

## Chronic Hepatitis C in the Latino population

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### Abstract

Latinos with Hepatitis C virus (HCV) infection have a more rapid progression of fibrosis and decreased efficacy to anti-HCV treatment. The high rates of metabolic syndrome, insulin resistance and hepatic steatosis, and genetic differences may explain the severity of chronic hepatitis C (CHC) in this population.

In addition, there are substantial barriers for Latinos to access medical care as language and cultural differences and socio-economical factors, including lack of medical insurance. In this article we review the evidence on the natural history of CHC in Latinos, efficacy of therapy and possible strategies to improve outcomes.

### Introduction

In March of 2002 there were 37.4 million Latinos in the United States, representing 13.3 percent of the total population and the largest minority in the United States (1). Two thirds (66.9%) were of Mexican origin, 14.3% were from Central and South America, 8.6% were Puerto Rican (including both those living in Puerto Rico and the continental US), 3.7% Cuban-American and 6.5% from other Latino country origin.

The growth of the Latino population is estimated to reach 18.3% of the total population for the year 2025 (1) and by the year 2040 there will be 87.5 million Hispanic individuals, comprising 22.3 % of the population (2).

Minorities have higher prevalence of HCV infection than Caucasians in all groups of age (3). Reports from Centers of Disease Control and Prevention (CDC), have shown that although total new cases have declined since 1989, new cases in African Americans (AA) and Latinos are increasing (1,3). There is evidence of higher histological activity and higher fibrosis progression rates in Latinos than in Caucasians or AA's (4-5). Despite these facts, Latinos have been absent from clinical research and under treated for a variety of medical conditions, including CHC (6). The large number of Latino patients with rapid fibrosis progression, foresee HCV infection as a severe public health concern in this population.

## **The Latino population in the United States**

The term Latino means ethnicity, not race, and Latinos may be of any race. The use of the term Latino refers to the common features of people from Latin America regarding history, geography and cultural background. Latino is preferred to the term Hispanic, because is more representative of the diversity of the Latin American countries. Latinos are recognized by the Federal Government as a different ethnic group since the 1970's, and include people from Spanish-speaking countries in the Western hemisphere such as Mexico, Central and South America (except Brazil), Puerto Rico and Dominican Republic and their descendants (2).

Latinos share many aspects of common heritage and language, but still, cultural differences exist among the different countries of origin. Most relevant to this discussion, there are also significant differences in public health profiles and health outcomes. For all Latinos, there are disparities in access to medical care and poor health outcomes compared to Caucasians (7). Using data from National Vital Statistics System and the 1990 and 2000 Censuses, age specific diabetes related death rates were calculated. Diabetes related deaths were two fold more numerous among Mexican Americans and Puerto Ricans, than for Cuban Americans. Socio-economical factors as income and achieved level of education are factors that add to the diversity among Hispanic populations (8).

## **Epidemiology of HCV infection in Latinos**

Minority populations in the US are disproportionately affected by acute and chronic hepatitis and other viral diseases (9). According to the NHANES 3 data, the prevalence of HCV infection in Latinos was higher than for Caucasians in all age groups (10). Latinos and AA are disproportionately affected by HCV infection compared to Caucasians (11). Both AA and Latinos are disproportionately represented in another blood borne viral infection HIV/AIDS, accounting for 70% of all cases. Moreover, AA and Latino women represent 78% of all female cases and 82% of all pediatric cases are AA and Latino (11). The only prevalence study in a 100% Latino population in the US was performed in the city of San Juan and reported that 6.3% of the population was HCV-antibody positive (12).

Co-infection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is common. In the United States, it has been estimated that 25% of persons infected with HIV are also infected with HCV. The prevalence of co-infection with HIV and HCV is highest among those infected via percutaneous routes. Data from drug treatment centers in these urban areas suggest that the prevalence of co-infection with HIV and HCV may be highest among African Americans (AA) and Hispanics (13).

A study in the changing trends in hepatitis C related mortality in the USA from 1995 to 2004, showed that the highest mortality rates for 2004 were among males, persons aged between 45-54 years, Hispanics, non Hispanic blacks, and non Hispanic native American/Alaskan natives. In fact, chronic liver disease is the seventh highest cause of death in Latinos aged 25 to 44 years and the third highest in the 45 to 64 age group (14).

