Outcomes of an Underserved Hispanic Population with Chronic Hepatitis C treated with Pegylated-Interferon and Ribavirin in a Government-Sponsored Clinic

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Objective: Treatment of hepatitis C virus (HCV) with interferon-based therapy has been shown to be less effective in Hispanics when compared to other populations. A pilot clinic was established at the University of Puerto Rico for the treatment of HCV in the government-insured population. The aim of this study was to describe the outcomes and treatment response to pegylated interferon and ribavirin in treatment-naïve patients enrolled at this government-sponsored clinic.

Methods: A retrospective analysis was undertaken to investigate the treatment outcomes with weight based peg-interferon-alfa-2b and ribavirin in patients with chronic HCV enrolled in the pilot clinic during 2003-2005. Descriptive statistics were reported. Continuous variables were summarized as means and standard deviations. Frequency distributions and percents were used for categorical variables. Statistical analysis was performed using STATA.

Results: A total of 155 patients (105 males and 50 females) with mean age of 42 years started treatment; 79 (51%) patients had HCV genotype 1. Completion of treatment was achieved by 59 patients (38.1%), of whom end of treatment response (ETR) was observed in 30 (50.9%), representing 19.4% of the intention-to-treat population (ITT). Sustained viral response (SVR) was achieved in 17 (28.8%) patients who completed treatment, resulting in 11% (17/155) SVR by ITT. The only significant predictor of SVR was treatment onset within 5 years of the diagnosis of HCV (p=0.026). Although no association was found between HCV genotype and SVR (p=0.192), those patients with HCV genotypes 2 and 3 were more likely to complete treatment (p=0.009).

Conclusion: SVR to pegylated interferon and ribavirin seems to be lower than expected in our population. The high rate of incomplete treatment surpasses previously reported rates in U.S. Latinos and Caucasians. Further studies should explore reasons for lower response and higher treatment discontinuation in our population. [*P R Health Sci J 2011;1:9-13*]

Key words: Hepatitis C, Hispanics, Treatment response

Chronic hepatitis C virus (HCV) infection is the most common cause of chronic liver disease in the United States (US), with up to 10,000 deaths per year (1). The prevalence of HCV in the U.S. is approximately 1.6 percent, equivalent to 4.1 million persons nationwide (2). Of this, 3.2 million people are chronically infected and therefore at increased risk of developing liver cirrhosis and hepatocellular carcinoma (HCC) (2). Cirrhosis secondary to chronic HCV is the main etiology for liver transplantation in the Western world, making chronic HCV a major public health problem (3). Conflicting data exist regarding ethnicity and the seroprevalence of HCV in the US. The National Health Administration Survey (NHANES III) showed that there is a higher prevalence of HCV among African Americans in comparison to Caucasians (3.2% vs 1.5% respectively) (4). Few data exists concerning seroprevalance in Hispanic populations. A population study among adults aged 21 to 64 years in the municipality of San Juan, Puerto Rico revealed an HCV seroprevalence of 6.3% in non-institutionalized adults,

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which is higher than that reported for Caucasians (5). Conversely, a recent study evaluating the general adult population of the entire territory of Puerto Rico, reported a prevalence of 2.3% (6). In addition, Hispanic ethnicity has been associated with a more aggressive course of HCV infection (7).

Current standard treatment for chronic HCV is a course of pegylated interferon and ribavirin with the duration dependent on viral genotype. Response to treatment is achieved after persistent loss of viremia 6 months after discontinuation of anti-viral therapy, known as sustained virological response (SVR). Multiple clinical trials have yielded an SVR rate of 46-76% (8-10). However, treatment response is influenced by ethnic/racial factors. A prospective study found differences in SVR between black patients (10%) and Caucasians (52%) treated with pegylated interferon plus ribavirin for chronic HCV, where black race was the only identifiable variable for the difference in response rate (11). Limited published data exist regarding treatment response to combination therapy in Hispanics, a population that has been underrepresented in HCV treatment trials. A prospective study found that Hispanics tend to be infected at a younger age, have lower SVR rates, and have higher rates of treatment discontinuation (12).

