**Perspective**

**Hepatitis C Virus, Inflammation, and Cellular Aging: Turning Back Time**

There is evidence that hepatitis C virus (HCV) infection, like HIV infection, may be associated with chronic inflammation, immune activation, and immune senescence, which contribute to increased risks for cardiometabolic or other diseases outside the liver, as well as to ongoing damage in the liver. These effects may persist after a sustained virologic response (SVR) is achieved with HCV therapy. Such findings support initiation of treatment for HCV-infected individuals before damage to the liver is apparent and monitoring of individuals for complications even after an SVR is achieved. Fibrosis is not always reversible after SVR is achieved, and this should serve as an argument against waiting until fibrosis develops before initiating treatment for HCV-infected individuals. This article summarizes a presentation by Susanna Naggie, MD, MHS, at the IAS–USA continuing education program, Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes, in New York, New York, in September 2015.

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Consider the case of a 37-year-old man who was diagnosed with HIV and hepatitis C virus (HCV) infections in the 1990s. He had a nadir CD4+ cell count of 9 cells/µL and presented with *Mycobacterium avium* complex and *Pneumocystis jiroveci* pneumonia. Since his HIV diagnosis, initiation of antiretroviral therapy, and treatment of his opportunistic infections, he has lived well with HIV disease. He was infected with HCV genotype 1b and had a plasma HCV RNA level of 1.2 million IU/mL on presentation. A liver biopsy in 2009, when he was 31 years of age, showed signs of cirrhosis, although he has no history of alcohol use or liver decompensation. He had portal hypertension with thrombocytopenia, splenomegaly, and portal gastropathy (at his last esophagogastroduodenoscopy in March 2014). He was immune to hepatitis A and B viruses by prior immunization.

The finding of cirrhosis at what should be a relatively early stage of HCV disease in a young man with no history of alcohol use is surprising and raises questions: What other end-organ diseases should be considered in an individual with chronic HCV? What does a sustained virologic response (SVR) mean in the context of the potential adverse effects of HCV infection? Are payers right to limit access to HCV therapy based on severity of liver disease alone?

In the natural history of HCV infection, age is an important factor in the progression of disease.1 A low percentage of individuals with chronic HCV infection diagnosed at 20 to 30 years of age will develop severe fibrosis and cirrhosis over the next 30 years. Individuals who acquire HCV infection at 50 to 60 years of age generally exhibit more rapid progression of disease.1 However, individuals who are coinfected with HIV often have accelerated liver disease, potentially part of a phenomenon that many have called “accelerated aging,” used to describe the high rates of death from non–AIDS-related conditions such as malignancies, cardiovascular disease, and liver disease than their age-, race-, and sex-matched HIV-uninfected counterparts.2-7 For example, data show that HIV/HCV-coinfected persons matched for other factors have a result of 9 kPa on transient elastography, consistent with severe fibrosis, approximately 9 years earlier than those with HCV monoinfection.1,8

**Inflammation and Immune Activation in the Context of HCV Disease**

Among the factors associated with more rapid progression of fibrosis in the context of HCV disease, apart from alcohol use, are age, steatosis, obesity, and insulin resistance.1 Factors in HIV infection that may contribute to the progression of fibrosis include chronic inflammation, associated metabolic disorders, medication toxicity, viral coinfections, and microbial translocation.9 Individuals with uncontrolled HIV infection, for example, often have elevated levels of lipopolysaccharide, resulting in monocyte-macrophage activation peripherally, but also the potential of activating hepatic Kupffer and stellate cells.10,11 Also, HIV proteins may potentially bind to cell receptors on stellate and Kupffer cells, activating intracellular pathways of fibrogenesis. Whether HIV directly infects these cell types is controversial.

In addition, whether the presence of inflammation and immune activation results in accelerated aging in the liver of an HIV/HCV-coinfected individual is a subject of current investigation. The ability to cure HCV infection with interferon-free regimens should provide the opportunity to evaluate the effects on the host immune system after the virus has been cleared from the body.

The relationship between inflammation, immune activation, and immune senescence is illustrated in the Figure. Inflammation is a general process, measured by levels of markers such as cytokines, interleukin-6 (IL-6), tumor necrosis factor (TNF), and high-sensitivity C-reactive protein (hs-CRP) and can be present in many different diseases.12 Immune activation is more specific, representing activation of certain cellular pathways, such as in monocytes and T cells (present in HIV and HCV infections), and is measured by such markers as soluble CD14 (sCD14), CXCL10, and CD38.12 Immunosenes- cence is the progressive deterioration of the immune system

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with age; for T cells, this results from chronic activation and inflammation due to persistent antigen expression. One of the main markers of immunosenescence is CD57, sometimes referred to as a marker of cellular aging. Increased levels of CD57 have been associated with many HIV-associated, non–AIDS-related conditions.

