June, 2009

Treatment Options for Hepatitis C and the Rationale for Low Response Rates in African Americans

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Hepatitis C virus (HCV), the leading cause for liver transplantation, is emerging as 1 of the infections that pose public health problems in the world since about 170 million people worldwide are infected with this virus. Inequality in addressing racial/ethnic disparities in treatment for hepatitis C is a pressing problem. HCV is more common among African Americans than among other racial groups in the United States. Although African Americans have been shown to have a lower rate of viral clearance and a higher rate of chronic hepatitis C, they may have at the same time a much lower rate of fibrosis progression compared to Caucasians. The purpose of this study is to summarize treatment options available for hepatitis C in African Americans and to describe the different mechanisms thought to be the reasons for the disparate response to treatment in African Americans.

Keywords: African Americans ■ hepatitis

J Natl Med Assoc. 2009;101:604-608

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INTRODUCTION

Hepatitis is an acute virus inflammation of the liver usually characterized by jaundice, fever, nausea, vomiting, weight loss, fatigue, and abdominal discomfort. Hepatitis is 1 of 6 currently identified viruses—hepatitis A, B, C, D, E, F, and G—all of which can attack and damage the liver. Widely viewed as one of the most serious of all, the hepatitis C virus (HCV) is spread primarily through contact with infected blood and can cause cirrhosis. HCV shares the same characteristics with the *Flaviviridae* and belongs to the genus, *Hepacivirus*. Based upon DNA sequences, HCV is classified into 6 genotypes, numbered 1 through 6. In the United States, genotype 1 accounts for 71.5% of the total cases, genotype 2 for 13%, and a lower percentage among the remaining genotypes.¹

HCV has emerged as an important public health

problem. This virus has affected 3.9 million Americans, 170 million people worldwide, and is the most common indication for orthotopic liver transplantation.²⁻⁴ African Americans face complications with chronic diseases disproportionately compared with other groups.⁵ Furthermore, most African Americans are often not given the chance to participate in clinical trials.⁶ There are also differences that exist with regards to HCV infection. In this case, African American subjects represent only 5% to 10% of those who take part in clinical trials that involve HCV infection. The natural history, prevalence, and response to treatment are different among African Americans and other population groups.^{6,7}

Even though African Americans represent only 12% of the US population, ~22% of them are estimated to have chronic HCV infection.^{3,8} The prevalence of HCV genotypes also differ among racial groups. Even though 70% of the total HCV isolates in the United States are of genotype 1, the prevalence rate of this genotype among African Americans is higher than among any other racial groups.⁸⁻¹⁰ Despite the fact that the rate of developing fibrosis may be slow in African Americans, developing hepatocellular carcinoma increases more quickly in this population. Compared with non-Hispanic white men, the age-adjusted incidence among African American men increased from 5.3 to 6.1 cases per 100 000 persons in the same time.^{3,11} Finally, even the rate of cancer-related mortality is 2-3 times higher among African Americans than among whites.¹²

IMMUNE DEFENSE TO HEPATITIS C INFECTION

In the early phase of viral infection, the body's immune response system becomes induced. The first defense is a nonspecific antigen mediated by natural killer (NK) cells, neutrophils, and macrophages.¹³ T helper 1 (Th1) cytokines, ie, interleukin (IL)-2, interferon (IFN)- γ and tumor necrosis factor (TNF)- α , stimulate antigens by induction of human leukocyte antigen (HLA) molecules on infected cells and activating CD8-positive T cells and NK cells.^{14,15} Furthermore, nitric oxide (NO) production in macrophages and hepatocytes

can induce resistance against viral infection in neighboring cells.^{16,17} CD8-positive T cells recognize endogenously synthesized peptides that are generated across the membrane of the endoplasmic reticulum by the heteromeric transporter complex TAP1 and 2 and bound to newly assembled MHC class I molecules and are then presented in the antigen binding groove of HLA class I molecules on the surface of virus-infected cells.¹⁸ HCV-specific major histocompatibility complex (MHC)-I restricted CD8⁺ cytotoxic T lymphocyte (CTL) and MHC class II-restricted CD4⁺ helper T-cell responses have been found in patients with acute and chronic HCV infection. CTL-mediated lysis of virus-infected host cells may lead to clearance of virus, viral persistence, or chronic hepatitis if the process is incomplete.^{19,20} Patients who clear HCV infection have a more vigorous CD4⁺ and CD8⁺ T-cell response. Although there is an immune response, HCV is rarely eliminated.

