CLINICAL—LIVER, PANCREAS, AND BILIARY TRACT

Adverse Outcomes in Alaska Natives Who Recovered From or Have Chronic Hepatitis C Infection

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BACKGROUND & AIMS: The factors associated with adverse outcome from hepatitis C virus (HCV) infection are incompletely understood. To determine the incidence and risk factors associated with the development of end-stage liver disease (ESLD) and liver-related death (LRD), we conducted a retrospective/prospective population-based study in a cohort of Alaska Native persons chronically infected with HCV from 1994 to 2005. **METHODS:** We followed 960 persons prospectively for an average of 7.2 years and retrospectively for 12.1 years with data from medical records and serum samples. We compared data from subjects that were chronically infected with those who recovered from HCV infection, stratified by alcohol use. Survival models were used to examine factors associated with ESLD and LRD in chronically infected patients. **RESULTS:** During prospective follow-up, 80 (8.8%) and 47 (5.2%) patients developed ESLD and LRD, respectively. In examining incidence per 100 person-years, no difference was found among heavy alcohol users in the incidence of LRD (2.28 versus 3.50; $P = .34$) or ESLD (3.21 versus 5.69; $P = .13$) in persons with chronic HCV compared with those recovered from HCV infection. In subjects that consumed <50 g alcohol/d, the incidences of LRD were 0.77 and 0.09 ($P = .01$) and of ESLD were 1.58 versus 0.36 ($P = .002$), respectively, in subjects with chronic infection versus those that recovered. Multivariate analysis showed that older age, heavy alcohol use, and HCV genotype 3 were associated with ESLD. **CONCLUSIONS: A history of heavy alcohol use is associated with the highest incidence of LRD and ESLD, regardless of whether patients are chronically infected or recover from HCV infection.**

Keywords: Hepatitis C Virus; Hepatitis C Population Outcome Study; Hepatitis C in Alaska Natives; Hepatitis C Liver Related Decompensation and Death.

Hepatitis C virus (HCV) infection is a significant cause of morbidity and mortality in the United States and the world.[1] There are estimated to be 170 million persons worldwide with HCV infection and 2.7 million in the United States.[1,2] Several large natural history studies of HCV infection have found differing incidence in the development of serious complications, mainly cirrhosis or hepatocellular carcinoma (HCC) or both, which vary from only a few percent to as high as 50% of persons.[3] The wide divergence in the outcome of these studies has been attributed to short duration of follow-up, limited sample size, and publication bias, which has made it difficult to project the long-term effect of HCV infection.[3] Most of these previous studies have been cross-sectional or used the patients' recalled history of date of transfusion or initiation date of injecting drug use (IDU) to estimate duration of infection.[4,5] In addition, most studies have been clinic based and likely include patients with more advanced disease. Published prospective studies are mainly restricted to persons with specific risk factors such as blood transfusion (BT)[6–9] or IDU[10] or those who already have advanced liver disease.[11] No studies examining the long-term outcome of HCV have been both population-based and prospective in nature. In addition, previous studies have looked at a limited number of the factors that contribute to the clinical outcome of HCV, and comparison among all these stud-

Abbreviations used in this paper: AFP, α-fetoprotein; ALT, alanine aminotransferase; AN, Alaska Native; ARR, age-adjusted relative rate; AST, aspartate aminotransferase; BT, blood transfusion; CI, confidence interval; CT, computerized axial tomography; ESLD, end-stage liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, injecting drug use; LRD, liver-related death; MRI, magnetic resonance imaging; RR, rate ratio.

0016-5085/10/$36.00
doi:10.1053/j.gastro.2009.10.056

ies is difficult because of differing methodologies.[5] Finally, no published studies include a comparison group of persons who are not chronically infected with HCV.

