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Chronic hepatitis C: treatment, complications, and long-term outcomes in a population of Latino veterans

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Abstract

Objectives—Chronic hepatitis C (CHC) is a major public health problem in Puerto Rico. It is the most common cause of chronic liver disease and the most frequent indication for liver transplantation in the United States." Our main objectives were to estimate the seroprevalence of CHC infection, to describe the demographic and histological parameters of the infection in our sample population, and to evaluate the treatment outcomes in Puerto Rican veterans.

Methods—To determine overall seroprevalence, we reviewed all the hepatitis C cases (encompassing from January 1, 2002, to December 31, 2009) of the VA Caribbean Healthcare System, Department of Veterans Affairs. The records of only those individuals who received treatment with pegylated interferon and ribavirin were reviewed to determine risks factors for infection, response rates, adverse events, and outcomes.

Results—During the study period, there were a total of 1,496 patients identified as being infected with HCV, for an estimated seroprevalence of 2.3%. Of these, approximately 10% (137) were treated with combination therapy and were included in this study. The mean age was 58 (±6.4); 96.4% were men. The most common genotype was type 1. The responses to treatment were generally poor, with only 48.4% of the patients achieving Ssustained virological response.

Discussion—Though the seroprevalence of chronic hepatitis C in the Latino veteran population of Puerto Rico is high, relatively few patients have received treatment, most probably because of the contraindications of the medications used. Combination therapy with pegylated interferon plus weight-based ribavirin was inefficient and plagued with side effects; as a whole, this therapy was not found to be overly beneficial to our patients. New emerging and approved therapies will change this paradigm, allowing the treatment of a larger population without the side effects of the studied therapy.

Resumen

La hepatitis C crónica (HCV) es un problema serio de salud en Puerto Rico. Es la causa más común de enfermedad hepática y la indicación más frecuente de trasplante de hígado en los Estados Unidos. Los objetivos del estudio fueron: el estimar la sero-prevalencia de la infección,

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describir los parámetros demográficos e histológicos, y evaluar la respuesta al tratamiento en veteranos de Puerto Rico.

Todos los expedientes de pacientes con HCV identificados en el Hospital de Veteranos desde 1 de enero del 2002 al 31 de diciembre del 2009, se revisaron para determinar la sero-prevalencia. Se evaluaron solo los expedientes de aquellos que recibieron tratamiento con interferón pegilado para determinar los riesgos de infección, efectos adversos y respuestas a tratamiento a largo plazo.

Durante el periodo de estudio se identificaron 1,496 pacientes infectados con HCV, para una sero-prevalencia estimada de 2.3%. De estos, aproximadamente un 10% (137) fueron tratados e incluidos en este estudio. La edad promedio fue de 58 años (±6.4), la mayoría fueron hombres (96.4%), con una predominancia de genotipo 1. La respuesta a los tratamientos fue pobre con solo 48.4% logrando respuesta sostenida.

Considerando la sero-prevalencia de hepatitis C crónica en la población de Veteranos Latinos en Puerto Rico, solo una pequeña fracción de la población recibió tratamiento. Esto debido probablemente a la presencia de contraindicaciones a tratamiento. La combinación de interferón pegilado con ribavirina ajustada por peso fue ineficiente y asociada a múltiples efectos secundarios; resultando en pobre beneficio clínico para nuestros pacientes. Las nuevas modalidades de tratamiento aprobadas parece que cambiarán este paradigma, permitiendo tratar a una mayor proporción de pacientes sin los efectos perjudiciales de las terapias reportadas en este estudio.

