EFFECTIVENESS OF ANTI-VIRAL (CONVENTIONAL INTERFERON AND RIBAVIRIN) THERAPY IN CHRONIC HEPATITIS 'C' PATIENTS WITH TYPE II DIABETES

Aliena Badshah[1], Mohammad Humayun[1], Shams Suleman[2]

ABSTRACT

Objective: To determine the effectiveness of anti-viral therapy in chronic hepatitis C patients with type II diabetes in terms of end of treatment response (ETR) by measuring the quantitative PCR at the completion of six months of treatment.

Study Design: Descriptive, Case Series Study.

Place and Duration of Study: This study was conducted in the Department of Medicine, Khyber Teaching Hospital, Peshawar from September, 2014 to February, 2015.

Materials and Methods: One hundred patients with type II diabetes mellitus and concomitant Hepatitis C infection were recruited in the study. They were started on conventional interferon therapy along with ribavirin capsule for 24 weeks. When the treatment was initiated, patients were evaluated at 4, 12 and 24 weeks. Blood tests were carried out, and serum HCV-RNA was repeated at the completion of therapy to determine the viral clearance. The end point for the study was taken as a normal ALT and loss of detectable serum HCV-RNA at 24 weeks after the start of therapy. Patients were monitored for ETR. Data was entered and analyzed by statistical package for social sciences (SPSS) version 17. Mean $\pm$ Standard Deviation (S.D) were calculated for numerical variables.

Results: Out of 100 patients included in the study, 77(76.2%) patients attained End of Treatment Response (ETR), while 23(22.8%) patients did not achieve ETR. Out of the 77 patients who attained ETR, 41 were males and 36 were females. Among the 23 patients who did not attain ETR, 16 were male patients, and 07 were female patients.

Conclusion: A poor therapeutic outcome is seen in HCV positive patients co-morbid with diabetes mellitus.

Key Words: Hepatitis C infection, type II diabetes mellitus, interferon alpha – 2b, ribavirin, end of treatment response.

INTRODUCTION

Chronic hepatitis C (CHC) and type 2 diabetes mellitus (T2DM) are widely prevalent diseases that are on the rise and will continue to increase in the future[1]. It has been postulated that diabetes could be one of the extra-hepatic conditions attributable to HCV infection[2,3]. This also raises the question of whether the rise in HCV infection is contributing to the increasing prevalence of type 2 diabetes[4].

Previous studies have determined some association between CHC and hyperglycemia[4-6]. Type 2 diabetes and insulin resistance appear to be more common among patients afflicted with chronic hepatitis C[6].

It has been found that diabetes mellitus reduces the efficacy of anti-viral therapy used in the treatment of hepatitis C, ie. interferon (IFN) alpha -2b and ribavirin[7,8]. IR and diabetes have a negative impact on the progression of viral hepatitis across all stages. This also includes the liver transplant candidates. Reduced responsiveness to antiviral therapy, more speedy evolution of fibrosis to cirrhosis and a higher incidence of hepatocellular carcinoma are the factors that directly have a negative effect on patient outcome[5,9,10].

The major risk in patients with CHC is development of fibrosis and ultimately cirrhosis, so patients with concomitant IR should initiate anti-viral therapy as soon as is indicated to eradicate the virus or at least trim down the viral load[11-13].

Most of the previous studies conducted on the topic are of the opinion that patients with T2DM have less chances of attaining a sustained virologic response (SVR)[6,8]. A study conducted in 2009 at the University of Dakota, USA found out that only 23% of HCV positive diabetics achieved SVR compared to 46% of HCV positive non-diabetics[9]. DM, genotype 1, high baseline viral load, and African-American ethnicity were independently associated with reduced SVR[9].

Another study carried out at the Ain Shams University, Cairo also revealed differences between diabetic and non-diabetic chronic HCV genotype 4 infected patients as regards to early virologic response (EVR)

1 Department of Medicine, Khyber Teaching Hospital, Peshawar
2 Department of Pharmacology KGMC Peshawar

Address for correspondence:
Dr. Aliea Badshah
Department of Medicine, Khyber Teaching Hospital, Peshawar
E-mail: alienabadshah@yahoo.com
Cell No: 03355950615

(80.0% vs 70.0%), end of treatment response (ETR) (75.0% vs 70%) and sustained virologic response (SVR) (75.0% vs 65.0%)[8].

