ORIGINAL ARTICLE

Treatment Response of Direct Acting Antiviral Agents on Glycemic Control in Diabetic Patients with Chronic Hepatitis C

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ABSTRACT

Aim: To Determine the Treatment Response of Direct Acting Antiviral Agents on Glycemic Control in Diabetic Patients with Chronic Hepatitis C.
Study Design: Hospital based Cross-sectional Study.
Place and Duration of Study: Department of Medicine, Mayo Hospital, Lahore from May, 2017 to July, 2018.
Methodology: 68 patients of either sex between the age group of 18-65 years and diagnosed cases of diabetes mellitus with detected HCV RNA by PCR and candidates for oral antiviral therapy for HCV infection were selected via Probability Simple Random Sampling. HbA1C levels were checked at the start of treatment with DAA agents and then at 3 months to assess the glycemic response.
Results: Out of the total of 68 patients enrolled in the study, 60.3% were male and 39.7% were female. SVR was achieved in 61(89.7%) patients and was not achieved in 7(10.3%) patients. The age of the patients ranged from 32 to 63 years with a mean value of 51.57 ± 8.48 years. The mean HbA1C at baseline and 3 months was 7.82±0.53% and 7.81±0.51% respectively. HbA1C at 3 months was only 0.0059% lower than baseline HbA1C (95% CI, -0.0291 to 0.0408).
Conclusion: The glycemic control improved during DAA therapy as compared to baseline level; however, improvement difference was statistically insignificant. (p=0.738)
Keywords: Direct acting antiviral agents, Glycemic control, Chronic hepatitis C

INTRODUCTION

Chronic Hepatitis C (HCV) virus is one of the leading causes of morbidity and mortality worldwide affecting approximately 170 million people.[1] Over the past decade, the treatment regimens for HCV have dramatically changed, switching over from interferon to the newer oral direct acting antiviral (DAA) agents.[2,3] With the advent of the novel treatment options for HCV virus, its association with various metabolic processes has also been a major area of interest for the physicians, primarily the hepatologists. The well recognized metabolic derangements associated with HCV infection include metabolic syndrome, dyslipidemias, hepatic steatosis and insulin resistance[4-7].

Insulin resistance in the general population is mainly caused by physical inactivity and overeating. But in HCV infected patients, modulation of cellular gene expression, inflammation of the hepatocytes, activation of the inflammatory cytokines and interference with the insulin and lipid signaling pathways have all been implicated[8-10]. These alongwith other contributory factors have led to a higher prevalence of insulin resistance in HCV infected individuals compared to the patients with other hepatic disorders as well as the general population.[11] Almost 30-70% of chronic hepatitis C patients have insulin resistance to some extent[12,13]. Type 2 diabetes mellitus develops 3.8 times more in these patients compared to HCV negative patients[1].

The presence of insulin resistance not only makes a person prone to develop type 2 diabetes mellitus but also augments the risk of serious complications including infections, cardiovascular and renal diseases. In cirrhotic patients, these complications of insulin resistance do not pose a serious threat to life but intrahepatic complication like hepatocellular carcinoma and extrahepatic complication in the form of gastric cancer are serious concerns[14,15].

In the era of interferon based therapy for HCV infection, patients with diabetes mellitus were considered to be relatively contraindicated to receive therapy owing to the negative effect of insulin resistance on sustained virological response (SVR)[16]. This response was assumed to be due to down-regulation of the interferon signaling pathway by the virus' core protein, leading to a decreased efficacy of the interferons[12,16] So HCV positive patients with type 2 diabetes mellitus were usually not considered for interferon based therapy and were, therefore, excluded from studies. So very limited data is available demonstrating the effects of HCV treatment on glycemic control.

The advent of newer direct acting antiviral (DAAs)agents for treatment of chronic HCV has given some hope to type 2 diabetic patients. Although the effect of DAAs on glycemic control is still obscure, it is hypothesized that treatment with these agents will lead to an improved insulin resistance, depicted by changes in post treatment hemoglobin A1C (HbA1C) levels and decreased dosages of anti-diabetic medications at the time of SVR. The objective of this study is to check the response of DAA agents on glycemic control in diabetic patients when they were treated for HCV infection.

METHODOLOGY

This Hospital based Cross-sectional Study was conducted in Mayo Hospital, Lahore from May, 2017 to July, 2018. 68 patients were selected via Probability Simple Random

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Sampling Technique keeping 95% Confidence level and 3% margin of error. The study was approved by the Ethical Committee of the institution. 68 patients of either sex between the age group of 18-65 years and diagnosed cases of diabetes mellitus (i.e., HbA1C levels≥ 6.5%) with detected HCV RNA by PCR and candidates for oral antiviral therapy for HCV infection were selected for the study . Patients with history of alcohol abuse, history of drugs causing hyperglycemia e.g., corticosteroids, thiazide diuretics etc. were not included in the study. Patients having decompensated liver disease, prior or ongoing cases of hepatocellular carcinoma as well as those patients having co-infection with HBV or HIV were excluded from the study. Likewise patients of chronic kidney disease as assessed by Creatinine Clearance < 30ml/min, patients having any kind of malignancy, pregnant females, extremely fragile and underweight individuals, patients with known psychiatric illness e.g., severe depression, or patients who were taking drugs like phenytoin, rifampin, carbamezepine etc, and patients with pancytopenia i.e., Hb <10g/dl, WBC $<4x10^{3,}$ platelet <100,000 were also excluded from the study.

