Success of Direct-Acting, Antiviral-Based Therapy for Chronic Hepatitis C Is Not Affected by Type 2 Diabetes

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Chronic hepatitis C virus (HCV) is a risk factor for type 2 diabetes. In the era of interferon-based HCV therapy, type 2 diabetes was associated with decreased likelihood of sustained virologic response (SVR). Preliminary studies suggest that type 2 diabetes may not reduce the efficacy of regimens involving direct-acting antiviral (DAA) medications. We aimed to determine whether preexisting type 2 diabetes is associated with a reduced rate of SVR achieved 12 weeks after treatment of HCV with DAA-based regimens.

Hepatitis C virus (HCV) is a blood-borne virus that causes chronic infection in 60–85% of infected individuals (1). Chronic HCV infects an estimated 2.7 million people living in the United States and is the leading cause of cirrhosis, liver transplantation, and hepatocellular carcinoma (HCC) in the Western world (1–3).

Chronic HCV also causes insulin resistance (IR), the physiological condition in which higher-than-normal concentrations of insulin are required to maintain normal blood glucose levels and adequate glucose uptake by insulin-targeted tissues (4). Research suggests that HCV induces IR by upregulating the production of enzymes involved in gluconeogenesis and downregulating intracellular insulin signaling and the expression of proteins responsible for glucose uptake (5). Other mechanisms by which HCV contributes to IR include activation of the host inflammatory response and induction of liver injury (4,6).

IR often leads to the development of type 2 diabetes (5). When pancreatic β -cells lose the ability to secrete sufficient insulin to compensate for IR, blood glucose levels rise; this marks the transition from simple IR to type 2 diabetes (7). Because chronic HCV is known to induce IR

and IR precedes type 2 diabetes, chronic HCV is a risk factor for type 2 diabetes (8). Those with chronic HCV are 3.8 times more likely to have type 2 diabetes than those not infected (8).

Until recently, chronic HCV was treated with a combination of interferon (IFN) (or pegylated IFN [PEG-IFN]) and ribavirin, antiviral medications that are not specific to HCV (9). The rate of viral clearance using these therapies, referred to as the rate of sustained virologic response (SVR), ranged from 40 to 80% with IFN-based regimens (10). Clearance was especially low (40–50%) in patients with viral genotype 1, the most common form of HCV (10).

The rate of SVR in patients treated with IFN-based regimens was also lower among those with IR or type 2 diabetes (6). Patients with IR were less than half as likely to achieve SVR as those without IR (11), and type 2 diabetes is sometimes considered a contraindication to IFN-based therapy (12). The precise mechanism underlying the association between IR and decreased response to IFN-based therapy remains elusive, but evidence suggests that HCV induces IR through the upregulation of a protein (suppressor of cytokine signaling 3) that inhibits both insulin sensitivity and IFN signaling (4).

Recently, the treatment of chronic HCV has been revolutionized by the advent of direct-acting antiviral (DAA) medications that target enzymes specific to HCV replication (i.e., HCV proteases and HCV polymerases). Although DAA medications were initially prescribed solely in conjunction with IFN, DAA-based regimens lacking IFN are becoming the mainstay of HCV therapy as evidence

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mounts for their superior efficacy (SVR >95% for genotype 1), tolerability, and convenience (13,14).

In addition, preliminary evidence suggests that the rate of SVR achieved with DAA-based regimens may not be affected by a diagnosis of type 2 diabetes (15,16), representing another potential advantage over IFN-based regimens. Our retrospective cohort study was designed to further evaluate whether preexisting type 2 diabetes impairs the efficacy of DAA-based regimens. We hypothesized that the presence of type 2 diabetes would not affect the rate of SVR achieved by 12 weeks beyond treatment (SVR12) with DAA-based regimens.

Design and Methods

We conducted a retrospective cohort study of all adults (age ≥ 18 years) treated for chronic HCV with DAA medications at the University of Virginia Health System in Charlottesville, Va., between May 2013 and April 2016. This study was approved by the health system's institutional review board, and all data were collected via examination of electronic medical records.

Chronic HCV was identified by International Classification of Diseases, 9th Revision (ICD-9) and 10th Revision (ICD-10), codes and confirmed by review of medical records. Type 2 diabetes was defined by corresponding ICD-9 and ICD-10 codes plus at least one of the following pre-treatment metrics: A1C $>6.5\%$, fasting glucose >126 mg/dL, or ongoing treatment with antihyperglycemic medication. The primary outcome, SVR12, was defined as undetectable serum HCV RNA at >12 weeks after completion of DAA-based therapy.