In Pakistan, a descriptive study conducted at Jinnah Post-graduate Medical Center, Karachi from 1998 to 2009 concluded that 54.2% diabetics achieved SVR, while 77% non-diabetics achieved SVR[10].

Patients with diabetes are more prone to the side effect profile of anti-viral therapy[14]. Hepatitis C is on the rise in Pakistan. Genetic and geographic differences as well as hepatitis C genotypic preferences may mean that the viral infection has different outcomes here than those in the West. The current study was conducted to determine the effect of diabetes mellitus on HCV infected patients in this part of the world, where HCV infection is more widely spread than in the West. Reduced effectiveness of AVT in diabetics may mean that this patient population may require treatment strategies different than those for non-diabetic patients with hepatitis C infection.

MATERIALS AND METHODS

This descriptive, Case Series Study was conducted at the department of Medicine, Khyber Teaching Hospital, Peshawar from September, 2014 to February, 2015, as a dissertation which is mandatory requirement for eligibility for FCPS – II examination with the College of Physicians and Surgeons, Pakistan (CPSP). Non-probability consecutive sampling technique was used to take a sample size of 100 patients, using effectiveness of anti-viral therapy in diabetics in terms of ETR as 50%[9], 10% margin of error and confidence level 95% with the help of WHO Software for sample size determination.

Patients from either gender with compensated Chronic Hepatitis C but without cirrhosis and type II diabetes mellitus lasting for more than 2 years were taken in the study group. Patients more than 14 years and less than 65 years of age were included in the study. Patients with decompensated cirrhosis, hepatocellular carcinoma, current pregnancy or breastfeeding, having history of prior or current anti-viral therapies, other liver diseases such as alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), drug-induced hepatitis, other viral hepatitis, hereditary haemochromatosis, wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and alpha 1 antitrypsin deficiency were excluded from the study. The study was proceeded with after approval from the hospital's ethical and research committee.

The idea and advantages expected from the study were explained to all patients and informed consent was obtained before recruitment to the study. Study sample was selected randomly from patients presenting to medical OPDs. Patients comprised of CHC patients who were type 2 diabetics for more than 2 years. They were started on conventional interferon therapy 3 million units subcutaneously three times per week along with ribavirin capsule 400mg twice daily for 24 weeks. Both drugs were initiated and terminated at the same time. The recruited patients were assessed in an outpatient basis for safety, tolerance and effectiveness of therapy every month during treatment. Once the treatment was started, patients were assessed at 4, 12 and 24 weeks. Blood tests were done, and serum HCV-RNA was repeated at the completion of therapy to determine the viral clearance. The end point for the study was taken as a normal ALT and loss of detectable serum HCV-RNA at 24 weeks after the initiation of therapy. All the patients were monitored for ETR. Impact of type II DM on the outcome of anti-viral therapy (AVT) according to duration of DM, control of DM (HbA1c) and treatment of DM was also evaluated.

Data was entered and analyzed by statistical package for social sciences (SPSS) version 17. Mean $\pm$ Standard Deviation (S.D) were calculated for numerical variables like age, FBS, RBS, HbA1c, duration of diabetes, and Hepatitis C viral RNA load as determined by PCR for ETR. Frequencies and percentages were calculated for categorical variables like gender, and also for the number of patients in whom anti-viral therapy was found to be effective. Anti-viral therapy was labeled as effective in patients attaining ETR. Effectiveness of anti-viral therapy was stratified among age, gender, SGPT and HbA1c at the completion of treatment, and duration of diabetes mellitus. Comparative analysis was performed with respect to various patients' characteristics by applying t-test and chi square test. A p-value $\leq$0.05 was considered statistically significant. All results were presented in the form of tables and graphs.

RESULTS

In this study, 100 type II diabetic patients with chronic hepatitis C were recruited. Of these 100 patients, 57 (57%) were males and 43 (43%) were females. Their mean age was 43.32 years.

77 (77%) patients attained ETR while 23 (23%) patients failed to achieve ETR with interferon and ribavirin therapy. Of the 77 patients that attained ETR, 41 were males and 36 were females. Of the 23 patients that did not attain ETR, 16 were males and 07 were females.