Another study in treatment-naïve Hispanic Veterans infected with HCV genotype 1 treated with pegylatedinterferon and ribavirin, revealed a SVR of 28.4% (13). Furthermore, the Latino trial compared Latino whites with non-Latino whites with HCV genotype 1 treated with pegylated interferon alpha 2a plus ribavirin, where SVR was 33.5% for Latinos and 49.3% for whites (14).

The access to medical services and treatment for chronic HCV is expensive. Approximately one third of the Puerto Rico population is insured under the government–sponsored managed care system. Treatment for chronic HCV is not covered by this medical insurance system. In an effort to improve access to treatment, and hypothetically decrease the prevalence of HCV in Puerto Rico, the University of Puerto Rico (UPR), and the Commonwealth of Puerto Rico Department of Health (PRDoH) established a pilot government-sponsored clinic for the treatment of this underserved population (15).

This study describes the outcomes and treatment response to pegylated interferon plus ribavirin in Puerto Ricans with treatment-naïve chronic HCV enrolled in this clinic during 2003-2005.

Methods

A medical record review of all patients who attended the hepatitis C treatment clinic at least once was performed. Information was collected from the medical history, laboratory and histology reports. Adverse events were collected from progress notes or identified from laboratory reports. Compliance with medications was obtained from progress notes as recorded by the treating physician. The study was approved by the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus.

Patients who received at least one dose of pegylated interferon and ribavirin for the treatment of HCV constituted our study cohort. To have received treatment, patients had to be treatment-naïve, between 18-70 years of age, have liver disease with a quantified HCV viral load (VL) and meet predefined laboratory parameters (hemoglobin more than 12mg/dl, neutrophil count more than 1500 cell/mm^3 or platelet count more than 85,000/mm^3). Patients who had evidence of co-infection with human immunodeficiency virus and/or hepatitis B virus, previous organ transplantation, autoimmune disease, significant heart disease, active illegal drug use, normal ALT, history of suicidal attempt or untreated major depression and decompensated liver disease were not considered eligible for treatment. Treatment consisted of 1.5 mcg of peg-interferon alfa-2b (Peg-Intron®, Schering-Plough) per kilogram of body weight subcutaneously weekly, and daily oral ribavirin 10.6 mg/kg (Rebetol®, Schering-Plough). Patients with HCV genotypes 2 and 3 received treatment for 24 weeks and those with genotypes 1 and 4 for 48 weeks per established guidelines. Decreases in dosages were undertaken by the clinic physician per-guidelines when appropriate, i.e. hemoglobin less than 10gm/dl required a ribavirin dose decrease of 200 mg daily, and absolute neutrophil counts of less than 750/mm^3 or platelet count less than 80,000/mm^3 mandated a reduction of 50% of interferon dose.

Response to treatment was determined by quantitative HCV RNA. Early viral response (EVR) was assessed at 12 weeks of treatment; if there was not a reduction of at least 2 logs from baseline levels, treatment was discontinued. Subsequently, a negative viral load or a two-log reduction from baseline at 24 weeks of therapy was required for continuation of therapy. End of Treatment Response (ETR) was assessed at termination of treatment and was defined as an undetectable viral load at 24 weeks for genotypes 2 and 3, and at 48 weeks for genotypes 1 and 6. SVR was defined as the absence of detectable HCV RNA in serum 6 months after therapy was stopped.

Statistical analysis

All patients who received at least one dose of treatment were considered for the intention to treat analysis (ITT) and those who completed treatment were evaluated per-protocol (PP) analysis. Descriptive statistics for continuous variables including mean, standard deviation, median and range (min.-max.) were computed. Frequency distributions and percents were used for categorical variables. To determine statistical associations, the Pearson's chi-square test or Fisher's exact test, when appropriate, were used for categorical variables. All statistical testing was two-sided and p-values less than 0.05 were considered statistically significant. Data entry was performed using Excel STATA (Version 9.0, College Station, TX, USA) and SPSS software was used to perform the statistical analysis.

