

Incidence of anti-HCV found among clinical trial participants during eligibility screening at NovumPRS from 2005 to 2011

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ABSTRACT

Hepatitis C (HCV) is a contagious viral illness and is the most common blood borne infection in the United States. It frequently remains undiagnosed until the ominous symptoms of liver disease, cirrhosis, or hepatocellular carcinoma become evident. This is because most acute infections follow an asymptomatic course. Center for Disease Control (CDC) Viral Surveillance data revealed the incidence rate for hepatitis C in the U.S. to be around 0.3 cases per 100,000. This means that nearly 4 million Americans have been exposed to HCV. World-wide 170 million people are affected by HCV. It is also known that despite these staggering numbers that the majority of HCV infected people go undiagnosed. Novum Pharmaceutical Research Services (NovumPRS) is a private, for profit, Clinical Research Organization (CRO) that has been recruiting and screening adult volunteers for Phase 1 bioequivalence and bioavailability drug studies since the early 1970's. Three sites collectively completed approximately 150 to 170 studies annually; and screened approximately 90,000 participants during the 2005 to 2011 period we reviewed. In this paper, we present our data regarding the 0.8% positive anti-HCV incidence found on screening laboratory evaluation for clinical trial volunteers prior to consideration for randomized trial enrollment at the three research facilities. Race/ethnicity and socioeconomic status were not considerations made in the reporting of our findings here. A positive anti-HCV test disqualified individuals from participation in all Phase I randomized trials conducted at our research organization not specifically related to hepatitis. All screened participants who tested positive were informed of these findings and appropriate reporting from our research organization to the epidemiology department at the appropriate state health agency was then carried out.

Keywords: Hepatitis, hepatitis C, trials, volunteers, screening, clinical research organization.

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INTRODUCTION

Hepatitis C virus is a *Flaviviridae* RNA virus with 6 genotypes and 50 subtypes (Seeff and Hoofnagle, 2003). The acute form of HCV infection is a short-term illness that may or may not be symptomatic within the first six months of contracting the virus (Seeff and Hoofnagle, 2003). In fact, it is estimated that 75 to 95% of acutely infected individuals are asymptomatic and therefore do not seek the care of a physician (Chen and Morgan, 2006). The chronic form is often found incidentally and predisposes older individuals who become infected with HCV to significantly increased potential for development

of chronic liver disease and hepatocellular carcinoma (Seeff and Hoofnagle, 2003).

Risk of transmission occurs through direct contact (percutaneous exposure) with the blood of an infected individual primarily in the setting of: illicit drug-use; sharing contaminated needles, syringes or other drug paraphernalia. It is less commonly transmitted through: sexual contact with infected persons; during childbirth; and direct contact with infectious blood during medical procedures. Intranasal cocaine use and even body tattoos have been implicated as risk factors for HCV

infection (Almario et al., 2012).

Symptoms are often insidiously silent until advanced liver disease begins to manifest. These often include: fatigue, myalgias (muscle ache), arthralgias (joint ache), decreased appetite and rarely, jaundice. Because the presenting symptoms of HCV are often vague physicians may not be prompted to obtain serologic testing for HCV. This further contributes to under-reporting and missed diagnoses of HCV.

Hepatitis C is the most common chronic blood borne infection in the United States (Seeff and Hoofnagle, 2003). Consequently, it remains the leading cause of chronic liver disease (cirrhosis and hepatocellular carcinoma) and the primary indication for liver transplantation (Kim et al., 2009). It is currently estimated that 2.7 to 3.9 million individuals are infected with HCV in the United States; this represents 1 to 2% of the general population (CDC, 2009d). Worldwide, an estimated 130 to 170 million people are infected with chronic HCV (Perez et al., 2006).

Select populations within the US have also shown a higher rate of cases than the estimated 1 to 2% seen in the general population. The rate for veterans that have received care through Veterans' Affairs Medical Centers is 4 to 35% (Cheung, 2000; Dominitz et al., 2005; Groom et al., 2008; Sloan et al., 2004). The rate among incarcerated individuals is 12 to 35% (Boutwell et al., 2005), and is presumably the result of intravenous drug abuse (IVDA) in this community prior to incarceration (Weinbaum et al., 2003). In 2009, a total of 205,997 reports of chronic HCV were submitted to the CDC by thirty-six US states (CDC, 2009d).

In 2007, the mortality rate of hepatitis was 4.6 deaths per 100,000 in the general population (CDC, 2008a). The complications of chronic infection develop in 75 to 85% of individuals infected with HCV. 5 to 20% of that group goes on to develop cirrhosis and another 1 to 5% of these individuals dies from hepatocellular carcinoma (CDC, 2008a; Lawrence, 2000). These complications are most common among non-Hispanic blacks, older men, obese individuals, alcohol users, and individuals co-infected with human immunodeficiency virus (HIV) (Ghany et al., 2009).