Maximum ETR was achieved by patients with duration of diabetes less than or equal to 5 years.

15 patients beyond 40 years of age were unable to achieve ETR, while 08 patients less than 40 years of age were unsuccessful in attaining ETR.

10 patients who failed to attain ETR had FBS between 76-100mg/dl and 7 patients failing to attain ETR had RBS between 226-250mg/dl. Mean FBS at the start of AVT for those patients who attained ETR was 102.58 $\pm$ 20.53 and for those who did not attain ETR was 119.52 $\pm$ 28.05; while mean RBS for patients

achieving ETR was 189.31 ± 41.94 and for those failing to achieve ETR, it was 231.95 ± 43.67.

HbA1c at the start of AVT for those achieving ETR was 6.58 ± 0.88, while it was 7.83 ± 0.809 for those not achieving ETR.

20 patients with SGPT greater than or equal to 50U/liter failed to achieve ETR, while only 3 patients with SGPT less than 50U/liter failed to achieve ETR. Mean SGPT at the start of AVT for those attaining ETR was 54.87 ± 12.71 and 60.52 ± 9.12 for those not achieving ETR.

Details of patients' characteristics are tabulated in table 01 with Mean ± S.D of the variables also incorporated, while statistical comparison of end of treatment response is shown in table 02.

DISCUSSION

The results of our study show that there is a likelihood that patients with type II diabetes may fail to attain an ETR as evidenced by 22.8% of the study patients unable to achieve an ETR. A study was conducted by Albert Lecube and colleagues[1] that investigated whether hyperglycemia (including impaired fasting blood sugar and established diabetes mellitus) has any effect on the response of chronic hepatitis C positive patients to interferon and ribavirin therapy. The study concluded that abnormal glucose homeostasis is an independent predictor of poor virological response to anti-viral therapy in CHC positive patients[11,12].

Insulin resistance is likely to cause progression of liver fibrosis in chronic hepatitis C positive patients and may be one of the reasons why these patients are unable to achieve sustained viral response (SVR)[15-17]. This was concluded in a study by Hesham and colleagues[13]. Adverse effects from the treatment itself were also more often reported in diabetics as compared to non-diabetic recruits.

Many patients with chronic hepatitis C (CHC) often have diabetes mellitus (DM)[18]. However, it is undetermined whether DM affects patient response to interferon (IFN) plus ribavirin therapy. Therefore, the objective of a study conducted by Ichiro Konishi[14] was to assess the effect of DM on the outcome of IFN-α2b plus ribavirin therapy. The findings indicate that DM reduces the response to IFN-α2b plus ribavirin therapy in CHC patients[14,19,20].

Another study conducted by Jason et al[15] hypothesized that virus-induced insulin resistance may be a mechanism for fibrogenesis in chronic hepatitis C virus infection. So, it can be concluded that the virus itself makes the patient prone to develop diabetes mellitus due to insulin resistance and then also makes the patient less likely to attain SVR due to the concomitant diabetes mellitus[21-24].

Chia Yen Dai and colleagues[16] aimed to explicate

Table 1: Patients' characteristics

Variable	N	%
Gender of patient		
Female	43	43.0%
Male	57	57.0%
Age		
<=30	9	9.0%
31-40	29	29.0%
41-50	40	40.0%
>50	22	22.0%
Mean±SD	43.32	9.42
FBS		
<=75	2	2.0%
76-100	53	53.0%
101-124	28	28.0%
125-150	13	13.0%
151-175	2	2.0%
>175	2	2.0%
Mean±SD	106.48	23.45
RBS		
<=125	7	7.0%
126-150	10	10.0%
151-175	7	7.0%
176-200	28	28.0%
201-225	23	23.0%
226-250	15	15.0%
251-275	5	5.0%
276-300	3	3.0%
301-325	1	1.0%
>325	1	1.0%
Mean±SD	199.12	45.82
HBA1c		
<=6	30	30.0%
6.1-7	32	32.0%
7.1-8	30	30.0%
8.1-9	6	6.0%
9.1-10	1	1.0%
>10	1	1.0%
Mean±SD	6.87	1.01
SGPT		
<=50	37	37.0%
51-70	54	54.0%
71-90	8	8.0%
>90	1	1.0%
Mean±SD	56.17	12.18