Results

During 2003-2005, a total of 308 patients, all Puerto Ricans, were evaluated for HCV treatment consideration of which 155 patients met criteria for initiation of treatment with peg-interferon alfa-2b and ribavirin. Mean age was 42.2 years (range 18 to 64), with males predominating (67.7%) Demographic data are shown in table 1. Time of HCV diagnosis was diverse among the sample of patients (range 1 week to 19 years), though the majority of patients (103, 73%) had received an HCV diagnosis within the 5 years preceding treatment initiation.

Table 1. Selected baseline characteristics and laboratory results of HCV infected patients.

Variable	Total Population	Completed Treatment
Number of patients (%)	155 (100)	59 (38.1)
Sex (%)		
Male	105 (67.7)	35 (59.3)
Female	50 (32.3)	24 (40.7)
Age, median years (range)	42 (18 - 64)	46 (21 - 63)
Alcohol use (%)	90 (58.1)	33 (55.9)
Risk factors (%)		
Intravenous drug user	84 (54.2)	27 (45.8)
Blood transfusions	38 (24.5)	20 (33.9)
High risk sexual practices	22 (14.2)	12 (20.3)
Tattoos	43 (27.7)	20 (33.9)
Not identified	7 (4.6)	N/A
HCV genotype (%)		
1a and 1b	79 (51)	22 (37.3)
2 and 3	25 (16.1)	15 (25.4)
4 to 6	4 (2.6)	2 (3.4)
Unknown	47 (30.3)	20 (33.9)
Biopsy fibrosis score (%)		
F0	3 (1.9)	1 (1.7)
F1	22 (14.2)	9 (15.3)
F2	20 (12.9)	9 (15.3)
F3	14 (9)	7 (11.9)
F4	19 (12.3)	6 (10.2)
Unknown/not done	77 (49.7)	27 (45.8)
Median baseline value (range)		
HCV (IU/ml)	407,500 (792 - 33,983,900)	
ALT	105 (15 - 3,370)	
AST	72.5 (11 - 3,560)	

HCV: Hepatitis C Virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

Of the 155 patients who began treatment, 58% had a history of alcohol abuse, 54% were intravenous drug users, 28% had at least one tattoo, 14% reported high-risk sexual practices, and 6.4% were diabetics. The majority of the population consisted of HCV genotype 1 (51%), whereas genotypes 2 and 3 were found in only 16% of the patients. Genotype data were not available in 47 (30%) patients either due to low viral loads or lost to follow up. The median viral load of HCV prior to starting treatment was 407,500 IU/ml.

Only 59 patients were able to complete treatment; of those who did not complete treatment (n=96), 50 (52%) patients discontinued treatment due to various reasons (table 2) and 46 (48%) were lost to follow-up. Adverse events that led to the re-adjustment of therapy dose and/or addition of supportive treatment are summarized in table 3.

Table 2. Distribution of patients not able to complete treatment.

Lost to Follow Up (%)	46 (29.7)
Discontinued (%)	50 (32.3)
Non Responder	24 (48)
Adverse Effects	13 (26)
Co-morbidity	7 (14)
Death*	2 (4)
Non-compliance	3 (6)
Patient's Decision	1 (2)

*Causes of Death: motor vehicle accidents.

Table 3. Complications during treatment.

Complications	No. (%)
Anemia	44 (28.4)
Depression	43 (27.7)
Neutropenia	33 (21.3)
Thrombocytopenia	19 (12.3)

Of the 59 patients who completed treatment, 14 did not return for viral load assessment at end of treatment to determine ETR, leaving 48 patients available for analysis, of which 30 patients (51%PP, 19.4%ITT) achieved ETR. At the 6-month post-treatment completion follow-up, 11 of the 30 with ETR were lost to follow-up leaving 19 patients available for SVR assessment, of which 17 patients achieved SVR and 2 relapsed, yielding SVR rates of 28.8% on a per-protocol and 11% on an intention-to-treat analysis (Figure 1).

