EDITORIAL COMMENTARY

Hepatitis C Virus Infection: When Is a Cure Not a Cure?

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(See the major article by Hara et al on pages 38–45.)

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In hepatitis B virus (HBV) infection, reactivation is concerning enough that the American Association for the Study of Liver Diseases recently hosted a course, Emerging Trends Conference: Reactivation of Hepatitis B, in March 2013. In contrast, hepatitis C virus (HCV) infection reactivation occurs infrequently, with the exception being hepatitis flares in HCV RNA–positive patients undergoing rituximab-containing chemotherapies [1]. Furthermore, patients who are HCV RNA negative and are only positive for anti-HCV while undergoing chemotherapy are not reported to have reappearance of HCV RNA [2]. This suggests that HCV infection, indeed, seems cured when HCV RNA is undetectable, independent of whether HCV has become undetectable spontaneously or through achievement of a sustained viral response (SVR) after antiviral treatment. SVR is defined as an HCV RNA load that remains undetectable for at least 24 weeks after completion of antiviral treatment and is considered equivalent to a cure.

There is a concordance of qualitative HCV RNA test results (positive vs negative) between week 12 after treatment and week 24 after treatment. Therefore, the Food and Drug Administration recently accepted the week 12 result as a surrogate for the week 24 result. Still, there is some uncertainty concerning persistent cure, as highlighted in an article by Hara et al in this issue of the *Journal*, which describes cases of delayed relapse [3]. Accordingly, the posttreatment week when HCV remained undetectable is suggested to be labeled as SVR_x, where *x* stands for the week after the end of therapy (ie, SVR_{12}, SVR_{24}, and SVR_{48} denote negative test results 12, 24, and 48 weeks, respectively, after completion of treatment). This reflects a remaining uncertainty with regard to when a cure is a cure. For most patients with relapse, onset of relapse occurs within the first 12 weeks, although relapse in a minority begins between weeks 12 and 24 [4]. The importance of monitoring beyond week 24 was highlighted in one study using direct antiviral therapy that reported late relapse in a patient at week 36 [5]; this patient thus achieved a SVR_{24} but not a SVR_{36}.

Most information about lasting responses are available for treatment regimens using interferon or pegylated interferon with or without ribavirin, whereas less information about the now available and emerging direct antivirals is available beyond SVR_{12} and SVR_{24} [6].

Physicians caring for patients with hepatitis C may encounter a patient who has a detectable HCV RNA load after having had a SVR_{24}. Is this renewed positivity for HCV RNA a result of reinfection or a case of delayed relapse?

In the current article, Hara et al answer this question in their report on 3 patients with late relapse out of 103 treated patients who achieved a SVR_{24}. These 3 patients had reappearance of HCV RNA 8, 65 (5.5 years), and 78 months (6.5 years) after their treatment ended. In an evaluation of the relatedness of virus from the 3 patients with late relapse and virus from 4 patients with early relapse, the authors found very high relatedness between the pretreatment and reappearing HCV sequence within the 5′ untranslated region (UTR) among the patients with early relapse and those with late relapse. This suggests that both groups suffer from relapse of their original virus, rather than a reinfection. One can debate whether the 5′ UTR is the ideal region to assess relatedness [7]; however, a similar finding was recently reported from Taiwan by Yu et al, using the core gene region to evaluate relatedness of HCV. These authors found relapse confirmed in 5 of 6 patients with

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delayed HCV recurrence [8]. The patients in the study by Yu et al had relapse mostly within the first year, and the sequence explored was the core region, with a sequence homology of 98.1%–99.5%; these findings, similar to those by Hara et al, confirm delayed relapse.

These key studies by Hara et al from the United States and by Yu et al from Taiwan indicate that most patients with late recurrence of HCV RNA have relapse, rather than reinfection. Crucial questions for the future remain and include the following: How frequent is a delayed relapse? Will delayed relapse be more frequent with direct antivirals? Where is the reservoir for such delayed relapse? and How can we identify those patients who will eventually suffer from delayed relapses?