In 1994, we began enrolling Alaska Native (AN) patients with confirmed HCV infection into a prospective follow-up study.[12] Patients were recruited if they tested positive for anti-HCV at a centralized laboratory that serves all Alaska Native hospitals and clinics. Potential treatment candidates were offered therapy with medications approved by the Food and Drug Administration. At consent, patients were asked permission for retrospective testing of sera, collected over a 40-year period and stored in the Alaska Area Specimen Bank, and for review of computerized records and medical charts for clinical information about their infection. We previously determined that this cohort of participants had similar risk factors and HCV genotype distribution compared with populations of infected persons from the general US population.[12,13] The cohort includes both persons with chronic HCV infection and persons who recovered from acute HCV. We herein report the clinical outcome of chronic HCV infection, including development of end-stage liver disease (ESLD), HCC, and liver-related death (LRD) in this cohort followed prospectively for 7 years, and we include retrospective data for an average of 12 years before study enrollment.

Materials and Methods

Recruitment and Follow-up

Since 1992, HCV serologic testing has been available to all AN persons at the Alaska Native Medical Center in Anchorage. Alaska has a population of 660,000 persons of whom approximately 130,000 (20%) are AN persons, who are eligible to receive health care through the AN health system, a statewide tribally operated health delivery system consisting of rural health clinics, regional hospitals, and a tertiary medical center, the Alaska Native Medical Center. The characteristics of the population and health care delivery system have previously been described as well as details on recruitment and enrollment procedures used in this long-term HCV outcomes study.[12] Patients were scheduled to be monitored every 6 months in urban and rural hepatology clinics across Alaska. In addition, every 6 months, all persons with HCV infection were mailed a letter reminding them to have their blood drawn for hepatic enzyme measurement and to be seen either in a hepatology clinic or by their primary care provider. For those patients not seen in one of the hepatology clinics, medical records were reviewed yearly. Treatment for HCV was offered to patients who fit the criteria for treatment outlined in the American Association for the Study of Liver Diseases evidenced-based practice guidelines that were published at the time of this study.[2]

Patients with HCV were divided into 2 categories: (1) patients who recovered from HCV, defined as persons who were HCV RNA-positive for <1 year who subsequently tested HCV RNA-negative or who were never found to be HCV RNA-positive but had a positive recombinant immunoblot assay and (2) patients who had chronic HCV infection defined as HCV RNA positive on ≥ 2 occasions, ≥ 1 year apart.

Risk Factor Definitions

We defined heavy alcohol usage as self-reported consumption of ≥ 50 g alcohol/d at the time of enrollment. For purposes of analysis, persons with a history of IDU were assigned to that risk exposure category. Persons who had received a BT before1992 were assigned to the BT risk exposure category, even if they also had a history of IDU. Persons without a history of IDU or BT were assigned to the "other" category. Details about how date of HCV infection was calculated are found in a previously published report.[14]

Outcome Definitions

The HCV clinical outcomes of interest were (1) ESLD, defined by the presence of ≥ 1 of the following: ascites, esophageal varices, hepatic encephalopathy, or coagulopathy; (2) HCC; and (3) liver transplantation or death (LRD) because of a liver-related cause. The diagnosis of ascites was made by imaging with liver ultrasound scanning, computerized axial tomography (CT), or magnetic resonance imaging (MRI), or paracentesis if not imaged. The diagnosis of hepatic encephalopathy was made by clinical evidence of mental impairment consistent with encephalopathy, a positive numbers connection test, or the presence of asterixis. The diagnosis of varices was made by esophagogastroduodenoscopy or coincidental finding on imaging (CT, ultrasound scanning, MRI). Coagulopathy was diagnosed by prothrombin time >1 second above the upper limit of normal or elevated International Normalized Ratio. The diagnosis of HCC was made by pathologic confirmation or on radiographic imaging examination (CT, ultrasound scanning, or MRI) consistent with a mass lesion on 2 studies or a mass lesion on 1 study and an α-fetoprotein (AFP) >200 ng/mL. LRD was defined as death with immediate cause from a complication of liver disease or death with liver disease listed as a contributing cause in the medical chart review and death certificate.

Statistical Analyses

For prospective follow-up, incidence of all-cause death, LRD, HCC, and ESLD was calculated per 100 person-years of follow-up. End of follow-up was defined by date of diagnosis or last clinic appointment. For comparison between persons with chronic HCV and those recovered from HCV, persons coinfected with human immunodeficiency virus (HIV) and hepatitis B virus