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Effect of Gender on the Response to Hepatitis C Treatment in an Inner-City Population

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A B S T R A C T

Introduction: Hepatitis C virus (HCV) is the leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation in the United States. Response to treatment has improved with the addition of direct acting protease inhibitors. However, there are limited real-world data on the role of gender in achieving a sustained virologic response (SVR).
Methods: We conducted a cross-sectional study in 70 patients treated for HCV, genotype 1 infection with pegylated alpha interferon, ribavirin, and either telaprevir or boceprevir at our inner-city liver clinic.
Results: The SVR was significantly lower in women than in men (24% vs. 59%; $p < .01$). Statistical significance persisted after adjusting for age, race, genotype, prior treatment status, duration of therapy, and stage of fibrosis. The adjusted odds ratio for achieving SVR was significantly lower in women than in men (odds ratio [OR], 0.13; 95% CI, 0.03–0.58; $p = .01$). Relapse after completing treatment was more likely to occur in women ($p = .02$). Thirty-four patients (48%) did not complete therapy. Discontinuation because of loss to follow-up was more likely in women, whereas discontinuation owing to therapy limiting adverse drug events were more common in men. Discontinuation rates owing to failure of therapy were similar in men and women.
Conclusions: There was a significant difference in SVR between men and women. Both biological and nonbiological factors, the latter including access to care, adherence to therapy, and attitudes of and toward health care providers all could play a role in contributing to the observed disparity between sexes in treatment response.

Hepatitis C virus (HCV) infection is a significant health problem, affecting 2.7 to 4 million people in the United States (Centers for Disease Control and Prevention Division of Viral Hepatitis, n.d.). It is the leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation, accounting for about 16,000 deaths annually in the United States (El-Serag & Mason, 1999; Poynard, Yuen, Ratziu, & Lung Lai, 2003). A recent study estimated the worldwide cost of treating HCV-related complications at USD 6.5 billion currently (Razavi et al., 2013), a number that is expected to increase considerably over the next two decades. Most of the cost is related to disease complications; the increasing cost of treatment will add to the economic burden of the disease. For these reasons, optimizing treatment success is extremely important. Sustained virologic response (SVR), defined as undetectable levels of HCV RNA in the blood 6 months after therapy (Ghany, Strader, Thomas, & Seeff, 2009) and considered equivalent to cure, results in reductions in liver-related morbidity and mortality (Morgan et al., 2010; Veldt et al., 2007).

Several factors including host factors like age, race, stage of liver fibrosis, host interleukin-28B genotype, prior treatment status, adherence, and viral factors like genotype and pretreatment viral load affected the response to dual therapy with

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The corresponding author, Donald P. Kotler, has full access to 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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pegylated interferon and ribavirin (Prati et al., 2012; Poordad et al., 2012). Sex is also known to affect HCV infection. Male sex is associated with accelerated hepatic fibrosis (Poynard, Bedossa, & Opolon, 1997) and with increased risk of developing hepatocellular carcinoma (Zavaglia et al., 2014). Female sex is associated with higher likelihood of spontaneous HCV clearance and slower progression to cirrhosis (Akuta et al., 2007; Guy & Peters, 2013; Kenny-Walsh, 1999). Sex has also been variably associated with both higher and lower SVR rates on pegylated interferon and ribavirin in different studies (Akuta et al., 2007; Conjeevaram et al., 2006).

Addition of the direct-acting protease inhibitors, telaprevir and boceprevir, to treatment regimens led to higher SVR rates in prospective clinical trials and decreased the role of host factors in influencing SVR. However, there are limited real-world data in populations with diverse demographic and socioeconomic influences. The aim of this study was to examine the effect of demographic and clinical variables on SVR in our inner city patient population cohort on triple therapy.

