A Systematic Review of Race and Ethnicity in Hepatitis C Clinical Trial Enrollment

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Abstract: The African American/Black population in the United States (US) is disproportionately affected by hepatitis C virus (HCV) and has lower response rates to current treatments. This analysis evaluates the participation of African American/Blacks in North American and European HCV clinical trials. The data source for this analysis was the PubMed database.

Randomized controlled clinical trials (RCT) on HCV treatment with interferon 2a or 2b between January 2000 and December 2011 were reviewed. Inclusion criteria included English language and participants 18 years or older with chronic HCV. Exclusion criteria included non-randomized trials, case reports, cohort studies, ethnic specific studies, or studies not using interferon-alfa or PEG-interferon. Of the 588 trials identified, 314 (53.4%) fit inclusion criteria. The main outcome was the rate of African American/ Black participation in North American HCV clinical trials. A meta-analysis comparing the expected and observed rates was performed.

Of the RCT's that met search criteria, 123 (39.2%) reported race. Clinical trials in North America were more likely to report racial data than European trials. Racial reporting increased over time. There was a statistically significant difference among the expected and observed participation of African Americans in HCV clinical trials in North America based on the prevalence of this disease within the population.

The burden of HCV among African Americans in North America is not reflected in those clinical trials designed to treat HCV. Research on minority participation in clinical trials and how to increase minority participation in clinical trials is needed.

Abbreviations: HCV, hepatitis C virus; US, United States; RCT, randomized controlled trial; FDA, food and drug administration

Keywords: Hepatitis C■Clinical Trial■African American/Black

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INTRODUCTION

African Americans are disproportionately affected by Hepatitis C Virus (HCV) in the United States. HCV infection is a leading cause of cirrhosis, hepatocellular carcinoma and is the most common indication for liver transplantation in the United States.[1] An estimated 3.2 million persons in the United States have chronic HCV infection and carry risk of severe morbidity and increased mortality.[2,3] While African Americans comprise approximately 13% of the US population, they make up approximately 23% of Americans with hepatitis C.[4] A report using NHANES III data (1999−2002) found that the rate of a positive HCV antibody test was higher in blacks than in whites (3.2% versus 1.5%). Black men had higher rates of infection, and the highest prevalence rate was 9.8% among black men ages 40 to 49 years.[5,6]

HCV treatment is undergoing rapid evolution with the first generation protease inhibitors released in 2011 and now multiple direct acting antivirals regimens that re interferon free.[7,8] Although the burden of HCV on African Americans is significant, this population has been traditionally underrepresented in clinical trials. Previous new-medicationshavebeenreleased withlimitedexperience in African Americans, and post-approval studies in the past have consistently demonstrated lower HCV treatment response rates among African Americans.[9-11] The purpose of this study was to review the participation of African Americans in HCV trials during the first decade of this millennium through the development of the first generation protease inhibitors.

METHODS

Literature Search

We performed the literature search in March 2012 using the PubMed search engine (US National Library of Medicine, National Institutes of Health, Bethesda, M.D., USA). With the dates of publication limited to between 2000 and 2011, we entered the following MeSH terms/supplementary concepts into the search: "Hepatitis C, Chronic," "interferon alfa-2a," and "interferon alfa-2b." The aforementioned terms were also searched for in titles and abstracts. Only the results of this search were further processed for data collection and analysis. The collection of results was not supplemented with other outside articles.

Data Collection

The PubMed search provided 588 search results, which were later screened for inclusion (see below). The results encompassed 132 different journals and 406 unique

authors. The research team manually collected the results using a pre-designed data collection form. Year of publication, name of first author, and journal were used to identify results in the form. In addition, several other fields were created to itemize data collected from individual results. In addition to basic information, the following data were collected: "Genotypes studied," "HIV co-infection (Y/N)," "US/Canadian sites (Y/N)," "Latin American sites (Y/N)," "European sites (Y/N)," "Asian sites (Y/N)," "African sites (Y/N)," "Australian/NZ sites (Y/N)," "IFN alfa or PEG- IFN alfa used (Y/N)," "Ribavirin used (Y/N)," "DAA used (Y/N)," "Amantadine used(Y/N)," "Other medications used," "Race reported (Y/N)," "Total patients," "Number white," "Number black," "Number Latino," "Number Asian," and "Number other". Studies were designated as "reporting race" or "reporting ethnicity" if they included a statement or table explaining patient racial or ethnic makeup.

Inclusion criteria were English articles with participants aged older than 18 years with chronic HCV. Exclusion criteria were non-human studies, non-randomized trials, letters/case reports, cohort studies, articles not reporting outcomes of interest or primary data (editorials, reviews, secondary analyses), studies enrolling specific ethnic groups, studies specifically enrolling patients with significant secondary conditions (e.g. thalassemia, cryoglobulinemia, coagulation disorders, etc.), or studies not using interferon-alfa or PEG-interferon.

Definitions and Statistical Analysis

Given that multicenter studies were conducted in multiple countries and regions of the world, trial site designations were regional descriptions designated with the terms "partially" or "only". The regions of interest in this analysis were North America and Europe. "Partially" indicated that a particular region was at least one of the trial sites, while "only" indicates that there were no other regions among the trial sites. "Partially" data groups were much larger than "only" groups, and were also skewed towards the mean reporting statistics.

We obtained HCV prevalence data from Armstrong, et al., a large survey by the National Center for Health Statistics reporting HCV prevalence in the United States between 1999 and 2002.[4] We hypothesized that the expected rate of African Americans in the HCV therapy clinical trials should be equal to the relative burden of this disease among African Americans within the HCV population. Using the data from Armstrong, et al., we estimated that African Americans make up approximately 23% of people in the United States with hepatitis C. For this analysis, we selected the HCV trials that included only North American or Canadian subjects.

The proportions of African-American subjects in studies of hepatitis C were summarized using a random effects model because of the clear heterogeneity of the studies.[12] We used the method of DerSimonian and Laird[13] as implemented in *Comprehensive Meta-Analysis*.[14] The estimated proportion was 0.148 with 95 percent confidence limits of 0.126 to 0.174. As a sensitivity analysis we calculated estimates using two other models as implemented in the FAST*PRO software.[15,16] The estimate for the empirical Bayes model was 0.145 (95 percent confidence interval of 0.118 to 0.175) and the estimate for the beta-binomial model was 0.158 (95 percent confidence interval of 0.130 to 0.188). All models clearly exclude the reported U.S. rate of 0.23.

RESULTS

Using the systematic review, 588 clinical trials on hepatitis C were originally identified. Of the 588 trials initially identified, 314 (53.4%) were randomized controlled trials (Figure 1). The trials identified within this analysis were representative of clinical trials from both North America as well Europe conducted between 2000 and 2011. Of the 314 eligible trials, 69 (22.0%) took place only within North American and 143 (45.5%) took place only within Europe (Figure 1). Many trials were multinational studies and therefore included North America, Europe, and other regions of the world. We identified 113 (36.0%) multinational trials that included North America and 187 (59.6%) multinational trials that included Europe (Figure 1).

Figure 1. Results of PubMed literature search.