Compliance with treatment among those who completed the regimen was acceptable. Although the majority (74.5%) missed at least 1 dose, they all received at least 80% of their treatment doses.

The only significant predictor of SVR was treatment onset within 5 years of the diagnosis of HCV (p=0.026). Although no association was found between HCV genotype and SVR (p=0.192), those patients with genotype 2 and 3 were more likely to complete treatment (p=0.009).

Discussion

This study describes the outcomes of pegylated interferon and ribavirin in a government-sponsored clinic for an underserved population with chronic HCV. It is generally accepted that treatment with pegylated interferon plus ribavirin results in a

sustained viral response rate in approximately one half of patients with genotype 1 HCV infection and over 80% of those with genotypes 2 and 3 (10). In contrast, our study results showed that in a very difficult to treat population and in the early experience of the pilot clinic, SVR rates fell way below expected rates at 11%, raising awareness of the difficulties encountered in such a population.

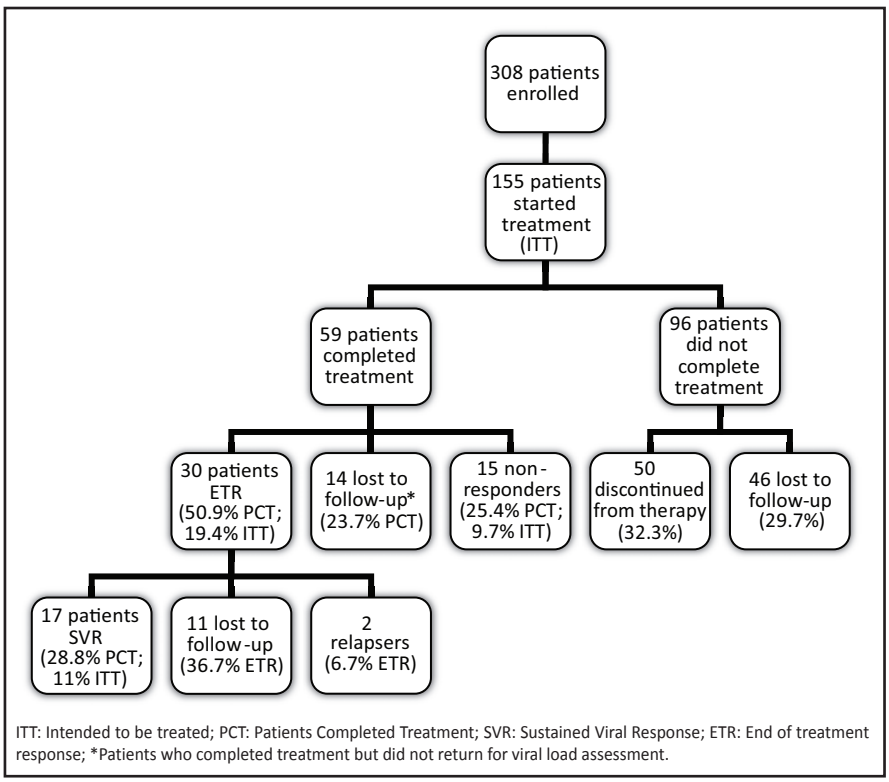

Figure 1. Study patients

We recognize that there are several limitations to this study. The retrospective nature of the data collection highly depended on the accuracy and completeness of the medical record. Furthermore, a potentially mobile and high-risk population could have been one of the reasons for such a high lost-to follow-up rate. Nonetheless, several attempts were made to contact patients who were lost-to follow-up through letters and telephone calls. The rate of discontinuation from treatment and lost-to follow-up in our population surpasses that of previously reported rates in U.S. Latinos and Caucasians (12). This finding reaffirms that access to treatment for HCV is not enough for achieving success, and that strategies to obtain high and thorough follow-up should be established when considering the development of government-sponsored clinics. Furthermore, access to medication in our clinic could have affected the completion rate since only one dispensing facility is located in the metropolitan area, which is available one morning per week to supply the needs for the entire clinic population. In fact, feedback from patients revealed that on many occasions their medication was not available either due to lack of adequate concentration/weight dosage, holiday breaks, or even absence of the person in charge of dispensing the drug during regular hours of operation.

