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Increased mortality in chronic HCV infection

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Article commented

Lee MH, Yang HI, Lu SN, Jen CL, You SL, Wang LY, Wang CH, Chen WJ, Chen CJ; for the REVEAL-HCV Study Group. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis* 2012; 206: 469-77.

Comment

Chronic hepatitis C is a worldwide growing health problem that has gained attention in recent years. Approximately 3% of the world's population (130-170 million people) is chronically infected with hepatitis C virus (HCV).[1,2] HCV is one of the most prevalent blood-borne infection, with a higher prevalence than HIV (~ 1.1 million infected) and hepatitis B virus (0.8-1.4 million infected) in western countries.[3] Chronic HCV infection progresses asymptomatically, and almost 75% of patients are unaware of the diagnosis when they presented with complications of cirrhosis, portal hypertension or develop a hepatocellular carcinoma (HCC) many years later.[4] In western countries HCV infection is one of the most frequent causes of death from end stage liver diseases and HCC.[5] In the last decade, HCV related morbidity doubled, and HCC related to HCV increased almost 3 times.[6] Its impact on liver related morbidity and mortality is expected to reach its peak in the next decade.[7]

In a recent issue of the *Journal of Infectious Diseases*, Lee, *et al*. reported the all cause mortality among a cohort of 1095 patients with chronic hepatitis C virus (HCV) infection who were identified by community screening in the Risk Evaluation of Viral Load Elevation and Associated Liver Cancer (REVEAL)-HCV Study in Taiwan, and followed for up to 16.2 years.[8] The study showed that antiHCV positive patients had an increased all cause and hepatic mortality rate. Not all antiHCV positive patients had detectable HCV RNA: 89% of the population was tested (975 patients), and 69% of them (677 patients) were HCV RNA positive. As expected the risks were higher in those HCV RNA positive: multivariate-adjusted hazard ratio (HR) and 95% confidence interval (CI) were 2.20 (1.90-2.55) for all causes, 28.02 (18.96-41.41) for liver cancer, 7.37 (4.22-12.87) for cirrhosis, respectively ($p < 0.001$). These patients had also an increased mortality risk from extrahepatic causes: HR 1.47 (1.23-1.77), $p < 0.001$. AntiHCV positive patients with undetectable HCV RNA had only an increased risk of dying from liver cancer (HR 4.70, 95% CI 1.68-13.11) when compared with antiHCV negative patients; none of these patient died due to complications of cirrhosis. Patients with detectable HCV RNA had a significantly increased all cause (30.1%), hepatic (12.8%) and non hepatic (19.8%) mortality rates when compared with antiHCV positive HCV RNA negative (12.8%, 1.6% and 12.2%) and antiHCV negative (12.4%, 0.7% and 11%) patients, respectively ($p < 0.01$). The cumulative mortalities from liver cancer and cirrhosis were 10.4% and 2.8% for antiHCV positive HCV RNA positive patients, 1.6% and 0.3% for antiHCV positive HCV RNA negative patients, and 0.3% and 0% for antiHCV negative patients, respectively ($p < 0.01$).

There are some other studies reporting HCV mortality rates.[9-16] Most of them are in selected populations, such as post-transfusion cases or in blood donors. Being a community based study is remarkable issue, because it reduces the possibility of selection bias. Another strength of the study is that it is prospective, while most of the previous studies are retrospective. Although this is big cohort, the

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number of antiHCV positive, and the number of HCV RNA positive persons is rather small. Another weakness of the study is that the studied population is Asiatic, and these results may not be reproducible in western countries.[8]

A retrospective study in blood donors from the US also found an increased mortality rate from extrahepatic diseases, mainly cardiovascular causes (HR 2.21, 95% CI: 1.41-3.46).[9] A similar study from Australia confirmed these results (HR 1.3, 95% CI: 1.2-1.5).[10] These and other previous studies had shown a higher mortality risk from hepatic causes in HCV positive patients.[9-16] Impact of HCV in morbidity and mortality rates in these studies may vary, since there are different population studied, different modes of transmission, etc. However, increased mortality rate in HCV patients may be related to other underlying conditions unrelated to liver disease, such as injection drug use and some of their consequences (overdose, suicide, and homicide), HIV infection, alcoholism, etc.[17]

Treatment induced sustained virologic response (SVR) reduce liver related mortality in HCV patients by 3.3- to 25-fold, reduce the incidence of hepatocellular carcinoma (1.7- to 4.2-fold) and hepatic decompensation (2.7- to 17.4-fold).[18] But, does SVR have an impact in reducing non hepatic related mortality? When selecting candidates for treatment, we evaluate the risk of liver disease progression. Do we have to begin to evaluate impact of treatment on extrahepatic diseases? Perhaps, there are still no answers to these question but these issues may need to be addressed in future studies.

Even though HCV liver disease progresses slowly, this study from Taiwan[8] as well as the other mentioned showed that HCV infection has a clear impact hepatic and non hepatic related mortality.[9-16] New treatments are now available, and other more effective drugs are expected in the near future. But most HCV infected patients do not receive treatment because 50 to 75% of them have not been diagnosed. In order to reduce HCV related morbidity and mortality, screening need to be expanded beyond the currently high risk populations recommended to be screened in international guidelines. Improving diagnostic rate will result in increasing number of patients treated and cured. Ultimately, this strategy will reduce HCV hepatic and extra-hepatic related morbidity and mortality.

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