Spontaneous Resolution of Chronic Hepatitis C Virus Infection: Are We Missing Something?

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(See the article by Scott et al. on pages 945–52).

One of the puzzling features of infection with hepatitis C virus (HCV) is that, even among healthy and fully immunocompetent individuals, up to 80% of individuals with HCV infection develop persistent viremia, with the potential consequences of liver cirrhosis, liver failure, and hepatocellular carcinoma [1]. On the other hand, one could argue that the glass is at least partially full, because a significant proportion of persons with HCV infection are able to gain control of their infection and most likely experience spontaneous eradication of the virus. This observation indicates that defeat of HCV infection can be achieved by means of weapons from the host’s own arsenal; however, employing these weapons for future therapies will require better identification of the mechanisms by which viremia is controlled in these circumstances.

HCV-specific cellular immunity has been shown to play a critical role in the spontaneous resolution of HCV infection [2, 3], but it remains unclear what exactly distinguishes a successful from an unsuccessful cellular immune response and how critical a role other parts of the immune system have in HCV control.

Because almost all persons who experience clearance of HCV infection spontaneously do so within the first 6 months after onset of infection, it is often overlooked that patients sometimes experience clearance of HCV many years after chronic HCV infection has been established. Most of these reports describe spontaneous clearance of HCV together with other significant clinical events, which are typically associated with extraordinary changes in host immunity, such as immune reconstitution following receipt of HAART [4], termination of immunosuppressive therapy [5], pregnancy, or onset of other acute viral infections [6].

In this issue of Clinical Infectious Diseases, Scott et al. [7] suggest that, at least among Alaska Natives, such sporadic episodes of viral control in patients with chronic HCV infection are more common than has been appreciated previously and are associated with lower baseline levels of viremia. They also recommend that cases with such a clinically surprising outcome should be investigated in more detail, because doing so might open new avenues for the development of future therapies. The latter cannot be emphasized strongly enough. Understanding the mechanisms by which resolution of HCV viremia is achieved during chronic infection might have even greater potential than a better comprehension of viral control during the acute phase of disease. The reason is that these persons have managed to control the virus under significantly more-challenging circumstances than those encountered by the immune system during the acute phase of infection and that this is the situation in which most of our patients find themselves. The challenge is that, in subjects with chronic HCV infection, the virus has already successfully managed to evade immune control for a prolonged period, and therefore, the host faces a more-uphill battle to regain control. For example, an increasing amount of evidence shows that HCV is able to escape the T-cell response by accumulating mutant sequences [8, 9], and consequently, certain HCV-specific T-cells will not recognize the circulating virus. Therefore, a boost of the frequencies or functions of those cells should have little effect. If this is the case, how can a patient succeed in turning around what seems to be an already lost battle, and what is the immune system’s equivalent to Wellington’s Prussians at Waterloo?

Based on circumstances in which spontaneous resolution of chronic HCV infection has been described in previous reports, we have a few starting points for speculation. Despite the fact that, during chronic infection, HCV often has evolved to circumvent cellular immune responses, restoration of the HCV-specific T-cell re-
response remains high on the list of mechanisms. This is supported by the observation that occasional patients have experienced clearance of the virus with increasing T-helper cell counts following initiation of HAART for HIV infection [4, 10]. Our laboratory has demonstrated that the vigor of the HCV-specific CD8+ T-cell response to coinfection with HIV-1 and HCV is tightly correlated with the total CD4+ count [11]; together, these observations suggest that restoration of the anti-HCV T-cell response might be the critical mechanism for viral resolution. That T-cell responses can be restored is also in accordance with our finding in a patient who experienced clearance of HCV after stopping immunosuppressive therapy after the removal of a solid organ transplant. In this patient, we detected an extremely vigorous CD4+ T-helper cell response against several HCV proteins, far beyond what is usually detected in persons with persisting viremia [5]. Additional provision of T-helper signals could also be important in the suppression of HCV during acute hepatitis B virus infection [6], although in this scenario, additional potential mechanisms for improved anti-HCV immunity come to mind. For example, the massive release of type I IFNs in an acutely infected liver could contribute directly to antiviral activity by waking up a dormant innate immune response. Another possibility is that HBV could monopolize the synthetic machinery of infected hepatocytes during acute infection and, thereby, could interrupt the HCV replication cycle. Just from this short list of possible mechanisms by which HCV clearance might be achieved in patients with chronic infection, it becomes clear that investigation of such patients, albeit challenging, has the potential to be highly rewarding.

However, first we need to identify more patients who experience resolution of chronic HCV infection spontaneously and determine the true incidence of these occurrences. In this respect, the message from Scott et al. [7] is ambiguous. Despite the careful execution of the study, it is not fully clear how many patients truly experienced clearance of HCV during chronic infection, and the authors correctly classify patients as possible and probableclearers. On the other hand, there were additional patients who also potentially experienced clearance but who did not fulfill the strict criteria for inclusion in the study. Another point of uncertainty lies in the finding that most of the patients who experienced clearance of HCV had extremely low viral loads at baseline. Indeed, this could be a prognostic factor, as suggested by the authors, but it could also be the result of viral loads oscillating around the level of detection of the PCR assay. To note these problems in defining spontaneous resolution during chronic HCV infection does not diminish the efforts by the authors, who should be congratulated for their attempt to pin down an elusive but most likely underreported fact concerning HCV infection. In conclusion, more studies are needed before we can feel confident about the incidence of spontaneous viral clearance in chronic HCV infection or before we start investigating the genetic disposition of Alaska Natives and its relevance to viral control. Meanwhile, clinicians should stay alert to this rare outcome of HCV infection, and further investigations of this phenomenon should be strongly encouraged.

Acknowledgments

References