Despite the various immune responses developed by the cells, mutations and the presence of quasi-species are very important in the role of viral escape. Another potential mechanism of viral persistence and pathogenesis is its molecular mimicry ability. It has been found that CTL induced by an HCV core-derived synthetic peptide, in some cases, also recognized cytochrome p450, which makes it probable that the HCV infection is causally linked to autoimmune hepatitis in some patients.²⁰

AVAILABLE TREATMENT OPTIONS FOR HEPATITIS C

In 1991, interferon- α was approved by the US Food and Drug Administration for the treatment of chronic HCV. When interferons bind to specific cell surface receptors, they set in motion a number of signal transduction pathways that lead to the induction of gene expression. Several interferon gene products have shown antiviral properties, including RNase L, 2'-5' oligoadenylate synthetase (it degrades both viral and cellular RNAs), Mx proteins known to inhibit the replication of RNA viruses by inhibition of messenger RNA synthesis or by blocking transfer of viral polymerase to the nucleus, and the double-stranded (ds) RNA-activated protein kinase (PKR).^{21,22} Interferon- α is effective for 10% to 20% of the HCV infected patients who receive it. Even in liver transplant recipients, standard dose interferon therapy has been largely unsuccessful. The infection persists post transplant and causes injury in two-thirds or more of patients. Six percent to 28% of HCV-infected liver transplant recipients progressed to cirrhosis within 5 years.²³

A combination of ribavirin and interferon- α is also used for the treatment of HCV. The treatment dramatically reduces HCV RNA levels even in liver transplant patients, although there is an increased side effect relative to interferon monotherapy.²³ It was also shown that the combination of ribavirin with interferon- α suppresses the replication of HCV, though not directly. In vitro and

in vivo studies have shown that ribavirin may modulate the production of T cell-derived cytokines such as interleukin (IL)-2 and interferon- γ (IFN- γ), and these cytokines may play a role in the HCV pathogenesis.^{19,24}

Pegylated interferon, a new form of interferon, used in combination with ribavirin, gives a better treatment. This combination stays in the body longer and the patients need only 1 injection a week, instead of 3. Masanori and Nobuyuki²⁵ recently published that statins also (atorvastatin, simvastatin, fluvastatin, lovastatin, and pitavastatin) enhanced the anti-HCV effect of this interferon. Saito and colleagues²⁶ report in their article, of the production of a replicon system for genotypes 2a (strain JFH-1) and a transfection system of genotype 1b. This gives more opportunity for biologists to be able to elucidate the molecular details of hepatitis C. A retrospective analysis of African Americans with genotype 2 and 3 who had received treatment for HCV was conducted. The purpose of this analysis was to compare their sustained virological response (SVR) to a group of Caucasian patients. These 2 populations were matched for genotype, the presence of cirrhosis, type of therapy, sex, and body weight, and those who received treatment during the same time interval. This retrospective analysis showed that African Americans with HCV genotypes 2 and 3 have a significantly lower SVR than the response exhibited by Caucasian Americans.²⁷

In a study carried out by Lennox et al²⁸ the SVR to peginterferon α -2a (40kd) in combination with ribavirin was assessed in black patients chronically infected with HCV genotype 1. In this study 78 black and 28 white American interferon-naïve patients were enrolled to receive once-weekly subcutaneous injections of 180 μ g peginterferon α -2a plus oral ribavirin (1000 mg/day for patients weighing less than 75 kg and 1200 mg/day for patients weighing 75 kg or more) for 48 weeks. This study showed that black Americans have a high prevalence of chronic HCV infection and respond poorly to therapy with interferon- α -based regimens, although they have been underrepresented in clinical trials.

RATIONALE FOR THE LOW TREATMENT RESPONSE IN AFRICAN AMERICANS

Despite the steady improvements in HCV treatments efficacy, many patients who are treated do not achieve viral clearance. One reason is because the treatments are often very expensive and produce their own level of morbidity.²⁹ The rate of failures is very significant. In the report by Lennox et al,²⁸ at the end of the follow-up period (week 72), the SVR rate was 26% in blacks. This was lower than the SVR rate of 39% in the white reference group. In a larger trial, a SVR rate of 46% was reported for 298 predominantly white patients infected with HCV genotype 1. The lower rate for whites was attributed to the relatively small cohort of patients, the relatively high rate of premature discontinuations, and

failure to return for the 72-week follow-up visit. In general, response rates in nonregistration trials or clinical practice settings are often lower overall.

