided into two groups of equal size viz group A=40 and Group B=40. The mean age of the patients was 47.05±6.36 in group A and 47.84±5.57 in group B which was significantly not different. A little high frequency of male patient noted in group B as 25(51%) and lower 24(49%) in group A with again insignificant difference. BMI, HbA1C, Hemoglobin, TLC, Platelet count, ALT and creatinine also had non-significant difference at baseline (Table 1).

RVR was achieved in 23(46%) group A patients compared to 22(45%) group B patients (p-value=0.88) (Fig. 1).

ETR was achieved in 13(27%) group A patients compared to 25(50%) group B patients (p-value=0.004). SVR was achieved in 18(37%) group A patients compared to 8(16%) group B patients (p-value =0.02).

A multivariate binary logistic regression analysis was performed to determine the risk factors associated with the achievement of SVR (table 2). The outcome variable was achievement of SVR. The independent variables included in the model were age, gender, BMI, Hba1c, RVR, ALT. The multivariate model shows that those who achieved RVR had a 3.1 times greater probability of achieving SVR in our study, the other independent variables were statistically non-significant in the multivariate model (Table II).

This figure illustrates the rapid viral response (RVR) i.e., below detectable limits of HCV (PCR) RNA after 4 weeks of treatment amongst patients in group A (n=37) and group B (n=38). RVR was 46% and 45%, p=0.88 in Group A and Group B respectively. The figure is saved in Jpeg 3.2 mega pixels

This figure illustrates the early viral response (ETR) i.e., below detectable limits of HCV (PCR)RNA after 24 weeks of treatment amongst patients in group A (n=37) and Group B(n=38).ETR was 27% and 50% ,p=004 in Group A and Group B respectively. The figure is saved in Jpeg 3.2 mega pixels.

This figure illustrates the sustained viral response (SVR) i.e., below detectable limits of HCV (PCR) RNA after 48 weeks of treatment amongst patients in group A (n=37) and Group B (n=38).ETR was 37% and 16%, p=02 in Group A and Group B respectively. The figure is saved in Jpeg 3.2 mega pixels

Table 1: Comparison of the baseline characteristics of Group A and Group B patients

Characteristics	Group A	Group B	P-value
Age (in years)	47.05 ± 6.36	47.83 ±5.57	0.56
Gender (Males)	23(49%)	25(51%)	0.87
Body Mass Index	27.28 ± 6.40	27.87 ± 6.57	0.68
HbA1C (%)	7.04 ± 1.28	6.78 ± 1.28	0.38
Hemoglobin (G/dl)	13.36±1.74	15.75±0.97	0.00
Total Leucocyte Count	7.04 ± 1.81	7.28 ± 1.87	0.54
Platelet count	189.67 ± 64.26	195.13 ± 53.70	0.68
Alanine Amino Transaminase (ALT)	121.75 ± 59.64	119.40 ± 46.23	0.87
Creatinine (mg/dl)	0.72 ± 0.14	0.713 ± 0.17	0.71

This table compares the baseline characteristics of both the Groups A&B .As evident from the data analysis shown in the table both the groups were comparable.

Table 2: Multivariate Logistic Regression Analysis to determine the risk factors associated with Sustained Viral Response (SVR)

Variables	Relative Risk	95% CI	p-values
Age (per year increase)	0.954	0.84-1.08	0.46
Gender (ref = males)	0.269	0.049-1.47	0.13
BMI (per unit increase)	1.043	0.934-1.160	0.47
RVR (ref = no)	3.107	0.643-15.01	0.009
HbA1c (per unit increase)	0.994	1.68-6.22	0.66
ALT (per unit increase)	1.001	0.992-1.01	0.79

ALT - alanine amino transaminase; RVR- rapid viral response; BMI – body mass index,

HbA1c- glycosylated hemoglobin (hemoglobinA1c)A significant relative risk was shown among patients achieving RVR with SVR rates.