MeSH terms

Hepatitis C; chronic; assessment outcomes; Hispanics; Puerto Ricans

Introduction

Chronic hepatitis C (HCV) is a major public health problem in Puerto Rico. It is the most common cause of chronic liver disease and the most frequent indication for liver transplantation in the Unites States (US) (1, 2, 3, 4). Chronic hepatitis C infection affects nearly 1.6% of the general population of the US (4.1 million people) and is the commonest indication of liver transplantation (5). In Puerto Rico, Perez et al. reported an overall weighted prevalence of CHC of 2.3%, similar to, although slightly higher than, the estimates obtained in the US population (6). The real prevalence of CHC in the veteran population in Puerto Rico is not known, since testing for the hepatitis C virus (HCV) is not universally done. In a population-based epidemiological study, in which our center participated with 19 other veterans hospitals, the prevalence of HCV infection was 4.0% (95% CI: 2.6–5.5%) (7). In that same study, the unadjusted prevalence for Hispanics was 6.9%. Latinos comprise 17% of the US population and are the country's fastest growing minority (8). Puerto Ricans are the second largest group of Hispanics in the US, representing 9.4% of all Latinos (8). Furthermore, chronic liver disease with cirrhosis represents the 6th leading cause of death among Hispanics in the US (8). Several studies affirm the notion that HCV treatment response among Hispanics is lower than that observed for non-Hispanic whites, therefore indicating the importance of studying health disparities in a Hispanic population (9, 10, 11).

Several risk factors have been linked to the transmission of CHC, the most common being intravenous drug use; the transfusion of blood and solid organ transplantation prior to July 1992; sex with an HCV-infected partner; and multiple sexual contacts. The illness progresses slowly, being mostly asymptomatic as it does, which is why the screening of high-risk populations is of utmost importance. Since 2012, the Centers for Disease Control (CDC) has been recommending the screening of not only those who voluntarily disclose risk factors but also anyone born from 1945 through 1965 (12). In 2013, the US Preventive Services Task Force endorsed this recommendation (13). The baby-boomer generation is 5 times more likely than any other population to be infected with the virus, and it is estimated that up to 75% of the adults infected with hepatitis C are part of this population (12). This fact is of particular importance for our veterans since a significant proportion of them were born in these decades.

CHC treatment modalities have evolved throughout the years as part of a concerted effort to achieve the eradication of this serious and deadly infection. Treatment regimens have evolved from the subcutaneous interferon that was used in the late 1980s to—most recently developed—oral agents that directly target viral replication. The ultimate goal is to be able to use all-oral interferon-free and ribavirin-free antiviral agents in the treatment of CHC. These new regimens are revolutionizing the treatment of HCV since they make possible the treatment of a population that previously had no choice other than to wait for a new kind of treatment to be developed. Veterans with high rates of comorbid psychiatric diseases, in particular, were affected by the lack of alternatives for therapy, since those available were contraindicated or poorly tolerated. A study published in 2008 reports that only 14% of all HCV-infected veterans have ever received antiviral therapy (14). Although the effectiveness and cost effectiveness of these new drugs have been proven, the high price of the new hepatitis C treatment will ultimately define who will be treated (15).

The aims of this study were 1) to estimate the seroprevalence of CHC in a population of Puerto Rican veterans, 2) to determine the histological parameters of that population who were suffering from CHC, and 3) to describe the demographics, treatment responses (to peginterferons), and long-term outcomes of that same CHC-infected veteran population.

Materials and Methods

The Veterans Affairs Healthcare System (VAHCS) maintains a registry of all patients who have tested positive for HCV infection. The records of those who received treatment for CHC with pegylated interferon in combination with ribavirin from January 1, 2002, to December 31, 2009, were reviewed retrospectively. This study was approved by the VAHCS Institutional Review Board. Patients were identified using the VA Caribbean Healthcare System laboratory and pharmacy databases.

Data regarding socio-demographics, risk factors, treatments received, medical comorbidities, and clinical features—such as early virological response (EVR), sustained virological response (SVR), and histologic stage—were assessed and recorded.

The efficacy of combination therapy was measured by the treatment endpoints (i.e., EVR at 12 weeks of therapy; SVR at 6 months after the completion of therapy). Reported adverse events were also recorded.

Descriptive statistics were used to characterize the patients. Using Fisher's exact or the Chi-square test for categorical variables, bivariate analysis was performed to compare adverse events and the laboratory results of the treatment group; in addition, the *t*-test or Mann–Whitney *U* test for continuous variables was used, whichever was appropriate.

Results

As of 2009, the HCV registry included 1,496 patients with confirmed HCV infections. During the corresponding period, our hospital served a population of 65,684 veterans, for an unadjusted HCV seroprevalence of 2.3%.

Of the 1496 patients, we identified 150 who received treatment for CHC with one of the peginterferons in combination with ribavirin. Of these, 13 were excluded from the analysis because of missing values, leaving a total of 137 patients. This group represented only 10% of those patients known to have the HCV infection.