One of the reasons for low drug response is the lack of patient education and the knowledge of the importance of adhering to therapy. The critical factors in maximizing the benefits of these costly antiviral therapies are essential in order to optimize treatment response, and the willingness to take part in the treatment process in the first place. In a study conducted by Gupta et al³⁰ change in the knowledge of patients with HCV and the willingness to accept treatment after a single session of on-site education was evaluated. The majority of these patients were African Americans and other minority groups. Before the study, there was a very low knowledge among patients with HCV about the etiological agent being a virus. 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 such as razors. Knowledge of the risk of developing liver cancer in patients with HCV also increased substantially (96% vs 77% at baseline). Most importantly was the increase in the willingness to accept treatment (88% vs 41% baseline).

There are factors primarily responsible for the soaring of sexually transmitted diseases (STDs)—HIV and HCV included. The birth control pill greatly reduced fears of unwanted pregnancy, an ideology of sexual liberation and permissiveness among young urban adults throughout the world, a new pattern of employment in developing nations in which young males migrate to cities for jobs and return to their villages on weekends to spend time with their spouses and girlfriends, thereby spreading STDs acquired in urban areas to the countryside; and most importantly is that of multiple sexual partners on an unprecedented scale.³¹

Although adherence and retention of female injection-drug users (IDUs) in clinical trials is not well studied, Richard et al³² evaluated 458 female IDUs in a clinical trial in Baltimore, Maryland. In all, 62.9% were adherent to visits. Of women with greater or equal to 1 visit after enrollment, 76% were adherent to treatment, took at least 80% of pills; 27.7% were lost to follow-up, missed at least 3 consecutive visits. Those nonadherent to visits were younger and less likely to be on methadone. Women who were lost to follow-up were younger, more often white, not on medication, and injected drugs daily. In patients undergoing antiviral treatment, side effects are usually the major cause of nonadherence. In most of these cases, patients turn to cannabis for symptom relief. Unfortunately, there are little data available about cannabis use on treatment outcomes. In order to look at the impact of cannabis use during HCV treatment, a prospective observational study of standard

interferon and ribavirin treatment in 71 recovering substance users, of whom 22 (31%) used cannabis and 49 (69%) did not. Overall, 48 (68%) were adherent, 29 (59%) nonusers, and 19 (86%) cannabis users ($p = .03$). Although cannabis users were not more likely than nonusers to take at least 80% of the prescribed interferon or ribavirin, they were significantly more likely to remain on HCV treatment for at least 80% of the projected duration, 95% vs 67% ($p = .01$). The conclusion drawn from these results is that modest cannabis use may offer symptomatic and virological benefit to some patients undergoing HCV treatment by helping them maintain adherence to the challenging medication regimen.³³

Genotype 1 infection is the most difficult to treat. Its treatment has been proven to work better when there is adherence to therapy. Patients with this type 1 genotype usually require 1 full year of drug therapy, hence their failure to recognize and manage any common hematologic or neuropsychiatric side effects, which usually lead to nonadherence or dose reduction. These complications then lead to reduction in treatment effectiveness.³⁴

Although the reasons for apparent racial differences in the virological response to interferon therapies for chronic HCV are understood, HCV genotype 1, which has been associated with a poorer response to interferon, is more prevalent among blacks than among whites. In recent reports that measured the effectiveness of interferon therapy, certain differences aligned with race were observed. Racial differences in therapeutic outcomes with standard interferon were attributed to differences in its effectiveness. These results were estimated at 98% for white patients and 87% for black patients ($p = .005$).^{34,35}

Stepwise regression analysis studies on the low level of response to treatment by African Americans were due to the difference reflected in higher HCV RNA levels (3.6 vs 3.0 million copies/mL) and a higher prevalence of genotype 1 (88 vs 66%; $p = .004$) among African Americans. Studies carried out with 420 African American patients showed that the racial difference, not the prevalence of genotype 1, was the main reason for the difference.^{28,34-36}

It has been estimated in the United States that 25% of persons infected with HIV are also infected with HCV.² The prevalence of coinfection with HIV and HCV is highest among those infected via percutaneous routes. Actually, in urban areas in the United States, 50% to 90% of persons infected with HIV via injection drug use are coinfecting with HCV. Limited availability of data from drug treatment centers in these urban areas suggests that the prevalence of coinfection with HIV and HCV may be highest among African Americans and Hispanics. In one study of 110 patients coinfecting with HIV and HCV, HCV RNA was undetectable at 12 weeks in 23% of the patients receiving combination therapy, compared with 5% of patients receiving IFN alone. In another published treatment trial, coinfecting patients discontinued therapy

prematurely due to adverse events, which include anemia, depression, anxiety, and fatigue.²

Conjeevaram et al,³⁷ in their study, found out that the reduced response rate to combination therapy of hepatitis C among African Americans as compared with Caucasian Americans is not caused by clinical patient characteristics, disease severity, or amount of medication taken. Even after controlling for important factors associated with a response to combination therapy, race remained significantly and independently associated with sustained response.