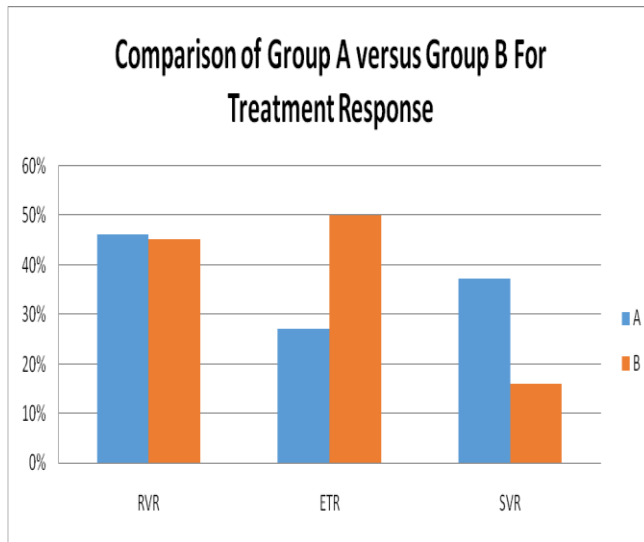


Fig.1: RVR, ETR and SVR Achieved by Group A and B.

DISCUSSION

The World Health Organization has referred to hepatitis C infection as a “Viral time bomb.” Hepatitis C is responsible for 65-75% cases of liver cancer and 2/3rd cases of liver transplant ⁽¹⁶⁾. According to an estimate given by WHO, liver cirrhosis is the 18th most common cause of worldwide mortality and by

year 2030 liver cancer will become the thirteenth^{17,18}. The connection between hepatitis C infection and type 2 diabetes (T2DM) was established as early as 1994 by Allison et al and has been studied extensively ever since. According to an analysis conducted at Nishtar Medical College Multan, a prevalence rate of 13.6% was noted among 3000 diabetic blood donors¹³. An earlier trial done in Peshawar showed a rate of diabetes, as high as 36% amongst 100 patients of Hepatitis C¹⁹. Hepatitis-C inhibits the insulin signaling leading to insulin resistance (IR) and ultimately type 2 diabetes, it also changes the host innate immune response. The IR and T2DM not only speed up the histological and clinical progression of disease but is also implicated in the reduced viral response to interferon therapy.⁽¹⁰⁾ This high disease prevalence and mortality has motivated scientist worldwide to continue their struggle for its more effective treatment. For this reason a new novel drug was studied in this trial. Unfortunately, our results are not very favorable for nitazoxanide, the new drug.

Nitazoxanide, a drug initial used to treat Cryptosporidium parvum and Giardiasis lamblia in patients with AIDS is being tried, in hope of favorable effect in addition to interferon therapy against Hepatitis C infection. It selectively induces double

stranded RNA activated protein kinase PKR phosphorylation, which leads to increase cell concentration of phosphorylated eukaryotic initiation factor 2 α ^{14,15}. Nitazoxanide, in this study given as a part of triple regime in combination with interferon alpha and ribavirin did not show increase in SVR as compared to dual therapy of interferon alpha and ribavirin. ETR rate was favorable for patients using nitazoxamide (Group B) compared to Group A, 50% vs 27%, p-value = 0.004, respectively. However, SVR was achieved in 37% vs 16% of Group A and Group B patients, respectively. This was contrary to what was expected.

The results of this study are contrary to those seen in other studies. Previous trial done on treatment naïve and relapse hepatitis C genotype 4 patients using nitazoxanide showed an increased SVR as high as 79-80%²⁰. It was a randomized control trial conducted in Egypt and showed an increase RVR and SVR rate amongst the HCV genotype 4 infected group receiving triple therapy (peg interferon, ribavirin in combination with nitazoxanide) as compared to the group receiving dual therapy (64% vs 38%, p=0.048; and 79% vs 50%, p=0.023), respectively²⁰. Similarly, two other studies done to evaluate the additional role of nitazoxanide in treatment naïve and non-responders genotype 1 chronic hepatitis C patients (STEALTH-2, and STEALTH-3) respectively. A better complete virologic response and EVR rates were seen amongst nitazoxanide + peg + ribavirin group compared to peg interferon/ribavirin (c EVR: 60% vs 49%, EVR: 80% versus 68%), respectively, but not at 4 week of treatment²¹.

Similar to our study, a trial in Cairo, Egypt in November 2010-2011 done on 100 hepatitis C genotype 4 patients using triple therapy (nitazoxanide along with peg interferon and ribavirin Group 2) vs dual therapy (peg interferon and ribavirin Group 1) did not show beneficial effect of nitazoxanide (triple therapy) compared to dual therapy in chronic hepatitis C infection (SVR rates was 48% in group 1 and 50% in group 2, p=0.84)²².

We conclude that nitazoxanide along with interferon and ribavirin (triple therapy) was not found to be superior to interferon and ribavirin (dual therapy) in terms of RVR, and SVR rates.

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