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Effect of Treatment with Direct Acting Antiviral on Glycemic Control in Patients with Diabetes Mellitus and Chronic Hepatitis C

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ABSTRACT

Introduction and aim. The effect of the new direct acting antiviral drugs (DAAs) for chronic hepatitis C (HCV) on glycemic control is unknown. **Materials and methods.** We conducted a retrospective cohort study of patients who were treated for chronic HCV with direct-acting antiviral medications at a single academic institution between May 2013 and April 2016. Univariate analysis was performed comparing subjects pre- and post-treatment. **Results.** One hundred seventy-five consecutive adult patients were treated for chronic HCV and met enrollment criteria. The majority (80.8%) were genotype 1 and overall cohort sustained virologic response at week 12 (SVR12) was 97.8%. Thirty-one (18.5%) had diabetes mellitus (DM); twenty-six had pre- and post-treatment HbA1c values. Of these, 76.9% were male and 61.5% had cirrhosis. Ninety-six percent were prescribed sofosbuvir-based therapy and all but one (96.8%) achieved SVR12. Three patients were started on treatment despite meeting the definition for poorly controlled DM (HbA1c > 9 mg/dL). There was no significant difference when comparing pre-treatment (7.36 mg/dL, 95% CI 6.55-8.16) to post-treatment HbA1c (7.11 mg/dL, 95% CI 6.34-7.88, p = 0.268). Thirty-one percent of subjects required dose escalation or the initiation of insulin based therapy during treatment. **Discussion.** Although chronic HCV is associated with exacerbation of insulin resistance, our results showed HbA1c to be unaffected by eradication of chronic HCV with DAA in diabetic patients with and without cirrhosis. Paradoxically, almost 1/3 of patients required escalation of anti-diabetic therapy during treatment. Long-term studies are warranted to understand the relationship between HCV viral eradication and insulin metabolism.

Key words. Hepatology. Cirrhosis. Liver. Portal hypertension. Viremia.

INTRODUCTION

Chronic hepatitis C (HCV) virus infects an estimated seven million people in the United States and 170 million individuals worldwide, with significant associated morbidity and mortality.[1] The landscape of HCV management is changing dramatically with the advent and approval of the new oral direct acting antiviral (DAA) medications.[2,3] With so many resources being placed into the development of novel therapies, investigation into how HCV interacts with other metabolic processes remains of interest to the hepatology community at large. It is widely recognized that HCV infection is associated with several metabolic derangements including hypolipidemia, hepatic steatosis and metabolic syndrome.[4-7] Several studies have also confirmed a multifold increase in the prevalence of glucose abnormalities in patients with HCV as compared to controls.[8,9] As such, the virus has been implicated in the development of insulin resistance (IR) by modulating cellular gene expression and interfering with insulin signaling pathways.

Insulin resistance is a complex pathophysiologic condition where higher concentrations of insulin are required to maintain normal glycemic ranges and glucose utilization in insulin target tissues. When pancreatic beta cells can no longer produce enough insulin to overcome insulin resistance, the condition is classified as type 2 diabetes mellitus (T2DM). Nearly 30-70% of patients with chronic hepatitis C (CHC) show some form of IR.[10,11] Patients chronically infected with HCV

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are 3.8 times more likely to have T2DM than HCV-negative subjects.[1]

Research has yet to definitively elucidate whether it is the virus itself or the inflammatory response of the host to HCV infection that contributes most to increased IR and long-term risk of developing T2DM.[12] Interestingly, insulin resistance is shown to be higher in CHC than in other chronic liver diseases, despite controlling for confounders of fibrosis stage, age and family history of T2DM.[13] At a molecular level, HCV decreases glucose transport into cells by down-regulating glucose transporter receptor (GLUT2). The virus also up-regulates expression of genes for phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6P-ase), which are integral enzymes within the hepatic gluconeogenesis pathway. HCV also induces degradation of insulin receptor substrate (IRS), which blocks intracellular insulin signaling. Clearance of the virus has been shown to result in improved IR as measured by reduction in homeostasis model of assessment (HOMA) value, suggesting the virus itself plays a significant role in mediating IR.[1,13,15]

Historically, poorly controlled diabetes was a relative contraindication to interferon (IFN) based HCV therapy as IR was shown to negatively affect rates of sustained virological response (SVR).[16] The underlying mechanism for this largely remains unknown; it is thought that the virus' core protein down-regulates the IFN signaling pathway, thereby decreasing IFN efficacy.[10,16] In light of this, patients with DM were often excluded from studies regarding HCV management. As a consequence, historical research looking into the effects of HCV treatment on glycemic control is lacking.

