Original article

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.

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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
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 multicracial, 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 historical 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 Hepitmax 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 χ² test. We used multivariable logistic regression to assess the association between SVR and various independent variables of interest. A two-tailed p value of <.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 served was reported as 221 per 100,000 people in 2010,
the second highest in New York City (The New York City Department of Mental Health and Hygiene, n.d.) Other real-world studies with triple therapy like the HCV-TARGET followed mostly Caucasian patients (Gordon et al., 2015).

Various biological, social, and psychological factors that affect SVR rates among women need to be considered. A few previously published studies using pegylated Interferon and ribavirin demonstrated higher SVR rates in men than in women (Akram et al., 2011; Sezaki et al., 2009; Villa et al., 2011). The response to HCV therapy decreases with age in women, especially after menopause. Early onset menopause was associated with failure to achieve SVR, which was theorized to be owing to increased cytokine-mediated hepatic inflammation occurring in the presence of decreased estrogen. Estrogen also suppresses interleukin-6, which mediates interferon resistance (Sezaki et al., 2009; Villa et al., 2011). These data were supported by the observation that hormone replacement therapy improves response to therapy (Codes et al., 2007). A previous study showed an age related response to interferon and an age–sex interaction in interferon response with women younger than 40 years with achieving SVR more often than their male counterparts, but women older than 50 years doing worse than men of similar age (Hayashi et al., 1998).

In our study, the average age of men was 56 years and women was 53 years, indicating that most women were either perimenopausal or postmenopausal. Thus, the lesser SVR rates of women in our study are consistent with what previous literature shows. However, we suspect that biological reasons may not be completely responsible for this observed disparity in SVR between the sexes.

Women also had a higher relapse rate than did men (24% vs. 6%) after achieving an end-of-treatment response. Menopause, the presence of fatty liver, and obesity were significantly associated with increased rate of relapse among women in another study (Highleyman et al., 2010). There was no difference in the incidence of fatty liver or sex adjusted body mass index between women and men in this study.

The HCV–TARGET study showed that women receiving triple therapy developed anemia three times more frequently than men (Gordon et al., 2015). Fatigue and other symptoms of anemia may have resulted in poorer adherence and missed medication doses among the women in this study who completed treatment. Because adherence to and correct dosing of medications greatly affects the success of triple therapy, this may contribute to their lower SVR (Gordon et al., 2013). It is possible that gender disparity may be less with the newer direct acting agents, but it still warrants investigation, especially in multiracial inner city populations.

In this study, all patients who were lost to follow-up were Women. Women in general have been shown to have lower adherence rates than men to regimens for various conditions (Manteuffel et al., 2014). Studies in human immunodeficiency virus (HIV)/AIDS have shown higher unscheduled interruptions and treatment dropouts among women on highly active antiretroviral therapy (HAART) attributed to increased adverse events and medication induced morphological changes (National AIDS Treatment Project, 2014; Galli et al., 2003). A study of HIV/HCV coinfected patients showed that women were more likely to interrupt HAART treatment, attributing this to a higher incidence of neuropsychiatric symptoms, particularly depression (Emery, Pick, Mills, & Cooper, 2010). Adherence to HCV therapy is an important predictor of SVR (McHutchison et al., 2002). A study examining health disparities in HIV, demonstrated that women were less likely to be high school educated and employed compared with men (Blackstock et al., 2012). Less education and decreased financial support negatively impacted treatment success. Last, women take on more caregiving responsibilities than men, and this may cause them to be less attentive to personal adherence.

Although duration of HCV therapy is shorter than that of HAART, there are common psychosocial factors in the affected populations. Although studies have examined social factors affecting response to HCV therapy, gender-specific factors have not been examined (Sublette, Douglas, McCaffery, George, & Perry, 2013). We found that several women in our study experienced the same social constraints of lack of education, primary caregiving responsibilities, and financial and insurance problems that might affect adherence.

Our women may not be representative of the general population, but they are representative of a large and vulnerable subpopulation of HCV-infected people.

Strategies shown to improve treatment success in these women include providing education, creating a multidisciplinary team to help patients deal with side effects and provide motivation for adhering to therapy (Lubega, Agbim, Surjadi, Mahoney, & Khalili, 2013; Valent, 2001). Identifying women with poor social support who are at risk for being lost to follow-up and providing frequent reminders before and after appointments may decrease the number of women dropping out from therapy.