The healthcare cost burden associated with hepatitis C infection has been substantial. It is believed that \$1.8 billion was spent on medical care associated with HCV infections in 1997 alone (Leigh et al., 2001); and was projected to significantly increase during the close of the last and the beginning of this century's first decade (Lawrence, 2000; Seeff and Hoofnagle, 2003). It has, however, shown a progressive and steady decrease in the general population statistical data recordings since that time (CDC, 2009d). The cost analysis profile has been found on mathematical models to be comparable to that seen in the quality of life reduction, healthcare expenditure, lost work hours, etcetera experienced by non-insulin dependent diabetics (Lawrence, 2000).

Preventive measures for hepatitis C among the general

population encompasses: the prompt identification of infected individuals; educating the public at-large about the potential modes of transmission; implementing safe injection measures; getting drug users into treatment centers that coordinate support programming which seeks to teach modification of risky behaviors (McGowan and Fried, 2012).

METHODS

NovumPRS completed 1,050 bioequivalence and bioavailability studies between 2005 and 2011 at its three Phase 1 facilities (Pittsburgh, PA; Houston, TX; Las Vegas, NV).

All participants, prior to completing any screening procedures were required to complete an informed consent process specific to the study they were screening for. Participants then underwent a comprehensive medical history and complete physical examination, including vital signs. If still considered "study-eligible" based upon these findings; they then proceeded on to screening laboratory (serum and urine) and cardiac evaluations (12 lead EKG).

The majority of the pharmacokinetic studies conducted at NovumPRS required the assessment of screening virology (anti-HCV, HBs Ag, HIV), chemistries, complete blood counts, and drug testing to confirm that a participant could be enrolled for study participation. Novum recruited and screened volunteers between the ages of 18 to 70 years excluding individuals with comorbid disease conditions and those individuals that required the regular use of prescription or non-prescription medication.

Positive results for anti-HCV found utilizing enzyme immunoassay (EIA) techniques carried out at Laboratory Corporation of America (LabCorp) performed with Siemens Centar instrumentation lead to disqualification from study participation. Each HCV-positive participant was individually counseled by a study investigator concerning their positive result and encouraged to follow-up with his or her primary care physician. If the subject did not have a current physician, the participant was provided with information about neighboring local medical clinics. All anti-HCV positive results were then reported to the respective State Health Agencies. Because current anti-HCV results are considered highly sensitive, further laboratory work-up including the recombinant immunoblot assay (if not completed) for anti-HCV, or nucleic acid testing for HCV RNA, were left to the discretion of the participant's own healthcare provider and were not obtained, monitored or tracked by Novum.

RESULTS

NovumPRS's complete database included 86,777 total participants "screened" between January 1, 2005 and December 31, 2011 (seven complete years), of which 57,487 participants (n value) were unique, first-time or "new" individuals (31,768 Males, 25719 Females). Among this group of unique first time volunteers who were screened; 451 individuals were found to be Anti-HCV positive. Our Las Vegas location had the highest anti-HCV positive findings at 316; Houston = 101; and Pittsburg = 34. More trials were conducted in Las Vegas than at any other site. For all sites collectively an incidence rate of 0.8% was calculated. The highest number of cases was seen during the months, May-September at all sites for each period year of our review.

Table 1. NAHNES survey 1999 - 2002.

NAHNES	
Total participants (excluded homeless and incarcerated individuals)	7410
Hep C+	1.6%

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- Anti-HCV positive (repeat reactive) by EIA, verified by an additional more specific assay (e.g. RIBA for anti-HCV or nucleic acid testing for HCV RNA),
or
 - HCV RIBA positive,
or
 - Nucleic acid test for HCV RNA positive,
or
 - Report of HCV genotype
or
 - Anti-HCV screening-test-positive with a signal to cut-off ratio predictive of a true positive as determined for the particular assay (e.g., 3.8 for the enzyme immune-assays) as determined and posted by CDC.
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Figure 1. Laboratory criteria for diagnosis of chronic HCV infection.

We then compared our own anti-HCV positive results collected during 2005 - 2011 to that of the National Health and Nutrition Examination Survey, (NAHNES) (n = 7410) data gathered between 1999 and 2002, as shown in Table 1 (Armstrong et al., 2006).

DISCUSSION

Diagnosis of chronic HCV is based upon criteria developed by the Centers for Disease Control and Prevention (CDC) shown here in Figure 1 (CDC, 2009d).