The effect of the new DAAs for CHC on glycemic control is equally unknown. Our retrospective cohort study was designed to investigate whether treatment with DAA regimens leads to improved post-treatment insulin resistance. We hypothesize that treatment of HCV with novel direct-acting antiviral medications will lead to improved glycemic control as evidenced by reduced hemoglobin A1c (HbA1c) values and decreased requirement for DM-modulating medications at the time of SVR.

MATERIAL AND METHODS

We conducted a retrospective cohort study of patients treated for CHC with DAA medications at the University of Virginia between May 2013 and April 2016. Only patients at or above age 18 were included in the analysis. Subjects were excluded if they were treated without at least one DAA medication. Baseline demographics (age, gender and HCV genotype), laboratory values [liver associated enzymes, creatinine, hemoglobin, coagulation parameters, HbA1c pre- and post-treatment, alpha fetoprotein (AFP)] and both HCV and DM treatment medications were reviewed. Post-treatment laboratory values were obtained at the time that sustained virologic response at 12 weeks (SVR12) was examined. Diabetes was defined by ICD-9 code and confirmed by a hemoglobin A1c > 6.5%, treatment with anti-hyperglycemic medications including insulin or a fasting glucose > 200 mg/dL. Changes in diabetes medications were made at the discretion of the treating provider, most often the primary care provider. Dose change in medical therapy of DM defined as a higher or lower dose of either insulin or oral-based anti-hyperglycemic medications at the time SVR12 was also extracted from the medical record.

Statistical analysis

Descriptive statistics were performed for the entire cohort and the subgroups with DM and cirrhosis respectively. Univariate analysis was performed using paired t-test and McNemar's test for categorical and continuous variables as appropriate. Pearson's correlation coefficients were calculated. All data set manipulation and statistical analyses were carried out using SAS (version 9.4, Cary, NC). No data involving prisoners were included in this analysis. All statistical tests for significance were two sided and a significance level of $p \leq 0.05$ was considered statistically significant. Institutional review board approval was obtained.

RESULTS

One hundred seventy-five consecutive adult patients with mean age 56 ± 9.5 years were treated for chronic HCV and were enrolled. Mean cohort body mass index was 29.9 ± 6.8 kg/m^2. Overall cohort SVR12 was 97.8%. Kidney function as measured by serum creatinine was unaffected by DAA treatment (mean increase post-treatment of 0.04 g/dL, 95% CI -0.03-0.10, p = 0.259). Twenty-two (12.6%) subjects had cirrhosis with mean Model for End-Stage Liver Disease (MELD) score of 7.7 ± 1.8. In general, when comparing subjects with cirrhosis to those without cirrhosis, no statistically or clinically significant differences were found across baseline demographics, laboratory values, post-treatment laboratory values or SVR12 with several exceptions with the exception of pre-treatment AST (cirrhosis 129.5 U/L, 95% CI 67.2-191.2 U/L *vs.* non-cirrhosis 80.5 U/L, 95% CI 69.2-91.9 U/L, p = 0.009) and pre-treatment HbA1c (cirrhosis 7.7, 95% CI 4.8-10.7 *vs.* non-cirrhosis 6.2%, 95% CI 5.8-6.5%, p = 0.016) despite similar distributions of diabetes in the two groups (Table 1).

Thirty-one (18.5%) subjects had DM; twenty-six had paired pre- and post-treatment HbA1c values. Of these,

76.9% (n = 20) were male gender and 61.5% (n = 16) had cirrhosis with mean Model for End-Stage Liver Disease (MELD) score of 8.6 ± 2.9. The majority (80.8%, n = 21) was genotype 1, with four (15.3%) subjects genotype 2 and one (3.9%) genotype 3. Almost all (96.8%) were prescribed sofosbuvir (SOF) based therapy [ten SOF + ledipasvir (LED), seven SOF + simeprevir (SIM), five SOF + ribavirin (RBV), two SOF + RBV + pegylated interferon (PEG-IFN), one SOF + LED + RBV]. Six subjects had undergone previous IFN based therapy and were either nonresponders or had post-treatment HCV recurrence. All but one subject with DM (n = 25, 96.8%) achieved SVR12.