Data collected included basic demographic information (e.g., age and sex), prescribed anti-HCV regimen, HCV genotype, and prior HCV treatment. Laboratory values were collected before and after treatment, including but not limited to HCV viral load, A1C, random plasma glucose, liver-associated enzymes, and alpha-fetoprotein. Collection of post-treatment laboratory values coincided with the time of SVR12 evaluation. Antihyperglycemic regimens were also reviewed.

Patients were categorized as having or not having type 2 diabetes. Those with type 2 diabetes were compared to those without type 2 diabetes with respect to rate of SVR12, baseline demographics, HCV genotype, prior HCV treatment, and laboratory values.

Statistical Analysis

Descriptive statistics were performed for the entire cohort and the subcohorts with and without type 2 diabetes. Univariate analysis was performed using paired *t* tests and McNemar's tests for continuous and categorical variables as appropriate. Multivariable logistic regression was performed to assess for clinical risk factors associated with reduced rates of SVR12. Variables entered into the model included age, type 2 diabetes, cirrhosis, MELD-Na (Model for End-Stage Liver Disease–Sodium) score, and the presence of anemia. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, N.C.). No data involving prisoners were included in the analysis. All tests for statistical significance were two-sided, and a significance level of $P \leq 0.05$ was considered statistically significant.

Results

A total of 164 consecutive adult patients treated for chronic HCV with DAA-based regimens at our tertiary care institution were enrolled. The mean age was 56.9 ± 9.5 years, and the population included 94 men (57.3%) and 70 women (42.7%) (Table 1).

One hundred twenty-one patients (73.8%) were infected with HCV genotype 1, 28 (17.1%) with genotype 2, 11 (6.7%) with genotype 3, one (0.6%) with genotype 4, and three (1.8%) with HCV of unknown genotype. Forty-five patients (27.4%) had received prior anti-HCV treatment, and 22 (13.4%) had cirrhosis with a mean MELD-Na score of 7.9 ± 2.9 (Table 1). Eleven patients (6.7%) were taking immunosuppressive medications.

Thirty-one patients (18.9%) had type 2 diabetes. Of the 26 patients with type 2 diabetes for whom antihyperglycemic regimens were known, 19 (73.1%) used oral antihyperglycemic medications, and seven (26.9%) required injectable insulin. Before treatment, patients with type 2 diabetes had higher A1C values (7.5%, 95% CI 6.6–8.3%, vs. 5.5%, 95% CI 5.3–5.6%, $P < 0.001$) and random plasma glucose values (151.1 mg/dL, 95% CI 125.0–177.3, vs. 94.1 mg/dL, 95% CI 89.6–98.7, $P < 0.001$) than those without type 2 diabetes (Table 2). Those with and without type 2 diabetes were otherwise similar with respect to baseline demographics, HCV genotype ($P = 0.727$), prior HCV treatment ($P = 0.263$), and other pre-treatment laboratory values.

DAA medications used for anti-HCV therapy included sofosbuvir (an inhibitor of HCV NS5B polymerase), simeprevir (an inhibitor of HCV NS3 protease), and

TABLE 1 Study Cohort Characteristics

	Type 2 Diabetes (n = 31)	No Type 2 Diabetes (n = 133)	P
<i>Patient characteristics</i>			
Age, years	58.0 (6.4)	56.6 (10.1)	0.361
Female sex	14 (45.2)	56 (42.1)	0.757
Cirrhosis	7 (22.6)	15 (11.3)	0.139
Immunosuppressed	4 (12.9)	7 (5.3)	0.222
Prior HCV treatment	6 (19.4)	39 (29.3)	0.263
<i>HCV treatment outcome</i>			
SVR12	30 (96.8)	130 (97.7)	0.571

Data are expressed as n (%) except for age, which is expressed as mean (SD).

ledipasvir (an inhibitor of HCV NS5A) (14). All anti-HCV regimens included sofosbuvir (Figure 1, Table 3). Specifically, 81 patients (49.4%) were treated with sofosbuvir and ledipasvir; 36 (22.0%) with sofosbuvir and ribavirin; 30 (18.3%) with sofosbuvir and simeprevir; 15 (9.1%) with sofosbuvir, PEG-IFN, and ribavirin; and 2 (1.2%) with sofosbuvir alone. Treatment regimens for those with and without type 2 diabetes were not statistically significantly different ($P = 0.428$).

Overall SVR12 was 97.6% (160/164). SVR12 was 96.8% (30/31) among those with type 2 diabetes and 97.7% (130/133) among those without type 2 diabetes, but this

difference was not statistically significant ($P = 0.571$) (Figure 2, Table 1). Likewise, no clinical variables were associated with a reduced rate of SVR12 via multivariable logistic regression (Table 4).