The study group was composed mainly of males (96.4%) and had a mean age of 58 years (Standard Deviation [SD] = 6.4). About 82% of the HCV patients were overweight or obese. The mean body mass index (BMI) was 28 (SD = 4.2). The most common risk factor for hepatitis C was intravenous drug use (IVDU) (38.5%). Approximately 29% of our study group had diabetes mellitus, and 69.5% reported that they consumed alcohol (ETOH). There was a predominance of HCV genotype 1 (77%), which is comparable with what has been seen in previous reports. (Refer to Table 1.)

Most of the HCV patients received combination therapy with peginterferon alfa-2b (90.5%). The METAVIR stage was moderate (~37%) for most of the patients in this study. About 19% of the patients in the fibrosis stage had cirrhosis. The frequencies of the other clinical features are shown in Table 2.

The patients treated with peginterferon alfa-2a and those treated with alfa-2b had similar laboratory results ($P>0.05$). There was a marginally significant difference (Mann–Whitney *U* test; $P = 0.06$) in the hemoglobin A1c levels of the patients receiving peginterferon alfa-2a plus ribavirin and those receiving peginterferon alfa-2b plus ribavirin (median [IQR]: 6.3 [5.8, 6.4] vs. 6.7 [6.4, 7.7], respectively).

An EVR was commonly observed (66.7%); nevertheless, only 48.4% achieved an SVR. No statistical difference was found for EVR (66.3% vs. 70%) or SVR (33.3% vs. 50%) between the types of peginterferon received. Likewise, the end-of-treatment results were similar between genotypes (i.e., genotype 1 vs. genotype non-1). The most common adverse event was anemia (26.2%). The frequency of adverse events was not statistically different between patients using peginterferon alfa-2a and those using peginterferon alfa-2b (both in combination with ribavirin) (P>0.05). About 49% of these patients had 2 or more adverse events.

Discussion

In this retrospective study we evaluated the prevalence of chronic hepatitis C in a population of Latino veterans in Puerto Rico and the response (of the patients) to the treatment available during the study period. The unadjusted seroprevalence of HCV during this period was calculated based on the number of veterans served; therefore, it has probably been underestimated, since not all of the members of the population served were tested. During the study period, only those who voluntarily reported known risks factors were screened for HCV. The universal screening of baby boomers started after the release of the 2012 CDC guidelines; since that time, around 81% of our patient population has been screened for HCV.

When compared to the universe of HCV-infected patients, only a small proportion of patients received treatment during the study period, probably because of contraindications to treatment. This is similar to what is reported in the literature, in which only a small proportion of the HCV-infected veterans had ever received antiviral therapy (14).

The studied population was composed of middle-aged baby boomers who were overweight, who had histories of alcohol abuse, who were found to have the HCV genotype 1 subtype, and in whom the presence of fibrosis was confirmed by liver biopsy. These are known risks factors for cirrhosis and are associated with a poor response. Some of the reported risk behaviors, such as the use of intravenous drugs and having sex with multiple partners, may have been underestimated because of the retrospective nature of this study; nevertheless, these behaviors and others, equally dangerous, were identified as being present in a large group of patients. The reported use of IV drugs is higher than what is found in the literature (7). A prior study in US veterans with hepatitis C identified drug use as a risk factor in 22.6% of the subjects, which is, as can be seen, lower than the 38.5% identified in our studied population (7).

Early and sustained treatment responses were similar, regardless of the type of peginterferon used. A better response was not observed in those with the non-1 genotype, which finding is contrary to what is commonly reported in the existing literature (9, 10, 11). Anemia was the most common side effect and is a well-known response to ribavirin-containing regimens. The overall SVR of 48% contrasts with the 28.8% that was reported in a government-insured HCV population (11). The reasons for this difference require further investigation. The government-insured population studied was younger, had a higher proportion of female patients, and had a high rate of discontinuation of therapy than did our own (11).