AFP decreased with DAA based treatment with mean value 14.8 IU/mL (95%CI 9.6-20.0 IU/L) pre-treatment compared to 5.6 IU/L (95% CI 4.4-6.8 IU/L) post-treatment (p = 0.002). The change in AFP with treatment was strongly correlated with change in HbA1c (r = 0.81). Aspartate aminotransferase (AST) levels also decreased with treatment (mean 101.0 IU/L, 95% CI 71.2-130.8 pre- *vs.* 33.4 IU/L, 95% CI 20.6-46.3, p < 0.001) as did alanine aminotransferase (ALT) levels (mean 98.2 IU/L, 95% CI 76.3-120.0 pre- *vs.* 32.7 IU/L, 95% CI 17.9-47.6, p < 0.001). Laboratory parameters that were unaffected by treatment included total bilirubin, creatinine, international normalized ratio (INR), and hemoglobin levels. MELD score was also not statistically significantly different when comparing pre- (8.6) to post-treatment values (8.2) for just those subjects with cirrhosis (p = 0.404). BMI also did not change when comparing pre- (28.9 ± 6.8 kg/m^2) to post-treatment values (29.5 ± 7.5 kg/m^2).

Three patients were started on treatment despite meeting the definition for poorly controlled DM (HbA1c > 9 mg/dL). There was no significant difference in the primary outcome comparing pre-treatment (7.36 mg/dL, 95% CI 6.55-8.16) to post-treatment HbA1c (7.11 mg/dL, 95% CI 6.34-7.88) (p = 0.268). Thirty-one percent of subjects required dose escalation or the initiation of insulin based therapy during treatment. Eleven (42.3%) subjects were on insulin therapy post-treatment compared to six (23.1%) pre-treatment, however this was not statistically significant. Fourteen (53.8%) subjects were on oral DM medications pre-treatment compared to fifteen (57.7%) post-treatment. This was also not statistically significant (Table 2).

Table 1. Baseline demographics, laboratory values and treatment breakdown for twenty-six patients with paired pre- and post-treatment hemoglobin A1c values.

Age, mean	56 ± 9.5 years
Male gender, n (%)	20 (76.9)
Cirrhosis, n (%)	16 (61.5)
MELD score, mean*	8.6 ± 2.9
Genotype, n (%)	
1	21 (80.8)
2	4 (15.3)
3	1 (3.9)
Treatment regimen, n (%)	
Sofosbuvir + Ledipasvir	10 (38.5)
Sofosbuvir + Simeprevir	7 (26.9)
Sofosbuvir + Ribavirin	5 (19.2)
Sofosbuvir + Ribavirin + Pegylated interferon	2 (7.8)
Sofosbuvir + Ledipasvir + Ribavirin	1 (3.9)
Boceprevir + Ribavirin + Pegylated interferon	1 (3.9)
Prior treatment, n (%)	6 (22.2)

** Calculated just for the 16 subjects with cirrhosis.*

DISCUSSION

In our retrospective cohort study at a single academic institution, we have demonstrated that HbA1c was largely

Table 2. Effect of treatment of chronic hepatitis C with direct acting antiviral medications on various laboratory parameters and diabetes treatment medications.

	Pre-treatment (n = 26)	Post-treatment (n = 26)
Change in laboratory values		
AFP (ng/mL)**	14.8 (9.6-20.0)	5.6 (4.4-6.8)
AST (U/L)***	101 (71.2-130.8)	33.4 (20.6-46.3)
ALT (U/L)***	98.2 (76.3-120.0)	32.7 (17.9-47.6)
Creatinine (mg/dL)	0.93 (0.83-1.03)	0.96 (0.85-1.08)
Hemoglobin (g/dL)	14.2 (13.4-14.9)	13.8 (13.0-14.6)
INR	1.04 (0.98-1.10)	1.05 (0.99-1.11)
HbA1c (%)	7.36 (6.55-8.16)	7.11 (6.34-7.88)
Change in medication prescription		
Insulin therapy, n (%)	6 (23.1)	11 (42.3)
Oral medications, n (%)	14 (53.8)	15 (57.7)

*No comparisons had this degree of significance.**

*AFP: alpha fetal protein. ALT: alanine aminotransferase. AST: aspartate aminotransferase. HbA1c: hemoglobin A1c. INR: international normalized ratio. MELD: Model for End-Stage Liver Disease. * Statistically significant p < 0.05 but > 0.01. ** p < 0.01 but > 0.001. *** Highly statistically significant p < 0.001.*

unaffected by treatment of chronic HCV with DAA in patients with and without cirrhosis. However, this may in part be attributable to clinical management of diabetes and hyperglycemia with pharmacologic therapy rather than a primary process of viral clearance itself as nearly one-third of our cohort had increasing dosages of their anti-hyperglycemic therapy. These findings are novel and important given prevalence rates of insulin resistance in patients with chronic HCV approach 70%[10,11] and the nearly four-fold increased risk of DM in patients with underlying chronic HCV.

