Acute Hepatitis C: A Window of Opportunity

David L. Thomas
Johns Hopkins School of Medicine, Baltimore, Maryland

(See the article by McGovern et al. on pages 1663–70)

McGovern et al. [1] describe 19 persons with acute hepatitis C virus (HCV) infection that was recognized during incarceration, a finding they refer to as “a window of opportunity.” Broadly considered, their report itself is a window into how, when, and in whom HCV infections occur.

In the United States, new HCV infections occur most frequently in injection drug users (IDUs). Occasionally, HCV is transmitted by sexual intercourse, as represented by recent cases reported among men who have sex with men. HCV is also rarely transmitted by sporadic blood exposures, as occurred in a man in this report who acquired infection during a prison fight [1]. However, the vast majority of infections involve sharing HCV-contaminated needles or other drug use equipment, and many of these occur within the first years of injection drug use [2]. HCV infection can occur during the first instance of injecting, when an experienced (HCV-infected) drug user injects the new initiate after first demonstrating the method on himself or herself [2]. As was also illustrated in this report, infection can occur when a new (infected) partner joins an injection drug use network or when stable injecting practices get more risky, such as happens when clean needles are not available.

Given the links between HCV infection and drug use and between drug use and time in correctional facilities, it is not surprising to see acute HCV infection through the prison window. According to one 1997 survey of inmates, 57% of state prisoners and 45% of federal prisoners reported using drugs in the month before their offense [3]. Acute HCV infection can also occur while in prison, although data on this subject are limited [4].

Chronic hepatitis C is even more common in prisons. In a multiple-center study of 18–35-year-old IDUs, 82.3% of subjects had a history of incarceration [5]. At any one time, approximately one-third of inmates have chronic hepatitis C [6]. Especially remarkable is the estimate made by the Centers for Disease Control and Prevention that 1.16 million HCV-infected persons are released from prison each year [3]. If correct, this means that, in any year, almost one-half of all HCV-infected persons in the United States are either released from prison (∼39%) or remain incarcerated (∼11%).

What you will not see through the prison window is most of the new HCV infections that happen there. The visible expression of acute HCV infection is jaundice, but that occurs in only one-quarter of patients [7, 8]. The 19 patients described by McGovern et al. [1] likely represent a small fraction of cases that occurred in that correctional facility.

The diagnosis of acute HCV infection is best made when HCV RNA is detected and HCV antibodies become detectable (i.e., after seroconversion). Viremia can be detected within 1 day of infection, especially when there is a high inoculum [9]. Within 2 weeks of infection, almost everyone with acute hepatitis C has viremia, making 14 days a good time to test for postexposure infection; liver transaminase levels peak later (median time to the peak, 6 weeks) [8, 9]. HCV-specific antibodies are detected a median of 7 weeks after infection, sometimes after resolution of symptoms. Clinicians should be aware of the delayed production of antibodies when monitoring for postexposure HCV infection. What happens next (i.e., during months 4–12) is harder to predict. Some patients remain viremic indefinitely (at more-or-less the same serum level); these patients have chronic hepatitis C [7–10]. Others rapidly and durably clear viremia. The clinical challenge is to manage patients with fluctuating HCV RNA levels. In our experience, most persons will end up with persistent infection if HCV RNA is detected for >4 months. However, durable, spontaneous viral clearance has been reported to occur as late as 24 months after initial infection [7].

Predicting whether acute HCV infection will become chronic is important, because the acute phase of infection is a...
window of opportunity for treatment. IFN-α–based treatment of acute HCV infection has been associated with >90% likelihood of sustained viral suppression, which is substantially higher than what would be expected with treatment of chronic hepatitis C (~50%) [11, 12]. It does not appear that the use of ribavirin improves the response of acute HCV infection to IFN-α. However, there are many unanswered questions, including the degree to which this higher viral suppression rate represents the effect of the IFN-α therapy versus late spontaneous clearance. It is even less clear when this window of enhanced IFN-α sensitivity will close, an important question given the potential toxicity and expense of IFN-α–based HCV treatment. A randomized, controlled study from Japan showed that treatment of acute HCV infection within 8 weeks after exposure resulted in a higher rate of sustained viral suppression (87%), compared with a delay in treatment until >12 months after onset (40%) [13]. In another study of chiefly symptomatic patients, treatment was often delayed 3–6 months after onset of symptoms, and 81% of patients had sustained virologic responses [10]. In another study of acute hepatitis C in Egypt, patients were randomized to start a 12-week course of pegylated IFN 8, 12, or 20 weeks after recognition of infection. A greater proportion of those who started treatment 8 or 12 weeks after recognition achieved sustained viral suppression, compared with those who started it 20 weeks later [14]. Thus, there is growing consensus that treatment with IFN-α should be offered to persons who still have viremia 2–6 months after acute HCV infection, but the optimal treatment regimen (dose, need for induction, duration, and IFN-α formulation) remains controversial.

The biological basis for the enhanced IFN-α susceptibility during acute HCV infection is also unknown. CD4-expressing lymphocytes orchestrate many immune responses, and there are accumulating data suggesting that these cells contribute to the suppression of HCV. Control of HCV infection is impaired in CD4 lymphocyte–depleted chimpanzees and in HIV-infected humans with low CD4 lymphocyte counts [15, 16]. Likewise, in the report by McGovern et al. [1], viral suppression in the acutely infected inmate was associated temporally with anticoag CD4 lymphocyte responses. In one study, the breadth and vigor of CD4 lymphocyte responses to HCV were greater in subjects who received pegylated IFN-α after acute HCV infection, compared with control subjects who did not receive treatment [17]. However, that finding has not been confirmed elsewhere [18, 19]. Better understanding of why IFN-α is more effective during the acute phase of infection may improve the outcome of therapy for chronic HCV infection.

Although the biological basis for enhanced IFN-α sensitivity remains unknown, acute HCV infection remains a window of opportunity to prevent chronic infection and the long-term complications of liver cirrhosis and cancer. However, at the risk of exhausting this metaphor, in most regions of the United States, this window is barred for inmates. In most correctional facilities, there are no procedures for detection of acute HCV infection, and even if there were, the effectiveness of treatment is seriously constrained by lack of IFN-α availability. If IFN-α were available in the facility, there are few states with programs to bridge HCV treatment services, such that inmates could continue treatment without interruption once released.

It has been 18 years since HCV was discovered, and there have been many advances, including elimination of transfusion transmission of HCV in the West. We now have treatments that can clear HCV infection in approximately one-half of those who receive them, and we have a number of potent anti-HCV compounds in various stages of development. However, current therapeutic strategies have done very little to reduce the global or even the US burden of HCV infection [20]. As McGovern et al. [1] show among IDUs, HCV infections still happen, and we clearly need better methods to prevent, detect, and treat acute HCV infection in this large segment of our population. If almost one-half of HCV-infected persons are in contact with correctional services each year, there is indeed a window of opportunity.

Acknowledgments


References