As the most common chronic blood borne illness and leading cause of chronic liver disease in the US; treatment decisions regarding incidental HCV infection continue to be a matter of deep deliberation (Wilck et al., 2009). Information on the genotype of the virus is needed to help guide treatment plans and appropriate stratification of subjects (Seeff and Hoofnagle, 2003). The three current prevailing opinions on treatment within this population include (1) expectant management with periodic assessment of the individual's liver function, (2) liver biopsy with treatment contingent upon biopsy results, or (3) initial aggressive interferon treatment regimens. Several new protease and polymerase inhibitors compounds are in advanced periods of development (Birerdinc and Younossi, 2010). Moreover, abstinence from alcohol cannot be overstated.

HCV is a considerable public health concern with serious consequences increasing morbidity and mortality nationwide. Screening clinical trial participants for HCV antibodies is a common practice that leads to exclusion of these individuals in most trial settings, regardless of study phase. But it also provides these individuals with

health information they did not previously have but that we strongly recommend that they act on. A majority of the participants recruited to Novum's Phase 1 pharmacokinetic studies are generally healthy adults who are either self-employed or current students looking to supplement their income. This appears to be representative and consistent with the "US civilian, non-institutionalized" participant data collected through NAHNES (Armstrong et al., 2006). The National Health and Nutrition Examination (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the United States. NHANES is a major program of the National Center for Health Statistics (NCHS). NCHS is part of the Centers for Disease Control and Prevention (CDC) and has the responsibility for producing vital and health statistics for the Nation. Our sample data demonstrated a 50% decrease in the amount of HCV seropositive individuals compared with NAHNES (0.8% vs. 1.60%).

The NAHNES participant's data met laboratory criteria for diagnosis of chronic HCV infection using anti-HCV positive (repeat reactive) by EIA, verified by the anti-HCV RIBA assay (nucleic acid testing for HCV RNA was also performed on positive test to quantify the viral load). Data collected from our Las Vegas and Houston facilities similarly used the anti-HCV with RIBA reflex-to-positive test, whereas data from our Houston location used the anti-HCV (without reflexive testing) alone. This does not appear to be a limitation, as the anti-HCV testing is highly sensitive when a high signal to cut-off (s/co) ratio is used for determination of positive tests.

NAHNES avoided the Case Classification of Chronic HCV infection ("probable" or "confirmed") and only presented the laboratory diagnosis of chronic HCV

infection or seropositive individuals. We elected to do this at Novum as well. This is not uncommon, as identifying true chronic HCV by Case Classification often requires additional separate tests and an extended time frame (6 months) for testing. Further, the presence of anti-HCV could be the result of a late acute infection, a resolved infection, or a chronic HCV infection.

Unlike the NAHNES participant data that represents all 50 states and the District of Columbia; Novum data was limited to three urban US centers of whom its volunteers predominantly reside within that facility's regional area.

Many infected individuals first learn of their positive results from tests that may have been completed at: a CRO similar to our own; public or non-clinical testing facilities including drug-treatment units; blood product donation centers; community sites testing for HIV and other sexually transmitted diseases; or other public health clinics. The HCV positive individual may not have access to further follow-up and confirmatory qualitative tests such as the HCV RNA test. They may also altogether ignore results and neglect follow-up. This then leads to unverified diagnoses and potential under-reporting by US health agencies.

Our study population far exceeds the number of individuals reported on in the NAHNES data collection, and our rates of Hep C+ individuals vary considerably [0.8% Novum, 1.6% NAHNES]. Though we did not confirm positive results with followup recombinant immunoblot assays as was the case with NAHNES; it is not universally believed to be necessary as current anti-HCV testing that uses a high s/co ratio which exceeds Center for Disease Control criteria (>3.8) have shown to be confirmed as positive using different methodologies >95% of the time. Thus assuring a high "true positive" test rate. We had our blood and urine samples performed at outside laboratories (Labcorp), who use a s/co ratio of >8.00 in order to call an Anti-HCV test positive.

CONCLUSION

It should be concluded that our study population is similar to the Hep C population analyzed in the NAHNES report; and by that, representative of a participant recruitment network that is not saturated with potential enrollees who might otherwise be considered a more sociocultural or socioeconomically questionable (at risk) cohort group. The incidence rate we found in our large clinical trial volunteer sample is reflective of a participant pool which came from all walks of life; and is, in our opinion, having greater statistical power more representative at the current time of the true incidence rate found in the population-at-large. It does not appear that there are any research papers in the body of literature we reviewed to prepare this report which describe the incidence of hepatitis C found in such a large population of individuals recruited to undergo screening for participation in pharmaceutical clinical trials.

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