Table 2: Statistical comparison of end of treatment response

Variable	ETR	N	%	P value
Gender: Female	No	7	7.0%	0.165
	Yes	36	36.0%	
Male	No	16	16.0%	
	Yes	41	41.0%	
		Mean	SD	
Age of patient	No	43.9565	10.03393	0.714
	Yes	43.1299	9.28404	
FBS at the start of AVT	No	119.5217	28.05007	0.012
	Yes	102.5844	20.53325	
RBS at the start of AVT	No	231.9565	43.67595	<0.001
	Yes	189.3117	41.94020	
HbA1c at the start of AVT	No	7.8348	.80994	<0.001
	Yes	6.5883	.88511	
SGPT at the start of AVT	No	60.5217	9.12474	0.05
	Yes	54.8701	12.71794	

effect of IR and beta-cell function on the response to anti-viral therapy in chronic hepatitis C (CHC) patients. IR was associated with reduced SVR to (PEG-IFN)/ribavirin therapy for CHC, especially among 'difficult-to-treat' patients[25-28]. These findings suggested that pretreatment testing of pancreatic beta cell function and IR could enable treatment outcome to be predicted and successful treatment regimens to be determined beforehand[29-32].

Currently, Direct-Acting Anti-Virals (DAAs) are being used for the treatment of Hepatitis C, and Interferon based therapy is virtually out of practice. But a school of thought still exists that believe we may need to revert to interferon therapy if the future unveils major adverse effects with the DAAs.

CONCLUSION

It can thus be concluded that a poor therapeutic outcome is recorded in HCV positive patients with co-morbid diabetes mellitus. Multiple factors come into play in this complex interaction of diabetes with viral hepatitis, of which insulin resistance is thought to be playing a pivotal role.

REFERENCES

1. Lecube A, Hernandez C, Genesca J, Simo R. Proinflammatory cytokines, insulin resistance, and insulin secretion in chronic hepatitis C patients. Diabetes Care. 2006;29:1096-101.
2. Abd El-Satar H, Mahfouz M, Rashed L, Ahmed D. Insulin resistance in patients with chronic hepatitis C infection. Aust. J. Basic Appl Sci. 2010;4:4554-8.
3. Nocente R, Ceccanti M, Bertazzoni G, Cammarota G, Silveri N, Gasbarrini G. HCV infection and extrahepatic manifestations. Hepatogastroenterology. 2003;50:1149-54.
4. Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M,Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. Ann Intern Med. 2000;133:592-9.
5. Pattullo V. , Heathcote J. Hepatitis C and diabetes: one treatment for two diseases?. Liver Int. 2010;30:356–64.
6. Konishi I, Horiike N, Hiasa Y, Tokumoto Y, Mashiba T, Michitaka K., et al. Diabetes mellitus reduces the therapeutic effectiveness of interferon-α2b plus ribavirin therapy in patients with chronic hepatitis C. Hepatol Res. 2007;37:331–6.
7. Bernsmeiera C, Heima MH. Insulin resistance in chronic hepatitis C: mechanisms and clinical relevance. Swiss Med Wkly. 2009;139:678–84.
8. Elgouhari HM, Zein CO, Hanouneh I, Feldstein AE, Zein NN. Diabetes mellitus is associated with impaired response to antiviral therapy in chronic hepatitis C infection. Dig Dis Sci. 2009 Dec;54(12):2699-705.
9. El-Shazly Y, Rafee M, Al-Swaf R. Effect of well controlled diabetes mellitus on sustained virologic response in chronic HCV genotype 4 infected patients. J Diabet. 2011;34(10):73-85.
10. Ahmed WU, Arif A, Qureshi H, Alam SE, Ather R, Fariha S, et al. Factors Influencing the response of interferon therapy in chronic hepatitis C patients. JCPSP. 2011;21(2):69-73.
11. Kita Y, Mizukoshi E, Takamura T, Sakurai M, Takata Y,

Arai K, et al. Impact of diabetes mellitus on prognosis of patients infected with hepatitis C virus. Metabolism 2007;56:1682–8.