Discussion

In this retrospective cohort study, the presence of pre-existing type 2 diabetes was not associated with a reduced rate of viral eradication among patients with chronic HCV treated with DAA-based regimens. This observation aligns with our hypothesis and adds to the small but growing body of evidence that type 2

TABLE 2 Pre-Treatment Laboratory Values

	Type 2 Diabetes (n = 31)	No Type 2 Diabetes (n = 133)	P
Viral load, 10^6 RNA/mL	7.7 (10.7)	4.6 (6.5)	0.155
A1C, %	7.5 (21)	5.5 (4)	<0.001
Random plasma glucose, mg/dL	151.1 (66.2)	94.1 (24.2)	<0.001
MELD-Na score	7.9 (3.1)	7.9 (2.9)	0.990
AST, units/L	96.3 (67.4)	85.0 (79.0)	0.492
ALT, units/L	94.8 (52.9)	101.3 (107.4)	0.643
AFP, ng/mL	15.6 (12.1)	14.1 (19.0)	0.683
Total bilirubin, mg/dL	0.85 (0.70)	0.76 (0.39)	0.505
Hemoglobin, g/dL	14.1 (1.4)	14.4 (1.7)	0.496
INR	1.08 (0.16)	1.07 (0.25)	0.996
Creatinine, mg/dL	0.83 (0.15)	0.90 (0.41)	0.119

Data are expressed as mean (SD). AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

FIGURE 1 DAA-based regimens. Patients were treated with five different anti-HCV regimens, all of which included sofosbuvir. There was no statistically significant difference between the treatment regimens prescribed to those with and without type 2 diabetes ($P = 0.428$).

diabetes does not impair the efficacy of DAA-based anti-HCV regimens.

To our knowledge, only two studies have previously examined the relationship between preexisting diabetes and rate of SVR achieved with DAA-based regimens. In 2015, Backus et al. (15) published a prospective study ($n = 4,026$) examining the rate of SVR achieved with sofosbuvir-based regimens, noting no association between diabetes and rate of SVR. Shortly thereafter, Butt et al. (16) published a retrospective study describing the rate of SVR achieved with both sofosbuvir-based ($n = 4,257$) and boceprevir-based ($n = 1,652$) regimens; diabetes was not associated with rate of SVR among sofosbuvir-treated patients (odds ratio [OR] 0.93, 95% CI 0.71–1.21) but was associated with a reduced rate

of SVR among boceprevir-treated patients (OR 0.73, 95% CI 0.53–1.00). Neither study explicitly distinguished between type 1 and type 2 diabetes. Regardless, accounting for the results of our study (in which all patients received sofosbuvir), all evidence suggests that type 2 diabetes does not impair the efficacy of sofosbuvir-based DAA regimens. It remains unclear whether type 2 diabetes impairs the efficacy of DAA-based regimens that do not include sofosbuvir.

The impact of type 2 diabetes on the efficacy of chronic HCV therapy is an important subject of study because chronic HCV is a risk factor for both IR and type 2 diabetes (6). Between 30 and 70% of patients with chronic HCV demonstrate IR (17) and up to 33% of those with chronic HCV also have type 2 diabetes (18). Of those

TABLE 3 Anti-HCV Medication Regimens

Regimen	Type 2 Diabetes ($n = 31$)	No Type 2 Diabetes ($n = 133$)	P
Sofosbuvir	0 (0.0)	2 (1.5)	0.428
Sofosbuvir + ledipasvir	14 (45.2)	67 (50.4)	
Sofosbuvir + simeprevir	8 (25.8)	22 (16.5)	
Sofosbuvir + ribavirin	5 (16.1)	31 (23.3)	
Sofosbuvir + PEG-IFN + ribavirin	4 (12.9)	11 (8.3)	

Data are expressed as n (%).

FIGURE 2 HCV treatment failure. The overall rate of SVR12 of HCV was 97.6% (160/164). The rate of failure to achieve SVR12 was 3.2% (1/31) among those with type 2 diabetes and 2.3% (3/133) among those without type 2 diabetes, but this difference was not statistically significant ($P = 0.571$).

living with both chronic HCV and type 2 diabetes, as many as 73% developed type 2 diabetes after acquiring HCV (19). Thus, a significant proportion of the 130–175 million people living with chronic HCV worldwide would benefit from optimization of the treatment of chronic HCV in the setting of type 2 diabetes (3). Although this subpopulation historically has responded poorly to anti-HCV therapy because of the aforementioned inhibition of IFN by IR (6), the recent advent of DAA medications

provides hope of improved cure rates by reducing the need for IFN (14).