Baseline HbA1C levels were recorded for all the enrolled subjects and was repeated at 3 months, i.e., at the end of therapy with DAA agents. Quantitative PCR was performed at the start of therapy to check the viral load and at the end of therapy with DAA agents and then at 3 months after the completion of therapy to assess Sustained Virological Response (SVR). Baseline Complete Blood Counts (CBC), Liver Function Tests (LFTs), Serum Albumin, Prothrombin Time (PT), International Normalized Ratio (INR), Ultrasonography of the abdomen and Renal Function Tests were carried out for all the subjects.

The treatment regimen of HCV for all the patients included DAA consisting of a Nucleotide analogue Sofosbuvir 400mg daily, NS5A inhibitor Daclatasvir 60mg daily. For the control of diabetes, either Oral Hypoglycemic Agents (OHA) or Injection Insulin, as per the patients' glycemic control and requirement were continued.

All the collected data was entered and analyzed using computer software SPSS Version 25.0. Quantitative data was calculated and presented as mean ±SD. Qualitative data was presented in the form of frequency and percentages. Independent sample t-test was applied to check the association between mean HbA1C levels at 0 and 3 months of DAA therapy with age, sex, type of antiglycemic agent used and the status of SVR.

RESULTS

Out of the total of 68 diabetic, Anti HCV positive patients who received DAA agents, 60.3% were male and 39.7% female. The SVR was achieved in 61 (89.7%) patients and was not achieved in 7 (10.3%) patients (Picture 1).

The age of the patients ranged from 32 to 63 years with a mean value of 51.57 ± 8.48 years. The minimum baseline HbA1C was 6.7% and maximum 9.3% with a mean value of 7.82±0.53%. The mean HbA1C at 3 months of DAA therapy was 7.81± 0.51% (Table 1).

The mean baseline HbA1C level before starting DAA therapy in male patients was 0.398% higher than that of female patients. Male patients had significantly higher baseline HbA1C as compared to female patients (p=0.002). The mean baseline HbA1C did not differ significantly in two age groups (p=0.115), type of antiglycemic agent used (p=0.875), and in group of patients who achieved SVR later (p=0.779) (Table 2).

The mean HbA1C at 3 months of DAA therapy of male patients was 0.339% higher than that of female patients. Male patients had significantly higher HbA1C at 3 months of DAA therapy as compared to female patients (p=0.007). The mean HbA1C at 3 months of DAA therapy did not differ significantly in two age groups (p=0.145), type of antiglycemic agent used (p=0.389), and in group of patients who achieved SVR later (p=0.531) (Table 3).

On average, HbA1C at 3 months of DAA therapy was only 0.0059% lower than baseline HbA1C (95% CI, -0.0291 to 0.0408). The glycemic control was better during DAA as compared to baseline level; however, the difference was statistically insignificant (p=0.738) (Table 4).

Fig. 1: Frequency distribution of sustained virological response (SVR) amongst patients treated with direct acting antiviral drugs (n=68)

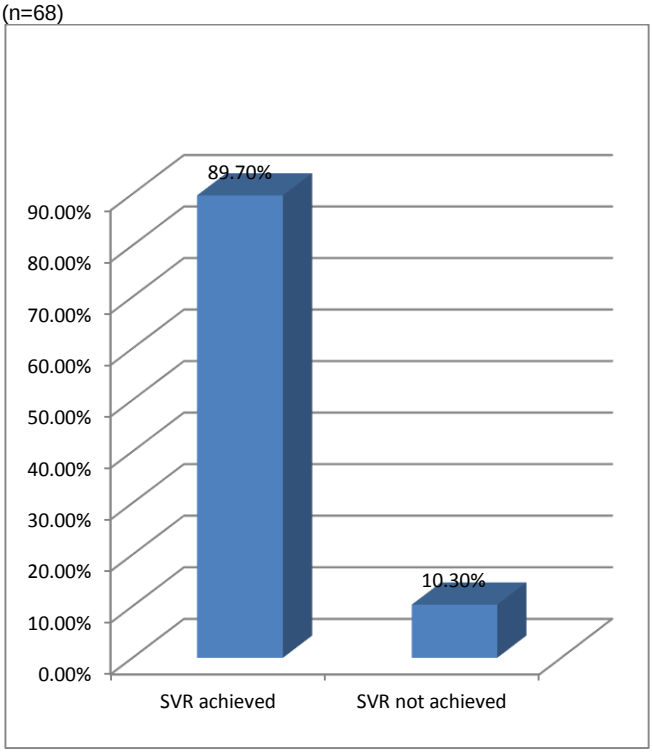

Table 1: Descriptive Analyses of Quantitative Variables (n=68)