12. Petta S, Camma C, Di Marco V, Alessi N, Cabibi D, Caldarella R, et al. Insulin resistance and diabetes increase fibrosis in the liver of patients with genotype 1 HCV infection. Am J Gastroenterol. 2008;103:1136 – 44.

13. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. Oct 9 2008;359(15):1577-89.

14. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. Jun 2012;35(6):1364-79.

15. Thuluvath PJ. Is there a link between hepatitis C virus and new onset of diabetes mellitus after liver transplantation? Liver Transpl2007; 13: 5–7.

16. Veldt BJ, Chen W, Heathcote EJ, *et al*. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. Hepatology 2008; 47: 1856–62.

17. Knobler H, Schihmanter R, Zifroni A, Fenakel G, Schattner A: Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. Mayo Clin Proc 75:355–359, 2000

18. Mason A, Nair S: Is type II diabetes another extrahepatic manifestation of HCV infection? Am J Gastroenterol 98:243–246, 2003

19. Wilson C: Hepatitis C infection and type 2 diabetes in American-Indian women. Diabetes Care 27:2116–2119, 2004

20. Hanouneh IA, Feldstein AE, Lopez R, *et al*. Clinical significance of metabolic syndrome in the setting of chronic hepatitis C virus infection. Clin Gastroenterol Hepatol 2008; 6: 584–9.

21. Carrion JA, Martinez-Bauer E, Crespo G, *et al*. Antiviral therapy increases the risk of bacterial infections in HCV-infected cirrhotic patients awaiting liver transplantation: a retrospective study. J Hepatol 2009; 50: 719–8.

22. Giordanino C, Bugianesi E, Smedile A, *et al*. Incidence of type 2 diabetes mellitus and glucose abnormalities in patients with chronic hepatitis C infection by response to treatment: results of a cohort study. Am J Gastroenterol 2008; 103: 2481–7.

23. Arase Y, Suzuki F, Suzuki Y, *et al*. Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C. Hepatology 2009; 49: 739–44.

24. Romero-Gomez M, Fernandez-Rodriguez CM, Andrade RJ, *et al*. Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. J Hepatol 2008; 48: 721–7.

25. Chehadeh W, Al-Nakib W. Severity of liver disease predicts the development of glucose abnormalities in patients with chronic hepatitis B or C following achievement of sustained virological response to antiviral therapy. J Med Virol 2009; 81: 610–8.

26. Chehadeh W, Abdella N, Ben-Nakhi A, Al-Arouj M, Al-Nakib W. Risk factors for the development of diabetes mellitus in chronic hepatitis C virus genotype 4 infection. J Gastroenterol Hepatol 2009; 24: 42–8.

27. Conjeevaram HS, Burant CF, McKenna B, *et al*. A randomized, double-blind, placebo-controlled study of PPAR-gamma agonist pioglitazone given in combination with peginterferon and ribavirin in patients with genotype-1 chronic hepatitis C. Hepatology2008; 48: 384A.

28. Romero-Gomez M, Diago M, Andrade RJ, *et al*. Treatment of insulin resistance with metformin in naive genotype 1 chronic hepatitis C patients receiving peginterferon alfa-2a plus ribavirin. Hepatology 2009; 50: 1702–8.

29. Guiltinan AM, Kaidarova Z, Custer B, *et al*. Increased all-cause, liver, and cardiac mortality among hepatitis C virus-seropositive blood donors. Am J Epidemiol 2008; 167: 743–50.

30. Ohki T, Tateishi R, Sato T, *et al*. Obesity is an independent risk factor for hepatocellular carcinoma development in chronic hepatitis C patients. Clin Gastroenterol Hepatol 2008; 6: 459–64.

31. Chen T, Jia H, Li J, *et al*. New onset diabetes mellitus after liver transplantation and hepatitis C virus infection: meta-analysis of clinical studies. Transpl Int 2009; 22: 408–15.

32. Sanchez-Perez B, Aranda Narvaez JM, Santoyo Santoyo J, *et al*. Influence of immunosuppression and effect of hepatitis C virus on new onset of diabetes mellitus in liver transplant recipients. Transplant Proc 2008; 40: 2994–6.