The reported frequency of 3% is minimally higher but not statistically different from the frequency of <1% recently reported by Manns et al in >1000 patients [8]. Definite relapse (quantifiable serum HCV RNA load with no subsequent undetectable HCV RNA load) was reported in 6 of 636 patients treated with interferon alfa-2b and 3 of 366 patients treated with pegylated interferon alfa-2b. On the basis of these relapses, the point estimate for the likelihood of maintaining response after 5 years was 99.2% for interferon alfa-2b and 99.4% for pegylated interferon alfa-2b [9]. A number of smaller studies reported similar frequencies of delayed relapse beyond 24 weeks after the end of therapy [4, 10, 11].

There are insufficient data available to estimate whether such late relapses might be more frequent in the future with the use of direct antivirals. This may depend on at least 2 factors. The first factor relates to viral fitness and replication capacity. An antiviral might lead to a substantial fitness cost to a virus, which means that only very unfit virus might be able to resist elimination, which in turn requires the mutated or selected unfit virus to revert to higher replicative capacity, which might take several months or years.

The second factor relates to the potential of late relapsing virus deriving from a reservoir. There is potential compartmentalization of HCV variants with reduced fitness, allowing for delayed relapse. Because interferon is not known to induce mutated unfit virus, it is most likely that late relapse of infection in patients who received interferon/ribavirin-based therapies involves virus from extrahepatic reservoirs, which might offer protection from the antiviral activity of drugs, or alternatively, that the harbored virus might have an intrinsically low replicative activity, making it less vulnerable to antiviral pharmaceuticals.

One attractive option for such a reservoir is the brain. There are several lines of evidence suggesting involvement of the brain in HCV infection [12], such as the high frequency of depression during interferon-based therapies in patients with HCV infection [13, 14], compared with a frequency of depression of <6% among patients with hepatitis B treated with the same regimen [15, 16]. Several studies have demonstrated HCV sequences in the brain, and most importantly, one study proved those sequences to be associated with a low virus replicative capacity related to mutational changes in the internal ribosome entry site [17]. Persistence of replicative reservoirs could potentially lead to reinfection of the liver after otherwise successful treatment. The virus would remain undetectable until reversion/conversion to a more replication-competent virus emerges, and once virus is detectable, no unusual sequences would be expected in these patients with late relapse.

With new direct antivirals against HCV currently not being assessed for their ability to cross the blood brain barrier, more late relapses might emerge in the future. However, clearance of the major viral pool might also allow a patient's immune system to control the remaining viral pools.

How can one identify those who will eventually have late relapse? Liver biopsy to ensure cure seems unfeasible; in addition, the fact that the patients with delayed relapse described by Hara et al had no detectable virus in their liver further limits the usefulness of such an approach. Peripheral blood mononuclear cells (PBMCs) might harbor HCV and have not yet been tested for presence of HCV in order to predict late relapses. Reservoirs other than the liver or PBMCs are unlikely to be amenable to biopsy. A remaining target to identify future delayed relapses could be cellular immune responses or antibody titers, both of which might decrease in the absence of remaining virus. Wiegand et al showed a decline in anti-HCV antibody responses after cure of HCV in the setting of acute hepatitis C [18]. Although the cellular immune response might, likewise, be a potentially interesting target to explore, Takaki et al reported that HCV-targeted T-cell function might be well preserved even decades after clearance of HCV [19].

It is likely that we will be able to cure almost all patients with HCV infection within the next 3 years, but we might only heal the livers in some of them. A recent long-term analysis found that only about 50% of cirrhotic patients experienced in reversal of cirrhosis after achieving a SVR, while a significant number of patients achieving SVR in the absence of cirrhosis still progressed to cirrhosis despite being cured of HCV infection [20]. But importantly, curing HCV infection has been associated with clinical benefits [21]. Thus, the less robust improvement in HCV infection as compared to HBV infection should not deter us from treating patients but should soften our expectations. Overall, this report by Hara et al indicates that when we treat HCV infection, although the phenomenon is rare, we should remain vigilant that patients may experience delayed relapse despite apparent cure.

Note

Potential conflicts of interest. H. L. T.'s wife is an employee of Abbvie, and together they hold stocks in AbbVie, Abbott, and Gilead. H. L. T. received travel support from BMS and Gilead to

attend advisory meetings, received honoraria from BMS and Gilead for lectures/advisory work, and served on the data safety monitoring board for Novartis. Biotest Ag, Roche.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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