

Hepatitis C

Does Hepatitis C Increase Mortality?

Hepatitis C patients without additional risk factors may not be at higher risk of death compared with HCV-uninfected individuals, according to a study in the September 2009 *Journal of Viral Hepatitis*. L. Prasad and colleagues analyzed all-cause mortality among 1,645 participants in the Swiss Hepatitis C Cohort seen at secondary and tertiary care centers. During a follow-up period averaging more than two years, 61 deaths were recorded. Compared with members of the Swiss general population matched for sex and age, hepatitis C patients had a crude all-cause standardized mortality ratio (SMR) of 4.5, indicating a 4.5-fold higher risk of death. Cohort participants with both HCV and HIV had a crude SMR of 20 compared with general population members

with neither virus.

However, when the researchers restricted the analysis to hepatitis C patients with HCV genotypes other than 3 who were not coinfecting with HIV or hepatitis B, did not have liver cirrhosis, had no history of injection drug use, and were not heavy (> 40 grams/day) alcohol users, the SMR was just 1.1, indicating that mortality was essentially the same as that of the general population. "We found little evidence of excess mortality in hepatitis C infected patients who were not cirrhotic, in the absence of selected risk factors," they concluded. "Our findings emphasize the importance of providing appropriate preventive advice, such as counseling to avoid alcohol intake, in those infected with HCV."

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Hepatitis C Treatment Improves Survival

People with hepatitis C have a higher mortality rate than uninfected individuals, but those who complete interferon-based therapy significantly reduce their risk of death, according to a study in the August 2009 *Hepatology*. A.A. Butt and colleagues studied the effect of hepatitis C and its treatment on survival in a national sample of U.S. veterans using the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) database. The researchers identified 34,480 matched pairs of HCV-infected veterans and uninfected control subjects.

HCV infection was independently associated with a higher mortality risk relative to uninfected individuals (hazard ratio 1.37, or 37% higher). Among participants with hepatitis C, those who received interferon-based treatment for 48 weeks or longer had the lowest mortality. But even those treated for less than 48 weeks had a lower risk of death than untreated individuals. "Subjects who are initiated on treatment, and particularly those who proceed to finish a

full course of treatment, have significantly reduced risk of mortality," the investigators concluded.

Does Genotype 3 Cause Faster Progression?

HCV genotype 3 may be associated with more rapid liver fibrosis progression, according to a study in the October 2009 *Journal of Hepatology*. While the link between genotype and treatment response is well established, less is known about the influence of genotype on disease progression; however, HCV genotype 3 has been linked to steatosis, or fatty liver. C.Y. Bochud and colleagues looked at predictors of fibrosis progression among 1,189 patients from the Swiss Hepatitis C Cohort who had at least one biopsy prior to starting interferon-based therapy and an assessable date of infection.

Independent risk factors for accelerated fibrosis progression (defined as > 0.083 fibrosis units per year) included male sex (odds ratio [OR] 1.60), older age at the time of infection (OR 1.08), greater histological activity (OR 2.03), and HCV genotype 3 (OR 1.89). In addition, participants who were infected through a blood transfusion, invasive procedure, or needle stick had

slower fibrosis progression rates than those infected through injection drug use. Patients with genotype 3 also were more likely than those with other genotypes to progress from one Metavir fibrosis stage to the next during the course of follow-up. "This study shows a significant association of genotype 3 with accelerated fibrosis using both stage-constant and stage-specific estimates of fibrosis progression rates," the researchers concluded.

In an accompanying editorial, S. Zeuzem noted that while some people with hepatitis C and their clinicians are awaiting new oral antiviral agents, the drugs furthest along in the development pipeline^{3/4}the HCV protease inhibitors telaprevir and boceprevir^{3/4}are most active against genotypes 1 and 2, and less so against genotype 3. "If indeed fibrosis progression in patients infected with HCV genotype 3 is faster than in HCV-1 infected patients, waiting for new treatment options should be strongly discouraged in this patient population," he wrote.

Treatment of HIV/HCV Coinfected Patients

Pegylated interferon plus ribavirin is an appropriate stan-

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dard of care for HIV/HCV coinfecting patients, according to a meta-analysis by the Cochrane Hepato-Biliary Group published in the September 2009 *American Journal of Gastroenterology*. The Cochrane Collaboration is an independent, non-profit network of experts that performs systematic reviews of healthcare interventions and promotes evidence-based medicine. L.L. Gluud and colleagues conducted manual and electronic literature searches to identify seven randomized clinical trials comparing pegylated interferon plus ribavirin versus other antiviral treatment regimens for HIV positive individuals with chronic hepatitis C.

Study participants had stable HIV disease and had not previously received interferon or ribavirin. The mean doses used were the standard 180 mcg/week for pegylated interferon alfa-2a (Pegasys) or 1.5 mcg/kg/week for pegylated interferon alfa-2b (PegIntron). However, the mean dose of ribavirin was 800 mg/day, below the current standard of 1,000-1,200 mg/day weight-adjusted dosing for HCV genotype 1 patients. Treatment duration ranged from 24 to 48 weeks (experts generally recommend 48 weeks for HIV positive patients regardless of genotype).

Patients treated with pegylated interferon plus ribavirin had higher end-of-treatment and sustained virological response (SVR) rates compared with those who received conventional interferon plus ribavirin or pegylated interferon monotherapy. Overall, 26% of coinfecting patients with genotype 1 or 4, and 57% with genotypes 2 or 3, achieved SVR (compared with about 70%-80% and 50%, respectively, for HIV mono-infected individuals). Adverse events included fatal lactic acidosis and liver failure. "Peginterferon plus ribavirin may be considered for treatment-naïve patients with HIV and chronic hepatitis C," the researchers concluded. "Adverse events should be monitored carefully."

Retrovirus Linked to Chronic Fatigue Syndrome

People with chronic hepatitis C often experience persistent fatigue associated with HCV infection and interferon-based treatment, but some also have chronic pain and other symptoms of a poorly defined syndrome that encompasses fibromyalgia and chronic fatigue syndrome (CFS). In the October 8, 2009 advance edition of *Science*, researchers with the National Cancer In-

stitute reported a link between CFS and a retrovirus known as xenotropic murine leukemia virus-related virus, or XMRV.

V.C. Lombardi and colleagues examined peripheral blood mononuclear cells (PBMCs) immune cells such as T-cells and B-cells from 101 patients with CFS and 213 healthy control subjects. They found that 67% of the CFS patients had cells containing XMRV DNA, compared with just 3.7% of unaffected individuals. XMRV, a human gammaretrovirus, is part of the same retrovirus family as HIV, but is more closely related to a group of viruses that cause cancers such as leukemia; XMRV has also been linked to prostate cancer. In cell culture experiments, XMRV derived from CFS patients was found to be infectious, and could be transmitted through exposure to either virus-containing cells or cell-free virus. These findings, the researchers wrote, "raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS."