In 2011, in an effort to improve response to treatment, the standard of care for patients with HCV genotype 1 became a combination of an oral protease inhibitor (boceprevir or telaprevir) along with pegylated interferon and ribavirin. These treatment regimens improved SVR rates but with the result of causing more side effects than previous ones and requiring closer patient follow-up than was needed with those prior therapies. The ultimate goal was to develop interferon-free regimens in order to decrease the number and severity of side effects and thereby broaden the population able to tolerate treatment. Fortunately, since 2013 the FDA has approved several new hepatitis C treatment regimens that are interferon- and

ribavirin-free. In late 2013, simeprevir and sofosbuvir received FDA approval for use in the treatment of HCV; a year later, the combinations of sofosbuvir and ledipasvir and of ombitasvir, paritaprevir, and ritonavir tablets co-packaged with dasabuvir tablets were also endorsed. These new therapeutic combinations are potent inhibitors of HCV replication, improving eradication rates and shortening the duration of therapy. The latter resulting in better compliance and adherence to the prescribed therapy. All these medications also have been proven to have better safety profiles than do the previously available drugs. These novel treatment combinations can be applied to most commonly encountered genotypes, as well as to other populations that in the past could not be treated, such as HIV–co-infected patients and patients with hepatocellular carcinoma awaiting liver transplant.

Hepatitis C, once believed to be an incurable disease, is now curable using current treatment regimens, which have success rates that range from 95 to 99%. Multiple patients not previously considered for treatment are candidates, now; however, the extraordinary treatment costs will now determine who will eventually end up being treated. Hispanic treatment responses to these new regimens now need to be studied to determine whether these regimens can be used in this population.

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Table 1

Characteristics of the study group [*]

Variable	Overall (n = 150)	Patients included in the analysis[†] (n = 137)
Age, years		
Mean ± SD	58 ± 6.4	58 ± 6.4
Gender		
Male	145 (96.7)	132 (96.4)
Female	5 (3.3)	5 (3.7)
BMI kg/m²[‡]		
Mean ± SD	28 ± 4.2	28 ± 4.2
Underweight	0 (0.0)	0 (0.0)
Normal weight	28 (18.9)	24 (17.8)
Overweight	77 (52.0)	69 (51.1)
Obese I	35 (23.7)	34 (25.2)
Obese II	6 (4.1)	6 (4.4)
Obese III	2 (1.4)	2 (1.5)
Risk factors[‡]		
Transfusion	13 (26.0)	13 (27.1)
IVD	27 (40.3)	25 (38.5)
ETOH	49 (68.1)	48 (69.5)
Tattoos	17 (30.9)	15 (28.9)
Body piercings	9 (18.0)	7 (14.9)
Risky sexual behavior	17 (34.0)	15 (32.6)
Medical history[‡]		
Diabetes mellitus	43 (28.9)	40 (29.4)
Hepatitis B	9 (6.0)	8 (5.9)
HIV	5 (3.4)	3 (2.2)
Genotype		
Genotype non-1	34 (22.7)	33 (24.1)
Genotype 1	116 (77.3)	104 (75.9)

Note: BMI = body mass index; IVD = intravenous drug; ETOH = ethyl alcohol; HIV = human immunodeficiency virus.

[‡]Risks factors (Refers to receipt/consumption/presence/practice of any of the listed factors)

[*]Number of participants (percent) is presented unless otherwise indicated.

[*]Includes patients receiving one of the treatments (peginterferon alfa-2a + ribavirin or peginterferon alfa-2b + ribavirin).

[†]Total may not equal the overall sample size because of missing values.

Table 2

Clinical features of the study group (n = 137)

Clinical features*	**n (%)**
EVR	64 (66.7)
SVR	30 (48.4)
Viral load>400	92 (78.0)
METAVIR stage	
Mild	19 (30.2)
Mild to moderate	2 (3.2)
Moderate	23 (36.5)
Severe	19 (30.2)
Fibrosis stage	
No fibrosis	1 (1.5)
Portal fibrosis without septa	6 (8.8)
Portal fibrosis with few septa	9 (13.2)
Numerous septa without cirrhosis	10 (14.7)
Cirrhosis	13 (19.1)
Other†	29 (42.7)

NOTE: EVR = early virological response; SVR = sustained virological response.

*Total may not equal the overall sample size because of missing values.

†Includes chronic hepatitis, hyperplasia of portal tracts, severe hepatocellular damage with necroinflammatory activity, fine bridging fibrous septae and early cirrhosis, moderate periportal or periseptal interface (cirrhosis) hepatitis.