The most common risk factor for HCV infection in Latinos is history of IDU (15). HCV infection is associated to: increasing years of injection, injecting in shooting galleries, tattooing

while at prison and self reported history of sexually transmitted diseases (16). In a study to assess the prevalence of viral infections among drug users at Los Angeles County, predictors of total number of co-infections were age at first infection, lifetime years in jail and Latino ethnicity. Latinos had the highest proportion of co-infections of HCV with Hepatitis A virus (HAV) and Hepatitis B virus (HBV) (17). A report on the prevalence and correlates of HCV infection among active IDU in Puerto Rico, reported troublesome high rates of HCV infection of 89%. The study documented that HCV sero-negative patients that initiated IDU had a 57% infection rate within a year. Similar to other studies, predictors for HCV infection were increasing years of injection, injecting in shooting galleries and self reported history of sexually transmitted diseases (STD) infection (16). This study also confirmed reports of higher rates of both HCV and HBV infection in addition to STD as HIV infection and AIDS, in Latinos that are IDU (16, 18).

There are differences in the risk behavior among IDU. Duration of use and sharing drug paraphernalia are predictive of HCV infection (19). Mexican Americans and Puerto Ricans were found to inject more frequently, share more paraphernalia and disinfect less often with bleach than AA (20).

Contrary to AA, reported to have higher rates of genotype 1 infection, Latinos appear to have the same risk of infection with genotype 1 HCV as Caucasians and other ethnic groups (15,17). A study that examined HCV patients in Puerto Rico under treatment by gastroenterologists, found that 82% of patients were Gen 1 and 18% were non 1 (21).

Latinos are infected at younger age than Caucasians and AA, are predominantly male, and more frequently co-infected with HIV (15, 22). A review of HCV/HIV co-infected patients in the VAH system found that this population was more likely to be Latino or AA and to have more diagnoses of mental disease including depression, alcohol abuse and both substance and hard drug use than the HIV mono-infected (23).

### **Severity of CHC in Latinos**

Latinos have a more aggressive form of chronic hepatitis C. Latinos have been reported to have higher serum alanine transaminase levels (ALT) (22, 24), aspartate transaminase levels (AST), total bilirubin and lower albumin levels than Asians, AA or Caucasians (22). Latinos have higher portal inflammation scores on liver biopsy than Caucasians or AA, and higher prevalence of cirrhosis than AA (24). A study of patients diagnosed with CHC in ethnic minorities at Los Angeles County, found Latinos to be over-represented (51%), as compared to the county non Latino population. AA and Caucasians had significantly lower fibrosis progression rate (FPR) than Latinos: 0.03F/y and 0.02F/y respectively, compared to 0.21F/yr in Latinos (4).

Other reports have reported more fibrosis (staging), grading (necroinflammation), faster FPR of 0.14F/y and more cases with diagnosis of cirrhosis at index biopsy in Latinos with CHC (24). Compared to Caucasians, Latinos had more history of blood transfusion, were heavier (BMI>30), had more diabetes mellitus, hepatic steatosis (79%) and obesity (50%) (25). Latino ethnicity and obesity were found to be independent predictors for steatosis, after adjusting for age, diabetes and alcohol (25).

The evidence for a more rapid progression to cirrhosis in Latinos with CHC deserves more attention. In a retrospective study conducted in Puerto Rico, that examined 470 patients, with liver biopsies, it was demonstrated a rapid progression to cirrhosis, with 50% of patients diagnosed with cirrhosis, 42 years after infection, but at relatively young median age of 53 years. This study showed that HCV/HIV co-infected patients had a more rapid progression to cirrhosis than the HCV mono-infected patients. However, further analysis demonstrated a marked difference in the risk to cirrhosis along gender with HCV mono-infected males having as severe a risk as the co-infected males. Independent predictors of cirrhosis were male sex, age at time of biopsy, grading in the HCV mono-infected cohort and ALT in the HCV/HIV co-infected patients (15). This study suggest that cirrhosis secondary to HCV infection may develop in a significantly higher number of Latino patients, 50%, as compared to Caucasians, whereas risk is estimated to be around 30% (15, 26). These findings contrast to reports in AA, whereas milder biochemical and histological liver disease is present (27). In a comparison between AA and Caucasians cohorts with CHC with similar modes of HCV transmission, amount of alcohol use, and duration of HCV infection, AA were found to be older and mostly infected with Gen 1. However, AA had less grading and liver fibrosis scores, lower ALT and lower iron levels (27).

There is scarce information about the prevalence of HCC in Latinos. CHC is the main risk factor for HCC in Caucasians and AA, whereas HBV is the main risk for Asians (28).