Materials and Methods

Data Collection

This prospective cross-sectional study analyzed data from a multiracial, inner-city patient cohort with HCV treated with pegylated interferon (180 μg/wk), ribavirin (weight-based dosing), and a protease inhibitor, either telaprevir (Incivek, Vertex Laboratories, Boston, MA) or boceprevir (Victrelis, Merck, Whitehouse Station, NJ). This analysis included all patients attending the Liver clinic at Mount Sinai St. Luke's and Roosevelt Hospitals in New York City and at the affiliated Ryan community health centers, who were treated with triple therapy from November 2011 to May 2013. Data abstracted from patient records included age at which treatment was started, sex, race, demographic characteristics, laboratory, radiographic and histological data, prior treatment, and reasons for discontinuation. HCV infection was diagnosed by presence of positive anti HCV antibodies and confirmed by presence of HCV RNA genotype 1a or 1b in serum. SVR was defined as undetectable HCV RNA using the Heptimax viral assay 24 weeks after cessation of therapy (Ghany et al., 2009) Relapse was defined as the reappearance of HCV RNA after therapy is discontinued, after previously being undetectable (Ghany et al., 2009). The Institutional Review Board at St. Luke's-Roosevelt Institute of Health Sciences approved this study and informed consent was obtained from all patients.

Statistical Analyses

Differences in continuous variables were estimated using the Student *t* test and in categorical variables by the χ^2 test. We used multivariable logistic regression to assess the association between SVR and various independent variables of interest. A two-tailed *p* value of $\leq$.05 was considered significant. All analyses were conducted using STATA version 13 (STATA Corp, College Station, TX).

Results

Data on 70 patients starting triple therapy for HCV were reviewed. Thirty-five patients were treatment naive and an equal number were treatment experienced. Fifty-eight patients were treated with telaprevir and 12 patients were treated with boceprevir. All patients completed at least 4 weeks of a telaprevir based regimen or 8 weeks of a boceprevir based regimen. Thirty patients (42.8%) achieved SVR. The demographics of patients who had SVR vs. those who did not are shown in Table 1. SVR rates were lower in women, African Americans, and previously treated patients, although there was no difference between SVR rates in genotype 1a and 1b patients.

Thirty-three of the patients (47%) were women. There were no differences in age, race, prior treatment status, HCV genotype, stage of fibrosis (when available), or aminotransferase platelet ratio index, a noninvasive marker of fibrosis (Petersen et al., 2014) between men and women. However, SVR was significantly lower in women compared with men (24% vs. 59%; $p < .01$).

Multivariate regression showed that, after adjusting for age, race, HCV genotype 1a or 1b, prior treatment status, duration of therapy, and stage of fibrosis, the odds of achieving SVR were significantly lower in females than in males (odds ratio [OR], 0.13; 95% CI [range: 0.03-0.58]; $p < .01$; Table 2). Women were more likely to relapse than men. (24% vs. 5.4%; $p = .02$). There was no difference in age, sex-adjusted body mass index or incidence of hepatic steatosis, by ultrasound examination, in men and women who relapsed (data not shown).

Thirty-four patients (48%) stopped treatment prematurely. The main reasons for discontinuing treatment were therapy failure (nonresponse or viral breakthrough), adverse drug events or side effects, and loss to follow-up. Drop out owing to loss to follow-up was more likely in women, (26.3% vs. 0%; $p = .04$), whereas drop out owing to therapy-limiting adverse drug events or drug side effects was more likely in men (53% vs. 26.3%; $p = .14$; Table 3). Discontinuation rates owing to treatment failure were similar between men and women.

Discussion

We found a significant, independent relationship between SVR and sex. Few studies have compared SVR rates among women and men on triple therapy in racially and socioeconomically diverse populations. Phase III clinical trials like ADVANCE (Jacobson et al., 2011) and RESPOND (Bacon et al., 2011) showed comparable rates among sexes, but there are well-recognized disparities in treatment responses between registration trials and real-world settings. The term "real-world" refers to heterogenous populations. Our study included predominantly inner-city African-American or Hispanic women. The number of reported HCV cases in the Central Harlem population we serve was reported as 221 per 100,000 people in 2010,

Table 1
Demographic and Treatment Characteristics of Patients Undergoing Treatment

	Male ($n = 37$)	Female ($n = 33$)	*p* Value
Age, mean (SD)	54.1 (10.3)	52.6 (9.5)	.53
Race, n (%)			.37
Caucasian	8 (21.6)	4 (12.1)	
African American	20 (54.1)	17 (51.5)	
Hispanic/Latino	8 (21.6)	12 (36.4)	
Other	1 (2.7)	0 (0)	
Genotype			.68
1a	25 (67.6)	19 (57.6)	
1b	10 (27)	12 (36.4)	
Unknown	2 (5.4)	2 (6)	
Completed Treatment, n (%)	22 (59.5)	14 (42.4)	.16
Not completed treatment, n (%)	15 (41.5)	19 (57.6)	.15