**Limitations**

The major limitation of this study is its small sample size. Biopsies were not performed in all patients, so we could not adjust for stage of fibrosis for all patients; however, there were no differences in the subset that underwent biopsy, nor were there differences in aminotransferase platelet ratio index, a noninvasive estimate of fibrosis. Accurate data on mode of acquiring infection or duration of HCV infection was not available. We did not adjust for interleukin-28B genotype polymorphisms. Importantly, our data may not be representative or generalizable to the whole population of HCV-infected women.

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**Table 2**

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<thead>
<tr>
<th>Univariable and Multivariable Logistic Regression for Factors Affecting SVR</th>
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<tr>
<td>All Patients (n = 150)</td>
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<tr>
<td><strong>Unadjusted Odds Ratio (95% CI)</strong></td>
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<td>Male (ref)</td>
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<td>Prior treatment</td>
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**Table 3**

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<th>Reasons in Patients Who Stopped Treatment (n = 34)</th>
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<tr>
<td><strong>Inadequate response to treatment, n (%)</strong></td>
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<td>Male (n = 15)</td>
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<td>Loss to follow-up, n (%)</td>
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<td>Adverse reactions, n (%)</td>
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<td>Male (n = 15)</td>
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<td>Female (n = 19)</td>
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Petersen, J. R., Stevenson, H. U., Vaccarino, T., Schaffner, R., Cross, R., ... Snyder, N. (2014). Evaluation of the aspartate aminotransferase/platelet ratio index and enhanced liver fibrosis tests to detect significant fibrosis.

### Implications for Practice and/or Policy

As treatment responses have improved, there has been increased emphasis placed on screening and treatment, to avoid the burden of end-stage liver disease on the patient and on the health care system. Telaprevir and boceprevir are no longer the standard of care in the era of newer, direct-acting agents. As the costs of antiviral treatment are high, a favorable cost/benefit rests on optimizing SVR rates. These data suggest that there is a sex disparity in the response to HCV treatment. Identifying subgroups of patients with suboptimal response rates is important as a first step in improving the outcomes of this population at risk. Whether or not the reasons for the difference in treatment response rates are biologic or psychosocial, it is important to identify and overcome the specific obstacles to effective treatment. If women continue to demonstrate a greater loss to follow-up despite improvements in care, especially the application of interferon-free regimens, other patient assistance programs may be needed. In particular, the use of patient navigators may be beneficial and inexpensive when examined as a function of cost per SVR. Clinical trials using newer direct acting agents in interferon-free regimens have shown SVR rates between 92% and 100%, even in difficult-to-treat patient populations. However, they have not compared SVR rates in patients like those reported here (Afdhal et al., 2014a; Afdhal et al., 2014b; Kumada et al., 2014; Sulkowski et al., 2014). It is unclear what effect the discontinuation of interferon use will have on the difference in response rates in men and women, and ongoing studies in real-world situations should monitor the effect of sex on treatment response.

In conclusion, our results highlight an important possible sex disparity in response to therapy. In the era of newer antivirals and interferon-free regimens, understanding the mechanisms of decreased treatment responsiveness and barriers to adherence in patients in general, and women in particular, and developing strategies to overcome them will have positive implications on the real-world success of the HCV treatments. Given the high cost of HCV treatment, it is extremely important to identify and overcome the remaining obstacles to effective treatment.

### References


Author Descriptions

Priya Simoes, MD, assisted in study design, generated protocol, data collection, performed statistical analysis, assisted in data analysis, manuscript preparation (primary author).

Adel Asaad, MD, handled the data collection and reviewed the manuscript.

Jean Abed, MD, assisted in study design, handled data collection, and reviewed the manuscript.

Ellen S. Engelson, EdD, assisted in study design, IRB liaison, assisted in statistical analysis, and assisted in manuscript preparation. Dr. Engelson currently is an Adjunct Professor at Lehman College, Bronx, NY.

Donald P. Kotler, MD, Principal Investigator, assisted in study design, data analysis, and manuscript preparation.