### **Why the more rapid progression to cirrhosis?**

#### *Alcohol*

Chronic alcohol ingestion is associated to increased rates of fibrosis progression and risk to cirrhosis (29). The prevalence rates self reported history of past heavy drinking among Mexican Americans and Puerto Rican males are three times higher than rates reported for non Latino males. Using data from the Hispanic Health and Nutrition Examination Survey (HHANES), it was found that 28-35% of Mexican Americans and Puerto Ricans reported past heavy drinking, while rates for Cuban males was much lower, 7-16%. The rates of past heavy drinking for Latino women were much lower (1-8%) (30).

Around 55.7% of total population of Puerto Rico admits alcohol consumption in the previous year. Data from year 2002 showed that 47.3% of the population ingested alcohol (more than 5 drinks at least once), males (49.7%) more than females (35.9%). The % of patients that admitted abuse and dependence to alcohol ranged according to sex and age group, from 10.9% to 18.3% in males, and 2.5% to 5.1% in females (31).

#### *Hepatic steatosis/Metabolic Syndrome*

Hepatic steatosis is common in patients infected with hepatitis C virus (HCV) and has been associated with accelerated progression of fibrosis (32, 33). It has been shown that alcohol and steatosis act additively to increase fibrosis (32) and worsening liver steatosis has been associated to fibrosis progression in paired biopsy studies (33). A recent study demonstrated that oxidative stress interacts with steatosis to promote the progression of CHC in alcohol-consuming patients (34). Studies of progression of CHC have shown that obesity and overweight (>25Kg/M<sup>2</sup>) are

independent factors for liver steatosis and that steatosis Grade 2/3 is associated to elevated ALT, and stage 3/4 fibrosis (35).

In the case of steatosis as in non alcoholic fatty liver disease, the metabolic syndrome is especially implicated (35, 36, 37). The Latino population suffers from higher rates of type 2 diabetes, obesity, metabolic syndrome and cardiovascular diseases (36). It has been shown that Latinos have higher prevalence of IR associated to metabolic syndrome (38).

### *Genetics*

It has been postulated that an interaction of environmental factors, as excessive caloric intake and sedentary lifestyle, plus genetic risk factors cause metabolic syndrome and type 2 diabetes. Linkage of diabetes or hyperglycemia to a region of human chromosome 1q21-q25 has been demonstrated. A link to chromosome 1q has been identified in Latinos with metabolic syndrome (39).

### **Barriers to treatment for CHC in Latinos**

There are no single explanations for the absence of Latino participation in all major HCV treatment trials. Cultural barriers, specially language, and economical and insurance issues and bias from the part of medical providers and staff, all may play a role in the lack of Latinos participation in clinical trials and limited access to therapy.

### *Insurance issues*

A study that considered factors such as health insurance coverage, socioeconomic status, attitudes about health care and neighborhood characteristics among different Hispanic subgroups reported that insurance status and socioeconomic differences explain a significant part of the health disparities among Latinos. This study also found substantial variation in the level of disparities among different groups of Hispanics (40). In 1998, fifteen percent of the U.S. population did not have any health insurance coverage. Nineteen percent of non-Hispanic black persons and 33% of Hispanics were uninsured in 1998, as opposed to 11% of non-Hispanic white persons. Further, 46% of poor Hispanics and 44% of near-poor Hispanics under age 65 years were uninsured. Lastly, 80% of non-Hispanic white persons under age 65 years had private health insurance coverage, as opposed to 55% of non-Hispanic black persons and 49% of Hispanics in this same age category. Latinos without insurance have no regular source of medical care and are less likely to have routine medical examinations.

### *Risk factor ascertainment, testing and referral for treatment*

Even in well identified populations with medical insurance, Latinos are not receiving HCV therapy. It has been reported that Latinos were more likely to meet all requirements for HCV infection therapy in the VAH system than Caucasians, (48.9% compared to 39.6%), but still the same % of patients received treatment, 20% and 19.2% respectively (22). A more recent study that examined 113,927 veterans with the diagnosis of HCV infection, reported the prescription rate to be only 11.8% (41). This study found that Hispanic ethnicity was a predictor of non treatment for CHC. What is troublesome is that even in well identified high risk populations,

documentation of HCV infection is infrequent, and referrals to therapy rare. A recent study designed to determine rates of hepatitis C (HCV) risk factor ascertainment, testing, and referral from four primary care sites in Philadelphia, reported on the effect of race and ethnicity. The study found that documentation of an HCV risk factor history in urban primary care is uncommon, that racial differences exist with respect to HCV risk factor ascertainment and testing and that minority patients positive for HCV, were less likely to be referred for subspecialty care and treatment. Overall, treatment providers documented history of IDU and transfusion for less than 20% and 5% of patients, respectively and only 55% of patients who admitted IDU were tested for HCV. Hispanics were less likely to have a risk factor history documented, compared to AA and Caucasians ( $P < 0.0001$ ). Overall, minorities were less likely to be tested for HCV than Caucasians in the presence of a known risk factor (23% vs. 35%,  $p=0.004$ ) (42).

