Racial Differences in Response to Interferon-Based Antiviral Therapy for Hepatitis C Virus Infection: A Hardwiring Issue?

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(See the article by Hoofnagle et al., on pages 1112–20.)

Chronic hepatitis C virus (HCV) infection is a major public health burden in the United States and worldwide. Between 2% and 3% of the world’s population has chronic HCV infection, although significant geographic variation results in a prevalence of chronic HCV of >10% in certain countries. As a result, complications of chronic HCV infection (mostly end-stage liver disease and hepatocellular carcinoma) comprise the leading indications for liver transplantation worldwide. Phylogenetic analysis has led to the description of 6 major viral genotypes, numbered 1 through 6, that differ from each other by >30% at the nucleotide level over the viral genome. The major genotypes can, in turn, be divided into subtypes (e.g., 1a or 1b) that differ by ~20%.

Interferon (IFN)-based regimens have been the mainstay of HCV treatment for nearly 2 decades [1, 2]. Patients with genotype 1 infection experience substantially lower rates of sustained virologic response (SVR), defined as an undetectable serum HCV RNA level 24 weeks after the end of treatment, compared with patients with HCV genotype 2 or 3 infection. With best current therapy consisting of peginterferon and ribavirin, genotype 1 infection is associated with a 45%–55% rate of SVR, whereas genotype 2 or 3 infection is associated with a 75%–80% rate of SVR. This observation underscores the importance of viral factors in determining the response to IFN-based therapy.

It has also become apparent that host factors influence the response to antiviral therapy. Several independent studies have shown that African Americans experience consistently lower rates of SVR to IFN-based regimens, compared with white persons [3–6]. In the Study of Viral Resistance to Antiviral Therapy of Hepatitis C (Virahep-C), a multicenter trial comparing the rates of response to peginterferon and ribavirin among 205 white and 196 African American patients with chronic genotype 1 infection, only 28% of African American patients attained SVR, compared with 52% of white patients [5]. The association between African American race and decreased IFN responsiveness remained significant even after adjustment for baseline HCV RNA level, sex, age, weight, stage of hepatic fibrosis, or amount of peginterferon or ribavirin taken. Intriguingly, this study also showed that only 10% of African American patients had an undetectable HCV RNA level after 4 weeks of therapy, compared with 22% of white patients, demonstrating that at least some of the difference in IFN responsiveness between African American and white patients could be explained by differences in early viral kinetics.

The article by Hoofnagle et al. [5] in this issue of the Journal extends this observation by analyzing HCV early viral kinetics in response to peginterferon and ribavirin in 301 patients (of whom 154 were African American and 187 were white) from the Virahep-C study population. Three kinetic measurements were assessed: the first-phase response, defined in this study as the decrease in HCV RNA levels between baseline and 24 or 48 h after the first dose of peginterferon, which ever was greater; the second-phase response, defined as the maximum weekly decrease in HCV RNA levels between days 7 and 28 or days 14 and 28, whichever was greater; and the total decrease from baseline to week 28. All 3 responses were predictive of SVR, although the 28-day decrease was most predictive by receiver operating curve analysis. The most striking finding of the study was that the ultimate antiviral efficacy of a 48-week course of IFN-based therapy for chronic HCV infection was, to a significant degree, determined by the viral kinetics only 24–48.
h after the first dose. All 3 kinetic measurements were significantly greater in white patients than in African American patients, such that white patients had a median decrease in HCV RNA level at 28 days that was 1.25 log_{10} IU/mL, or nearly 18-fold, greater than that for African American patients (2.56 log_{10} IU/mL vs. 1.31 log_{10} IU/mL). In multivariate analysis, the only factors independently associated with 28-day decrease in HCV RNA levels were race and higher baseline white blood cell and platelet counts, which the authors interpreted as being markers for lesser degrees of hepatic fibrosis, but not sex, weight, or homeostasis model assessment (a validated measure of insulin resistance), factors also previously associated with response.

An important finding was that the SVR rate remained higher for white patients, compared with African American patients, and for women, compared with men, even for the same 28-day decrease in HCV RNA level, after controlling for other factors shown to be associated with SVR. This observation indicates that the difference in SVR between white and African American patients (and between women and men) cannot be explained solely by early viral kinetics.

What might explain the substantial and reproducible differences in HCV treatment response between African American and white patients? One explanation would be that African American patients have unfavorable peginterferon and/or ribavirin pharmacokinetics, compared with white patients. Hoofnagle et al. [7] found that peginterferon levels at 28 days were significantly but only slightly greater among patients with a >2 log_{10} decrease in HCV RNA level than among patients with lesser decreases. A recent analysis of the same Virapeh-C study group showed that the African American patients actually had higher serum peginterferon concentrations on days 1, 3, 14, and 28, compared with the white patients [8], which renders this hypothesis implausible as the sole or primary explanation for poorer treatment responses in African American patients.

The more likely explanation is that many African American patients have a relative impairment in the induction or the function of the key innate and/or adaptive immune antiviral effectors of exogenously administered IFN. As Hoofnagle and colleagues [7] have found, impaired IFN responsiveness occurs in African American patients even 24–48 h after the first dose of peginterferon/ribavirin, suggesting that the defect in early viral kinetic responses more likely resides in the innate immune system rather than in the adaptive immune response. In theory, this block could occur at one or more levels. Alpha-IFNs bind to type I IFN receptors on the cell surface of hepatocytes and immune cells, leading to activation of the Jak-STAT pathway and IFN-stimulated gene (ISG) transcription. Several of these ISGs, such as PKR and OAS, have been shown to have direct antiviral effects in HCV-infected hepatocytes. Impaired responses to exogenous IFN, therefore, could result from defective Jak-STAT activation and/or ISG transcription, from impaired function of one or more key antiviral ISGs, or from the increased activity of genes that inhibit IFN signaling or ISG function.

Indeed, recent expression profiling studies of liver tissue from HCV-infected humans have demonstrated that, after receipt of a dose of exogenous IFN, patients known to have a strong IFN response display degrees of ISG induction above their pretreatment levels that are greater than in patients with poor IFN responses [9, 10]. A counterintuitive finding in each of these studies, however, was that poor responders had increased baseline levels of ISG expression, compared with strong responders, but could not further increase ISG transcription in response to exogenous IFN. Surprisingly, Sarasin-Filipowicz et al. [10] found that rapid responders did not have a greater absolute level of ISG expression after IFN administration, compared with nonrapid responders; rather, the difference between the 2 groups appeared to reside in the pretreatment levels of ISG expression.

We do not yet understand the mechanistic basis for the observation that the IFN pathway appears to be preactivated in nonresponders before therapy initiation. Several HCV proteins directly interfere with cellular proteins in the IFN signaling pathway [11–13], but there has not yet been any strong evidence that HCV isolates from IFN nonresponders differ from isolates from responders in terms of their ability to block IFN signaling. Another hypothesis is that the increased baseline levels of ISG expression in nonresponders also result in the increased expression of negative regulators of the IFN-mediated antiviral response, such as SOCS3 [14, 15]. Alternatively, IFN nonresponders may have polymorphisms in key antiviral ISGs that impair their activity, resulting in a preactivated but ineffectual ISG response to chronic HCV infection.

The article by Hoofnagle et al. [7] demonstrates that the low rates of SVR among African American patients in response to IFN-based therapy appear to result, in large part, from impaired early viral kinetics. Further studies are necessary to uncover the relevant mechanisms that underlie this defect in IFN signaling or ISG function, with the hope that such mechanisms can be manipulated to restore IFN responsiveness in the otherwise nonresponsive host.

References