Interestingly, we did not find a significant change in MELD score following HCV cure, which is contrary to the findings of others, who report a decrease in MELD following HCV cure,[17,18] in addition to regression of portal hypertensive complications. A recent multi-center report by Belli, *et al*.,[17] of 103 European patients found that 33% of patients listed for liver transplantation could be delisted following HCV cure and that this effect persisted to 60 weeks post-treatment, albeit it was attenuated to 20%. However, the largest benefit was seen in the most advanced liver disease (MELD > 15), a patient population that is significantly sicker than our cohort of low-MELD patients with well compensated liver disease and therefore our findings are not surprising.

Anemia related to HCV treatment has been well described with RBV therapy.[20-22] Traditionally, RBV has been shown to induce a hemolytic anemia through direct oxidative damage.[4] In this setting, a decreased lifespan of the RBC may provide an inaccurate HbA1c with falsely lower values, inducing bias towards the null hypothesis of our study. 34.6% of subjects were on RBV based therapy. DAAs, contrarily, have not been implicated in contributing to hemolysis. Accordingly, we did not observe a change in pre- and post-treatment hemoglobin values and thus indirectly controlled for any potential confounding when interpreting our results.

An important secondary outcome of our study is the observation of decreased AFP levels following treatment with DAAs; this provides several opportunities for future investigation. Based on this, we put forth the notion that AFP may be used as a biomarker surrogate for likelihood of SVR. Obtaining AFP early during therapy (e.g. week 4) rather than a viral load may be useful as a biomarker to predict response to HCV therapy and should be validated with future studies. There presently is little data that investigates the effect DAAs may have on AFP in comparison to IFN-based therapy. Future study may be warranted to compare the magnitude of difference in incidence of post-treatment HCC between therapy classes to assist in stratification practices, especially as IFN is still prescribed to patients with genotype 3 CHC based on current consensus guidelines.

Our study has several limitations. One, it is retrospective in nature and despite aggressive data extraction and verification, suffers from missing data. Two, our study was not powered to examine the effect of DM and more specifically those subjects with poor glycemic control as defined by HbA1c values, and thus no strong conclusions can be drawn about the effect of pre-existing DM and the likelihood of HCV cure. Regardless, the overall cure rate as defined by SVR12 in our cohort was similar to other post-marketing studies. Future large-scale investigation of this relationship seems warranted, including the impact of glycemic control on SVR12, including potential pooled post-hoc analysis of pre-marketing clinical trial data. Lastly, our study was fairly homogenous as > 95% of the population was treated with SOF-based therapy and with newer DAAs on the horizon including anticipated SOF-free regimens, the validity of these findings may be drawn into question when extrapolating to other therapies.

ABBREVIATIONS

- **AFP:** alpha fetoprotein.
- **ALT:** alanine aminotransferase.
- **AST:** aspartate aminotransferase.
- **CHC:** chronic hepatitis C.
- **DAA:** direct acting antiviral.
- **DM:** diabetes mellitus.
- **G6P-ase:** glucose-6-phosphatase.
- **GLUT2:** glucose transporter receptor.
- **HbA1c:** hemoglobin A1c.
- **HCV:** hepatitis C virus.
- **HOMA:** homeostasis model of assessment.
- **IFN:** interferon.
- **INR:** International Normalized Ratio.
- **IR:** insulin resistance.
- **IRS:** insulin receptor substrate.
- **LED:** ledipasvir.
- **MELD:** Model for End-Stage Liver Disease.
- **PEG-IFN:** pegylated interferon.
- **PEPCK:** phosphoenolpyruvate carboxykinase.
- **RBV:** ribavirin.
- **SIM:** simeprevir.
- **SOF:** sofosbuvir.
- **SVR:** sustained virologic response.
- **SVR12:** sustained virologic response at week 12.
- **T2DM:** type 2 diabetes mellitus.

AUTHOR CONTRIBUTIONS

Stine JG and Shah NL designed research; Stine JG, Wynter JA, Niccum B and Kelly V performed research; Stine JG analyzed data, Stine JG, Wynter JA, Niccum B, Kelly V Caldwell SH and Shah NL wrote the paper.

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CONFLICTS OF INTEREST STATEMENT

We have no conflicts of interest to report.

DATA SHARING STATEMENT

No additional data are available.

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