The finding that patients with genotypes 2 and 3 were more likely to complete treatment is probably related to the shorter duration of treatment compared to those with genotypes 1 or 4 (24 vs. 48 weeks).

Several lessons can be learned from this study. Resources are needed to successfully run a government-sponsored clinic to treat HCV in the medically underserved Hispanic population. Proper identification of suitable candidates and a suitable infrastructure that can address compliance with medication and management of adverse effects is needed. The clinic, which provides access to an underserved population who would otherwise be left untreated, could benefit from the following weaknesses identified during the conduct of this study: 1) A clinic educator/coordinator can improve patient and primary physician education; this can lead to improved compliance with clinic appointments and follow up evaluations. 2) Access to a psychiatry consultant can address the management of depression secondary to interferon-based therapy as well as other psychiatric symptoms which decrease the compliance with treatment and increase the rate of discontinuation in our population. 3) Allowing the clinic providers to prescribe non-covered medications to manage the most common adverse effects will provide easier access to these medications for our patients and will help to decrease the rate of discontinuation from treatment and/or dosing modification which decreases response rate. 4) Multiple drug dispensing facilities with flexible hours of operation should be available throughout Puerto Rico to make access to medication more uniform.

In summary, our study shows that the treatment of HCV in a high-risk underserved Hispanic population through a government-sponsored clinic achieved a low SVR rate and a high rate of treatment discontinuation and lost-to follow-up. Although we have identified some disparities in access to health services in our population, and have identified opportunities for improvement, other factors such as cultural, gender and economic differences may also play a role in the

response to HCV treatment that needs to be further clarified and addressed appropriately.

Resumen

Objetivo: Los hispanos infectados con hepatitis C tienen una respuesta inferior a tratamiento basado en interferón comparados con otras poblaciones. La Universidad de Puerto Rico estableció una clínica piloto para pacientes con hepatitis C asegurados por el plan de salud del gobierno. El propósito de este estudio fue describir los resultados y la respuesta a tratamiento con interferón pegilado y ribavirina en pacientes con hepatitis C sin previo tratamiento los cuales asistieron a esta clínica. Métodos: Se hizo un análisis retrospectivo de los resultados de tratamiento en pacientes con hepatitis C que asistieron a la clínica piloto del 2003 al 2005. Se utilizaron estadísticas descriptivas. Las variables continuas se reportaron como medias y desviaciones estándar. Se utilizaron distribución de frecuencias y porcientos para las variables categóricas. El análisis estadístico se hizo con el programa STATA. Resultados: En total 155 (105 varones y 50 mujeres) pacientes con edad promedio de 42 años comenzaron tratamiento, de los cuales 79 tenían el genotipo 1 de hepatitis C. Solamente 59 pacientes (38.1%) completaron tratamiento. Respuesta al final de tratamiento se observó en 30 (50.9%) pacientes que completaron el tratamiento y 19.4% de los que comenzaron. Respuesta viral sostenida se observó en 17 (28.8%) de los pacientes que completaron la terapia y en 11% (17/155) de los que comenzaron. La única variable asociada con una respuesta viral sostenida fue el inicio de terapia en los 5 años subsiguientes a un diagnóstico de hepatitis C (p=0.026). Aunque no se observó la asociación entre el genotipo de hepatitis C y la respuesta viral sostenida (p=0.192), los pacientes con genotipos 2 y 3 completaron el tratamiento más frecuentemente (p=0.009). Conclusión: La respuesta sostenida a interferón pegilado y ribavirina aparenta ser inferior a lo esperado en nuestra población. La tasa alta de tratamiento incompleto sobrepasa la reportada previamente en latinos en Estados Unidos y caucásicos. Estudios adicionales deben explorar las razones para esta respuesta inferior y la descontinuación de tratamiento más alta en nuestra población.

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