Tumor suppressor protein p16\(^{INK4a}\) has been associated with normal aging outside the context of HIV or HCV infection. Individuals with uncontrolled HIV infection have very high levels of this marker, and as the virus is controlled with antiretroviral therapy, the marker returns to near normal levels in the blood.\(^{13}\) Of interest, this marker is a tumor suppressor and is predictive of risk for malignancy.\(^{14}\) It is not known if the return to baseline blood levels of tumor suppressor protein p16\(^{INK4a}\) after full viral suppression with antiretroviral therapy correlates with levels in the liver or other tissues. This marker has not been studied in the setting of HCV infection or other liver diseases.

**The Broad Effects of HCV Infection**

Chronic HCV infection has been associated with many end-organ diseases including neurocognitive effects; atherosclerosis and cerebrovascular disease; insulin resistance, hyperglycemia, and diabetes; fibrosis and steatosis; and B-cell non-Hodgkin lymphoma (NHL) and hepatocellular carcinoma (HCC).\(^{15,16}\) These diseases have many similarities with those attributed to chronic inflammation and immune activation in the context of HIV infection. Whether the pathogenesis is the same for HIV and HCV infections or if there are parallel mechanisms at play in the case of HIV/HCV coinfection is not known at this time.

**HCV as a Cardiometabolic Disease**

There is considerable evidence that HCV infection is a metabolic disease. Numerous studies have reported an increased risk for metabolic disorders among individuals with HCV infection compared with uninfected counterparts, including insulin resistance (odds ratio [OR], 2.06),\(^{15}\) diabetes (OR, 2.31),\(^{16}\) and atherosclerotic disease (OR, 4.2).\(^{17}\) Prevalence of steatosis in HCV has been reported as high as 50%, and when controlled for known risk factors such as diabetes, alcohol use, and obesity, the prevalence remains 30% to 40%.\(^{15,16}\) However, some of these data have been recently challenged. In reanalyzed National Health and Nutrition Examination Survey data on diabetes from 1999 to 2010, the adjustment for elevations in levels of aspartate aminotransferase and alanine aminotransferase, which are considered attributable to steatosis, eliminated the increased risk for diabetes associated with HCV infection.\(^{16}\) However, higher markers of inflammation have been observed among HCV-infected individuals with elevated liver enzymes than among those without such elevations, suggesting a relationship between liver and systemic inflammation.\(^{15}\)

Markers of cardiometabolic diseases that are elevated in HIV- and HCV-infected individuals include markers of inflammation (IL-6, hs-CRP), hypercoagulable state (fibrinogen, dimerized plasmin fragment D), endovascular dysfunction and cell adhesion (soluble vascular cell adhesion molecule–1 [sVCAM-1]), N-terminal fragment of the prohormone brain natriuretic peptide [NT-proBNP]), and markers of T-cell activation and immune senescence (sCD14 and sCD163).\(^{16}\) These markers have been associated with increased risk of cardiovascular disease–associated mortality, acute myocardial infarction, all-cause mortality, and more generally with atherosclerotic disease, diabetes, and insulin resistance.\(^{15,16}\) More research is needed to conclusively identify and quantify risk for such outcomes among HCV-infected individuals before and after an SVR is achieved.

On a similar note, positive HCV serology is reportedly associated with higher all-cause mortality, although the reasons behind this remain unclear.\(^{18}\) There are data indicating that most deaths among HIV/HCV-coinfected individuals are attributable to non–liver-related events. For example, in the SMART (Strategies for Management of Antiretroviral Therapy) trial of HIV-infected individuals, liver-related events were not the main drivers of death among participants with viral hepatitis; yet, HIV/HCV-coinfected individuals contributed to the majority of the study’s primary events.\(^{19}\) This suggests that HIV/HCV-coinfected patients are at greater risk of non–liver-related disease than HIV-monoinfected patients. Therefore, the argument can be made that treatment of HCV infection has benefits outside the liver and that all individuals should have an opportunity to achieve HCV cure before cardiometabolic conditions emerge.

**HCV Infection and Cancer**

Cancer is now the leading cause of non–AIDS-related death in HIV-infected persons.\(^{20}\) In a study reported by Nyberg and colleagues, unadjusted analysis showed that HCV infection was associated with statistically significantly increased risks for esophageal, stomach, colorectal, liver, pancreas, lung, head and neck, renal, and prostate cancers, myeloma, and NHL compared with no HCV infection.\(^{21}\) After adjustment for alcohol use or dependence, smoking status, and diabetes,
these associations were no longer statistically significant except for HCC and NHL. Thus, whether the increased risk of cancer among HCV-infected individuals is driven by known traditional risk factors or whether there is a component of this risk attributable to immune activation and inflammation remains unclear.

**Immune Activation and Immune Senescence**

Sustained virologic response has been associated with impressive decreases in liver-related events, but its effects on risk for other diseases over the short and long term is not known. A knowledge gap remains about the overall risks associated with HCV infection beyond liver fibrosis; this will be important to understand if care and outcomes are to be optimized beyond virologic cure. Improved insight may come from investigations into chronic immune activation and immune senescence in the context of HCV infection.