### **Efficacy of HCV treatment in Latinos**

The standard of care (SOC) for CHC is Peg IFN and RBV combination; 48 weeks for Gen 1 using weight dosed RBV and 24 weeks for Gen 2/3 with fixed dosed RBV (43). As Latinos have been under represented in all pivotal CHC treatment clinical trials, these studies do not support any conclusion on the efficacy of therapy for Latinos.

Published reports so far, are either small or retrospective analyses, and not designed to examine the effect of ethnicity on efficacy. Nevertheless, all reports place the efficacy of anti-HCV treatment in Latinos between Caucasians and AA. In a secondary analysis, of a study that analyzed 2 multi-center trials to determine predictors of treatment success for naïve patients treated with combination therapy of IFN and RBV, SVR was achieved in 61% of Asians, 39% of Caucasians, 23% of Latinos and 14% of AA. After adjusting for known factors that impact response as genotype, ethnicity was predictive of SVR with Asians most likely to respond, and Latinos and AA less likely to respond than Caucasians (44). Results from a cross sectional secondary analysis from a prospective study conducted at 24 VAH also showed differences in outcome according to ethnicity. The results showed lower end of treatment (EOT) and SVR responses for Latinos as compared to Caucasians, although the difference was not significant (22). The recent large randomized USA WIN-R trial comparing treatment with Peg IFN alfa-2b and weight dosed versus fixed doses of RBV, resulted in significant differences in SVR: 34% for Latinos, 46% for Caucasian ( $p=0.002$ ) and 52% for Asian, ( $p=0.0057$ ). For patients with genotype 1 differences were also significant; 24% for Latinos, compared to 35% for Caucasians,  $p=0.005$  and 41% in Asians  $p=0.045$  (45).

The only prospective study to date designed to examine the impact of ethnicity in efficacy of treatment with Peg IFN alfa-2a and RBV for Gen 1 patients was recently completed. The LATINO TRIAL was designed to test the hypothesis that SVR rates in Latino whites would be not inferior to 15% of the SVR of Non Latino whites. The study enrolled 267 Latino Caucasians and 302 Non Latino Caucasians. All patients were treated with Peg IFN alfa-2a 180mcg/ml and RBV 1000-1200mg/day according to weight. The Latino population was 51% Mexican, 32% Puerto Rican, 9% Cuban, and 8% from other Latino countries. Both groups were well matched at baseline, although Latinos were slightly younger and the percentage of cirrhotic patients was slightly larger in the Latino group, (13% compared to 10%). At week 4, HCV PCR was

undetectable in 14% of Latinos compared to 20% of non Latinos;  $p < .05$ , at week 12, undetectable was achieved by 48% Latinos compared to 63% of non Latinos,  $p = .0003$ . The SVR was significantly higher in non Latinos than in Latinos 49% compared to 34%,  $p < .001$  (46).

The impact of evolving new STAT-C drugs on the efficacy of anti-HCV therapy in Latinos is unknown. It is possible that bypassing the host characteristics with a direct anti-virus agent could improve the efficacy of anti-HCV therapy in Latinos.

### **Possible explanations to decreased efficacy with Peg-IFN/RBV therapy in Latinos**

There are multiple explanations for lower efficacy of treatment with Peg IFN/RBV in Latinos. Viral kinetic studies have not been reported in Latinos. There are no differences in the pharmacokinetics of RBV or Peg IFN among Latinos and Caucasians. However, a significant decrease in Peg IFN concentration is seen when standard doses are used in patients that weight more than 85 kg. Lower exposure to Peg- IFN with increased body weight is associated to decreased antiviral response and may explain decreased efficacy in Latinos with higher rates of obesity. Obesity, high body weight, hepatic steatosis and insulin resistance have been demonstrated to be associated to decreased antiviral response (47).

More hepatic fibrosis, would also contribute to decreased efficacy. Earlier intervention, with programs to screen and diagnose Latino patients, could improve the chance to have success with therapy.