Patients with chronic HCV who also have type 2 diabetes are at increased risk for pathological changes in the liver compared to patients who have chronic HCV but do not have type 2 diabetes. Among patients with chronic HCV, IR is an independent predictor of hepatic fibrosis, and diabetes is associated with a two- to threefold increase in the risk of developing cirrhosis and hepatic decompensation (19,20). Improved eradication of HCV in patients with type 2 diabetes would not only reduce the progression of liver fibrosis and dysfunction, but also decrease the burden of HCC, a condition to which this cohort is particularly susceptible (19). HCC is the most common cause of death in those with chronic HCV (21). At baseline, individuals with chronic HCV are 17 times more likely to develop HCC than HCV-negative individuals (22). Among those with chronic HCV, individuals with diabetes are nearly twice as likely to develop HCC (19), and HCC risk has been shown to correlate with the degree of IR (19). Eradicating HCV in this population would reduce the risk of HCC by eliminating the carcinogenic effects of HCV. However, because chronic HCV and type 2 diabetes independently increase the risk of HCC, future risk of HCC remains elevated if IR persists after HCV eradication, albeit to a lesser degree (21–23). In a 2016 retrospective study ($n = 10,817$) investigating predictors of HCC development after curing of chronic HCV, El-Serag et al. (24) found that patients with diabetes after treatment were significantly more likely to develop HCC than patients without diabetes (hazard ratio 1.88, 95% CI 1.21–2.91).

Although some patients continue to have IR after HCV eradication, several studies suggest that there is potential for IR improvement or resolution after HCV treatment. In the era of IFN-based regimens, numerous studies found that eradication of HCV led to reductions of IR, particularly in patients with viral genotype 1 (6,25). Improvement of insulin sensitivity was consistently noted several months after antiviral therapy, suggesting that IR decreased as a result of the eradication of HCV, a driver of IR, rather than as a side effect of the IFN-based regimens. Thus, one would expect that HCV-infected patients achieving SVR via IFN-free DAA-based regimens would experience similar reductions of IR.

It remains unclear, however, whether DAA-based regimens lead to similar reductions of IR in patients achieving SVR. In a retrospective case series ($n = 21$) published in 2016, Pavone et al. (26) noted mid-treatment reductions in fasting glucose and A1C values in

TABLE 4 Logistic Regression Output Corresponding to the Likelihood of Achieving SVR12

Variable	OR	95% CI	P
Age	0.967	0.779–1.202	0.764
Type 2 diabetes	0.356	0.019–6.526	0.486
Cirrhosis	0.119	0.005–2.817	0.187
MELD-Na	1.325	0.547–3.206	0.533
Anemia	0.127	0.005–3.194	0.210

patients being treated for HCV with IFN-free DAA-based regimens. In contrast, our recent retrospective study ($n = 26$) found no significant difference between pre- and post-treatment A1C values in HCV patients who were similarly treated (27). Thus, further study is needed to determine the impact of DAA-based regimens on insulin sensitivity. Going forward, treatment strategies targeting patients with chronic HCV and type 2 diabetes should seek to cure HCV while simultaneously reducing IR to most decrease the risk of developing HCC.

Our study is primarily limited by the low event rate of failed treatments. In the context of our small sample size, the low event rate makes it difficult to decipher whether DAA-based regimens are equally efficacious in patients with and without type 2 diabetes. Regardless, our results support the notion that type 2 diabetes should not be considered a contraindication to the use of DAA-based regimens for treatment of HCV. The study is also limited by a lack of homogeneity with respect to DAA regimen, viral genotype, stage of liver disease, and prior HCV treatment. Finally, the retrospective nature of the study led to missing data points and increased susceptibility to documentation errors.

Conclusion

This retrospective cohort study examined whether pre-existing type 2 diabetes was associated with decreased efficacy of DAA-based regimens in the treatment of chronic HCV. We found that the presence of type 2 diabetes was not associated with a reduced rate of viral clearance achieved by 12 weeks after completion of antiviral therapy. This study adds to preliminary evidence that type 2 diabetes should not be considered a contraindication to DAA-based treatment of chronic HCV. Because related studies remain few and our study was limited by a low event rate of failed treatment, future study is justified to further define the relationship between type 2 diabetes and the efficacy of DAA-based anti-HCV regimens.

DUALITY OF INTEREST

J.G.S. has received research funding from Bayer and Target PharmaSolutions. S.H.C. has received research funding from Conatus Pharmaceuticals, Galmed Pharmaceuticals, Genfit, Gilead Sciences, Mallinckrodt Pharmaceuticals, NGM Bio-pharmaceuticals, and Vital Therapies. He has also received patent royalties from Halyard Health. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

B.A.N. wrote the manuscript, acquired data, and analyzed data. J.G.S. and N.L.S. designed the study, acquired and analyzed data, and reviewed/edited the manuscript. J.A.W., V.K., and S.H.C. acquired and analyzed data and reviewed/edited the manuscript. N.L.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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