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EDITORIAL COMMENTARY

The Impact of Chronic Hepatitis C Virus Infection on Mortality

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In this issue of the *Journal of Infectious Diseases* Lee and colleagues report the overall and cause-specific mortality among a cohort of 1095 persons with chronic hepatitis C virus (HCV) infection who were identified by community screening in 7 townships in Taiwan in 1991–1992 and followed until 2008 [1]. In the Risk Evaluation of Viral Load Elevation and Associated Liver Cancer (R.E.V.E.A.L.)-HCV Study the mortality among subjects who were HCV RNA positive was compared with mortality among subjects who were anti-HCV enzyme immunoassay positive/HCV RNA negative and those who were negative for all HCV markers. Persons who were hepatitis B surface antigen seropositive or anti-human immunodeficiency virus (HIV) seropositive were excluded from the analysis; 19 636 controls who were negative for all HCV markers were included as controls. The overall mortality for those who were HCV RNA positive was increased; the hazard ratio (HR) for mortality after 16.2 years of follow-up was 1.89 (1.66–2.15) for all causes. The HR for hepatic death was 12.48 (9.34–16.66), and the HR for extra hepatic deaths was 1.35 (1.15–1.59). Of interest, there was significantly increased mortality from circulatory disease and several cancers in subjects with active HCV infection. The mortality rates of subjects who were only HCV antibody positive were similar to the rates of those without markers of HCV. This is one of several studies in which the effect of chronic HCV infection on overall and specific causes of mortality was examined. However, in this study recruiting a cohort from the community minimized selection bias. In addition, subjects with hepatitis B virus (HBV) or HIV coinfections were excluded in order to estimate the specific effect of chronic HCV on mortality.

The strong causative effect of chronic HCV infection on mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC) has been observed in several investigations since the virus was identified [2–11]. Liver diseases have contributed substantially to the overall increased mortality in patients with chronic HCV infections. However, the increased mortality among persons with chronic HCV infections also may be related to several underlying causes in addition to chronic liver diseases and liver cancer [12]. In countries where most HCV infections are from injection drug use, a substantial proportion (eg, from 15% to 27%) of deaths have been drug related [9]. In addition, many persons with chronic HCV acquired by injection drug use also have HIV infections, which contribute to their mortality [11]. Nevertheless, liver diseases, drug-related deaths (overdose, suicide, and homicide), and HIV infections do not account for all of the excess mortality in every population of patients with chronic HCV infections [9].

Several retrospective cohort and case-control studies have been conducted to evaluate the causes and rates of mortality in patients with chronic HCV infection. In a study of mortality among 568 patients who acquired non-A, non-B hepatitis after a blood transfusion and 984 controls without infection identified between 1967 and 1980, researchers found similar overall mortality rates (ie, 50%) in the 2 groups after 18 years and only a slight excess of cirrhosis deaths in those with hepatitis [13]. Researchers in another study followed 1980 women in Germany who had received HCV contaminated anti-Rh immunoglobulin [14]. Although 79% of these women were HCV antibody positive on follow-up and 427 were HCV RNA positive, only 9 developed cirrhosis and 16 died; 300 were treated and 115 (38%) were cured.

Researchers in another study reported the follow-up of 924 transfusion-acquired HCV recipients in the United Kingdom for 16 years after their infection [15]. The mortality was similar between HCV-infected patients and controls who were free of HCV after transfusion (HR, 1.17; 95% CI, .92–1.49). However, liver-related deaths

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were greater in patients with HCV infections (HR, 2.71; 1.09–6.75).

In contrast to these earlier studies, increased mortality from liver-related and extra hepatic causes in patients with chronic HCV infection was recently reported in 2 large follow-up studies. The first was a retrospective cohort study of 10 259 blood donors in the United States from 1991 to 2002 who screened positive for HCV antibodies [8]. They were matched with HCV-negative blood donors and their mortality evaluated after a mean follow-up of 7.7 years. The HR for mortality among the HCV-positive donors compared to the HCV-negative controls was 3.13 (2.60–3.76). The mortality from liver-related causes, drug or alcohol causes, and trauma was increased. However, the mortality from cardiovascular causes was also elevated, with a hazard ratio of 2.21 (1.41, 3.46).