It is known that host ethnicity or race affect the antiviral CD4 T-cell responses during the course of CHC. In HCV infection, the severity of liver damage is regulated by the cellular immune responses. HCV clearance correlates to a vigorous HCV specific CD4 cells and IFN- $\gamma$  production. To our knowledge no antiviral CD4 T cell responses studies have been reported in Latinos with CHC.

### **Strategies to improve outcomes to treatment for CHC in Latinos**

#### *Education*

Studies have shown that CHC patients often have low levels of knowledge about the disease, including knowledge about modes of transmission and available treatment options. However, there is evidence that education and improvements in the willingness of patients to accept treatment may be achieved in only a clinic visit.

A study based in two inner-city hospitals in Brooklyn, New York, evaluated the change in knowledge of patients with HCV and their willingness to accept treatment after a single session of on-site education which was delivered as part of a clinic visit. After the educational intervention there was an increase in knowledge about risk factors for transmitting HCV, such as unprotected sexual intercourse (100% vs. 88% at baseline), tattooing and body piercing (88% vs. 64% at baseline), and sharing personal items like razors. Knowledge of the risk of developing liver cancer in patients with HCV also increased substantially (96% vs. 77% at baseline). There was a marked increase in the expressed willingness to accept treatment (88% vs. 41% baseline).

The results of the educational intervention are very encouraging. These results have implication in setting up a structured educational intervention in liver clinics for CHC patients. Ideally education programs should be developed for the general community and especially to high risk populations. The cultural and language barriers especially have to be taken into account in those programs in order to be effective (48). Physicians need to be educated in the severity of the HCV disease in Latinos and to consider this population a target for screening and early referral for treatment.

### *Improvement of risk assessment and continuity of care*

There is a need to improve continuity of care, patient-provider communication and patient education regarding HCV treatment options for treatment rates to improve. Although clinicians have been encouraged to offer chronic hepatitis C virus (HCV) treatment to patients with injection drug use histories for many years, many do not receive therapy. A study that examined HCV patients who were treatment-naive and receiving regular medical care at an HIV or methadone clinic in New York City found that 65% of the patients were offered treatment but only 7% were treated. Reasons for failure were mostly loss to follow-up at the original site of care. Strategies to assure the continuation of patient evaluation and treatment are required (49). Treatment guidelines recommend all HIV/HCV-co-infected persons be considered for hepatitis C virus (HCV) treatment, yet obstacles to testing and accessing treatment for HCV continue. A study to assess awareness of HCV and describe diagnostic referrals and HCV treatment among women in the Women's Interagency HIV Study (WIHS) reported that one quarter of women with HCV in this cohort were not aware of their diagnosis. Among those aware of their HCV infection, 1 in 4 had a liver biopsy and received treatment for HCV. In multivariate regression analyses, African-American race, Latino ethnicity, poverty, and current crack/cocaine/heroin use were negatively associated with treatment referrals, whereas elevated (ALT) was associated with increased likelihood of referral and increased likelihood of treatment.(50).

The cost of anti-HCV therapy should be covered by the government for patients unable to pay for medical insurance, or insurance options made to be accessible to poor patients. The cost of managing the complications of cirrhosis and end stage liver disease secondary to HCV infection would be significantly greater.

### **Research in Latinos**

Clinical trials in Latinos are required in order to study possible strategies to improve efficacy by optimizing available treatment and also to consider this population for testing of new drugs.

### **Conclusion**

Latinos with Chronic hepatitis C have a challenging type of CHC. Latinos have a rapid progression of fibrosis and decreased efficacy to treatment with Peg IFN /RBV. The explanations for more aggressive progression and decreased response are complex and include: high rates of metabolic syndrome, insulin resistance and hepatic steatosis, and genetic differences not only for metabolic syndrome but for immune responses to IFN.

There are substantial barriers for Latinos to access medical care. Language and cultural differences and socio-economical factors, including lack of medical insurance are significant obstacles toward diagnosis and treatment. Structured programs to educate, diagnose and treat Latinos with HCV infection are urgently needed. Researchers and policymakers need to broaden the scope of factors they consider as barriers to access if the goal of eliminating disparities in health care is to be achieved. Education programs for medical providers are mandatory to educate physicians on the severity of CHC in Latinos and to consider this population as a special population with priority for therapy. Finally clinical trials in Latinos are required in order to study possible strategies to improve efficacy by optimizing available treatment and also to consider this population for testing of new drugs.

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