In a study carried out by Golden-Mason et al,³⁸ where the relative program death 1 (PD-1) expression in 42 Caucasian American and 30 African American patients with chronic hepatitis C (who were enrolled in the Virahep C trial in preparation for antiviral therapy with peginterferon and ribavirin) was compared, there were no statistically significant differences in PD-1 expression on total CD4, CD8, and NK cells between African American and Caucasian American patients. However, in African American patients, PD-1 expression was significantly lower on HCV-pentamer⁺ CTLs compared with Caucasian American patients ($p = .0058$). Pretreatment viral level, previously shown to be associated with the likelihood of an individual patient experiencing SVR, did not correlate with the levels of PD-1 on immunocytes. In this same study, PD-1 expression as a predictor of SVR was further examined for each cell type by using relative risks in a Poisson regression analysis with adjustment for race. It was found that among African Americans with chronic HCV, PD-1 expression on HCV-specific CTLs before treatment was negatively associated with SVR ($p < .0001$). The plots of the proportion of SVR vs PD-1 expression on HCV-specific CTLs in the 2 racial groups indicated that the higher the mean pretreatment PD-1 on HCV-specific CTLs in African Americans, the lower the likelihood of developing SVR.

It was found that African Americans who as a group have been previously reported to demonstrate lower rates of spontaneous clearance of acute HCV, milder degrees of liver injury, and lower rates of response to antiviral therapy, show relatively abrogated HCV-specific CD4⁺ T-cell response. Since CD4⁺ Th1 response in promoting the generation of CTLs is very important, it is therefore conceivable that impairment in HCV-specific cell-mediated immunity might result in less hepatic immunopathology and may be also associated with a greater likelihood of nonresponse to antiviral therapy.³⁸

Previous studies³⁴⁻³⁶ have indicated that racial differences in HCV-specific immunity show that although African Americans had a higher frequency of proliferative responses to HCV antigens, as a group they do not produce IFN- γ . With this in mind, Rosen et al³⁹ found an impaired HCV-specific Th1 response in African Americans as compared to Caucasian Americans. Due to the large sample size, adjustment for possible interactions of

liver injury was possible with immune response by multivariable modeling. Race was found to be independently associated with decreased HCV but not generalized immune responsiveness. Therefore, the lower level of HCV-specific responsiveness in African Americans could reflect differential antigen processing and presentation, defects in the priming of expansion of naive HCV-specific helper T cells, selective deletion of memory cells, preferential sequestration in the hepatic compartment, or more robust counterregulatory mechanisms.

In a study by Layden-Almer et al,⁴⁰ where the difference in treatment response between African Americans and Caucasian Americans was looked at, there was no difference in the body mass index (BMI) and treatment dropout rates between the 2 races. Body weight in past studies has been shown to affect IFN blood levels and treatment response, but in this study, there was a weak correlation with BMI and treatment effectiveness ($p = .05$). When controls for this factor were utilized, however, the difference in effectiveness between the 2 races was still apparent ($p = .014$). Furthermore, in this study, adherence to treatment, which has been shown to influence treatment outcome, could not be used solely for the differences noted between African Americans and Caucasian Americans. There was also no significant difference for dropout rates between the 2 races. Summarizing this study, it was concluded, due to the kinetic results, that the major problem in treatment response between African Americans and Caucasian Americans is substantially lower in terms of effectiveness of IFN in African American patients. This problem in treatment then leads to an impaired second-phase viral decline and impaired viral negativity rates.

CONCLUSION

Due to the low level of responsiveness in most patients, especially in African Americans, to the available drug therapy and the fact that vaccines have not yet been developed, the best way to avoid being infected is to prevent contact with the HCV, which can be done by:

- Screening blood for the presence of HCV before transfusion to patients—This has greatly reduced transmission in developed countries to below 1%.
- Prevention of unlawful use of drugs, which is the main cause of infection through needle stick and intranasal cocaine use.
- Sexual behaviors with multiple partners—Abstaining from the frequent changing of partners will prevent sexual acquisition of the HCV. This abstention will also help to prevent prenatal transmission to newborn infants.
- Provision of specially trained personnel to educate the population on the risks involved in certain behaviors and on the history of the HCV infection will help in both developing and developed

countries, where the main cause of the disease is lack of education.

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