Quantitative Variables	Minimum	Maximum	Mean	Standard deviation
Age (years)	32	63	51.57	8.48
HbA1C (%)at start of therapy	6.7	9.3	7.82	0.53
HbA1C(%)at 3months of therapy	6.8	9.1	7.81	0.51

Table 2: Association of mean value of baseline HbA1C with different parameters (n=68)[1]

Parameters/Categories	Mean	Standard deviation	Mean difference	p-value	95% Confidence Interval
Gender: Male Female	7.976 7.578	0.508 0.478	0.398	0.002	0.152 - 0.644
Age group: Young adults[2] Middle aged adults[3]	7.627 7.872	0.704 0.764	-0.245	0.115	-0.551 - 0.061
Antiglycemic agent: OHA[4] Insulin	 7.812 7.835	 0.533 0.535	-0.023	0.875	-0.322 - 0.275
Sustained Virological Response: Achieved Not-achieved	 7.811 7.871	 0.545 0.403	-0.060	0.779	-0.485 - 0.365

1= Independent sample T-test was used, 2=Age group from 18 to 44 years, 3= Age group from 45 to 65 years, 4=Oral hypoglycemic agents

Table 3: Association of mean HbA1C level at 3 months of DAA therapy with different parameters (n=68)[1]

Parameters/Categories	Mean	Standard deviation	Mean difference	p-value	95% Confidence Interval
Gender: Male Female	7.946 7.607	0.529 0.431	0.339	0.007	0.096 - 0.582
Age group: Young adults[2] Middle aged adults[3]	7.640 7.860	0.654 0.465	-0.221	0.145	-0.519 - 0.078
Antiglycemic agent: OHA[4] Insulin	7.780 7.906	0.501 0.560	-0.126	0.389	-0.414 - 0.163
Sustained Virological Response: Achieved Not-achieved	 7.798 7.929	 0.530 0.368	-0.130	0.531	-0.543 - 0.282

1= Independent sample T-test was used, 2=Age group from 18 to 44 years, 3= Age group from 45 to 65 years, 4=Oral hypoglycemic agents

Table 4: Paired Samples statistics of HbA1C levels on 2 different occasions in diabetic hepatitis C patients taking DDA therapy (n=68)[1]

Paired differences (Initial HbA1C – HbA1C at 3 months of DAA therapy)	Mean	Standard deviation	p-value	95% Confidence Interval (lower-upper)
	0.0059	0.1444	0.738	-0.0291 - 0.0408

1= Paired T-test was used, DAA=Direct acting antiviral agents

DISCUSSION

Chronic hepatitis C virus infection, apart from damaging the liver, has several extrahepatic manifestations, that not only affect the course of the disease but has negative impact on the outcome as well. The effect of HCV infection on glucose metabolism has been an area of interest for the clinicians ever since the discovery of this virus in 1989.

In a study conducted by Hashim et al, out of 378 patients with sustained virological response after 3 months of DAA agents, 292 (77.2%) patients achieved Improved Glycemic Control and 78 (26.7%) patients needed to decrease their dose of antiglycemic agent. Improved Glycemic Control was assessed by the reduction of Fasting Plasma Glucose of ≥20mg/dl or Homesostasis Model Assessment- Insulin Resistance (HOMA-IR) of a minimum of 0.5 or HBA1C reduction of at least 0.5%[17].

In another study, Justine Hum and colleagues concluded that DAA-based eradication of HCV is associated with improved glycemic control in patients with diabetes as evidenced by decreased mean HbA1C and decreased insulin use. Pretreatment HbA1C levels were kept similar in patients who achieved SVR (7.20%) and those who did not (7.27%). The drop in average HbA1C level after treatment was greater in those achieving SVR (from 7.2% to 6.82%), a mean drop of 0.37 ±1.2%) than in those for whom treatment failed (from 7.27% to 7.08%) , a mean drop of 0.19 ±1.3%), yielding a mean difference of -0.18% (P = 0.03)[18].

The results of both these above mentioned studies differed from our study as there was no significant reduction of HbA1C in our diabetic patients who were treated with DAA agents for HCV infection.(p=0.738, 95% CI= -0.0291 - 0.0408)

Another study carried out by H. F. Huang et al, no significant difference in HbA1C levels at end of follow up (EOF) was observed i.e., from 5.5±0.6% to 5.6±0.6%, P=0.17. EOF was defined as the visit 12 weeks after the end of treatment. Also no significant difference in the mean insulin resistance (IR) was observed i.e., 2.6±1.8 at baseline to 2.7±2.9, P= 0.75 at EOF[19]. The results of this study were similar to the results recorded in our patients.

CONCLUSION

The glycemic control improved during DAA therapy as compared to baseline level; however, improvement difference was statistically insignificant. Male gender had significantly inferior glycemic control before and during DAA therapy as compared to female gender. The glycemic control did not differ significantly amongst young adult and middle-aged adult groups as well as amongst patients using insulin or oral drugs as antiglycemic agents.

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