The second large study to evaluate the effect of chronic HCV on mortality was from Australia [7]. In this study 75 834 persons reported to have HCV infection, either because of HCV seropositivity or the presence of HCV RNA, and 2604 persons who had HCV and HBV coinfection between 1990 and 2002 were linked to mortality records. Among 4008 deaths in persons with HCV infection, the age- and sex-adjusted standardized mortality ratio (SMR) for liver-related deaths was 16.8 (15.4–18.3) and 19.3 (18.1–20.5) for drug-related mortality. In addition, the SMR for cardiovascular causes of death was 1.3 (95% CI, 1.2–1.5) for persons with HCV infection and 2.6 (1.6–4.0) for persons with HBV and HCV coinfection. Increased death rates for drug-related causes were more common among younger persons and increased liver-related deaths predominated among older persons.

Although the discrepant findings of these studies are somewhat difficult to resolve, several overall conclusions can be made. First, chronic HCV infections are a major cause of liver-related morbidity and mortality. However, progression of HCV infection to cirrhosis and hepatocellular HCC is slow, especially in younger patients who do not have comorbid conditions. Second, chronic HCV infection is associated with increased overall mortality, especially in older persons. Although SMRs are very large for liver-related causes of death, there is evidence of increased mortality from nonliver-related deaths as well. The other causes of death include renal failure and cardiovascular deaths, likely from chronic inflammation, among older subjects and drug-related and violent deaths among younger patients who inject illicit drugs.

Several investigators have hypothesized that chronic infections with HCV or other organisms might be important risk factors for atherosclerosis [16–19]. Although an association with HCV infection has not been confirmed in some case-control studies [20, 21], the hypothesis has gained considerable traction recently with the results of these large linkage studies [7, 8] in addition to this report from Taiwan [1].

In addition, in a study of the possible role of HCV in coronary atherosclerosis, researchers evaluated the electronic records of 87 083 HCV-infected patients receiving care at US Veterans Administration hospitals [12]. These patients were matched with 89 582 controls who were free of HCV infection. Compared with controls, HCV-infected patients had an HR for coronary artery disease of 1.25 (1.20–1.30), despite having a lower prevalence of hypertension, hyperlipidemia, and diabetes. The HCV-infected patients were more frequently alcohol or drug abusers and more likely to have renal failure and anemia.

Important host factors affect mortality in patients with chronic HCV. The age at the time of infection and the presence of risk factors for liver, drug-related, and cardiovascular disease influence the overall mortality and causes of death. In addition, the host's genotype, especially polymorphisms of the IL28B gene, affects the rate of spontaneous clearance of HCV and may also influence the progression of disease and mortality [22].

The data reported in the Taiwan study are important because most patients had iatrogenic infections from medical, traditional health care or other parenteral exposures and were free of comorbid conditions [23, 24]. Yet, overall mortality was significantly increased due to liver and other causes compared with uninfected controls from the same communities. These data raise important public health issues. HCV infections commonly progress slowly in many chronically infected patients. Nevertheless, they are an important cause of mortality in the United States and worldwide. However, many patients with chronic HCV infections are never identified. Among those whose infections are detected, few are medically evaluated and effectively treated [25, 26]. However, the efficacy of treatment regimens is improving dramatically. Most experts predict that interferon-free oral antiviral regimens will become available in the next few years, with the potential to cure the majority of patients with chronic HCV infections [27]. But in order to experience a significant reduction in HCV-related mortality in the population, screening will need to be expanded substantially to identify the remaining 50%–75% of patients who are unaware of their infection.

One strategy is to expand screening beyond the high-risk groups currently recommended for screening. The selective screening policy has failed. One-time screening of the birth cohort born between 1945 and 1965 would identify a substantial proportion of HCV-infected persons in the United States. A recently published decision analysis of this strategy found it to be cost effective if referral and treatment resources were expanded to accommodate the large number of patients identified to be in need of evaluation and care [28]. Because mortality from chronic HCV has surpassed that from HIV in the United States in the last few years, now is the time for chronic HCV infections to be taken more seriously as an important public health problem [2].

Notes

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