In the liver, the stellate cell has a primary role in fibrogenesis. It is the resident pericyte in the liver; pericytes are pluripotent cells found throughout the body, including in the endovascular space, blood-brain barrier, kidney, and heart. Natural killer T cells are the primary immune cells in the liver. We are currently investigating markers of active inflammation, chronic immune activation, and cellular aging in liver tissue of HIV and HCV-infected individuals.\(^1\) The preliminary results suggest that T-cell markers are substantially increased stepwise from uninfected healthy controls to those with HIV monoinfection, HCV monoinfection, or HIV/HCV coinfection. Levels of natural killer T cell markers are also higher in HIV-monoinfected individuals than in uninfected controls and are higher in HCV-monoinfected individuals than in HIV-monoinfected individuals.\(^2\) Markers of immune senescence (CD57) also exhibited stepwise increases from uninfected controls to those with HIV monoinfection, HCV monoinfection, and HIV/HCV coinfection, with a similar pattern evident for the marker for aging (P16\(^{INK4a}\)). Such findings raise numerous questions, including why these markers are elevated in the liver tissue of HIV-monoinfected individuals who are HIV virally suppressed and whether cellular senescence and cellular aging are reversible processes with HCV clearance.

In addition, we have explored the possibility that aberrant Hedgehog pathway signaling may be involved in the accelerated aging observed in HIV/HCV-coinfected individuals. This pathway, which is involved in fetal organ development, is activated during tissue injury and acts as a primary factor in the healing of skin, the epithelium, and organs.\(^3\) Numerous inhibitors of the Hedgehog pathway have been evaluated for treatment of cancers,\(^4\) and inhibitors of this pathway might be of value in treatment of HIV/HCV coinfection. In preliminary studies, we have found that markers of Hedgehog pathway signaling (the Shh ligand and transcription factor GLI2) are elevated in the liver tissue of individuals with HIV monoinfection and are more elevated in those with HCV monoinfection, and levels observed in those with HIV/HCV coinfection are similar to those observed in individuals with HCV monoinfection.\(^5\)

Whether aberrant Hedgehog pathway signaling drives HCV disease processes outside the liver has been studied in animal models. Pericytes are activated during injury to the kidney, endovascular space, brain, and liver, and exhibit increased levels of Hedgehog transcription markers. The pericytes then transform into myofibroblasts that contribute to fibrosis.\(^6\) Implications of the above research are that the Hedgehog pathway is active during HIV monoinfection, with additive effects in the context of HIV/HCV coinfection, and that HIV/HCV coinfection increases T-cell recruitment, terminal differentiation, and immunologic aging and senescence. Further study is needed to confirm these findings and assess whether this intrahepatic immunologic phenomenon is reversible.

**The Impact of SVR**

All-cause mortality is higher among HCV-infected individuals who do not achieve an SVR than those who do achieve an SVR.\(^6,16\) In addition, liver-related outcomes, including incident hepatocellular cancer, hepatic decompensation, and liver-related death, are lower in patients achieving SVR.\(^6,18,26,27\)

A study reported in 2008 that examined paired liver biopsies showed improvements in virtually all liver-related outcomes in 59 participants who had SVRs compared with 57 participants who did not have SVRs.\(^28\) However, liver cancer developed in 8% of participants who had an SVR. Although the follow-up period of the study was only 3 years, a minority of participants exhibited regression of cirrhosis (18% with regression vs 78% without regression), which was a better predictor of reduced liver-related outcomes than was SVR. For example, HCC was found in 22% of individuals who did not have regression of cirrhosis versus 0% of those who did (\(P = .036\)). Such findings reinforce the concept that cirrhosis is not as reversible in the context of HCV infection as may generally be thought. Reversal of cirrhosis in the context of HCV infection appears to be a slow process, different from that observed in hepatitis B virus infection, in which 50% of individuals have resolution or improvement of cirrhosis by 5 years after nucleoside analogue initiation.\(^29\) Waiting until patients are already at risk of cirrhosis before initiating HCV treatment sets them up for a process that cannot be completely reversed and likely puts them at considerable risk for major liver-related events.

With regard to the impact of SVR on extrahepatic diseases, there is evidence that SVR achieved via treatment with peginterferon alfa and ribavirin is associated with improvements in coronary artery disease, diabetes, and renal disease, and possible regression of B-cell NHL. Thus far, there are few data on the effects of an SVR achieved with direct-acting antiviral therapy on extrahepatic disease apart from potential regression of B-cell NHL and improvement of renal disease.\(^15,16\)

Based on considerations such as those discussed herein, 2 commonly held assumptions regarding HCV treatment are inaccurate: 1) that HCV is only a liver disease; and 2) that HCV-associated fibrosis is always reversible. That fibrosis is not always reversible after SVR is achieved should serve as a
potent argument for not waiting until fibrosis develops before initiating treatment for HCV-infected individuals.

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