Correspondence

NS5A Sequences of Hepatitis C Virus Genotype 1 and Interferon Resistance: Where Are We?

To the Editor—In an article recently published in the Journal, Dal Pero et al. [1] showed a relationship between the frequency of mutations in NS5A sequences of hepatitis C virus genotype 1a (HCV-1a), early viral kinetics, and pegylated interferon-α (pegIFN) efficacy, represented mostly by amino acid substitutions in the V3 region at the C terminus of NS5A. However, no specific selection of particular NS5A sequences after a single dose of pegIFN occurred in any patient, and no correlation was uncovered between specific altered amino acid configurations in NS5A sequences and the second viral kinetic phase that is associated with more sustained responses.

The interference of HCV proteins with IFN-induced intracellular signalling could be an important mechanism that results in viral persistence and treatment resistance. The interference of viral proteins with the Jak-Stat pathway could be responsible for IFN resistance in patients with chronic HCV infection [2], although this hypothesis remains unproven. In the past, several groups have reported that the HCV protein NS5A and E2 can interfere with the IFN-α–induced antiviral effector protein PKR [3,4]. A relationship has been reported between the sequence of the central region of the NS5A and the likelihood of sustained virologic responses in patients infected with HCV-1b, and a meta-analysis of conflicting reports confirmed that viral amino acid sequences from patients with sustained virological response differ more markedly from a prototype Japanese HCV-1b sequence than do sequences from patients who fail to eradicate infection [5]. The corresponding 40-aa region was designated the “IFN-sensitivity determining region” (ISDR) solely on the basis of this observed relationship. However, in a study of NS5A gene quasi species, no HCV-1b NS5A sequence appeared to be intrinsically resistant or sensitive to IFN-α [6]. Furthermore, the role of the NS5A-PKR interaction was not confirmed in another in vitro model [7].

In addition, another study found no relationship between NS5A functional-site amino acid sequences (in particular the so-called ISDR, the PKR-binding site, and the V3 variable region) and IFN-α blocking efficiency on day 1 of treatment in HCV genotype 1–infected patients [8]. Phylogenetic analyses of the full-length protein and functional domains showed no relationship between the baseline protein sequence and the antiviral response. Relative to a prototype sequence, NS5A quasi species sequences from viral responders and nonresponders showed no differences in the number of mutations in the putative ISDR, nor did they show any difference according to IFN-α antiviral efficacy. No relationship was found between antiviral efficacy at 24 h and the baseline sequence of any NS5A region. Amino acid changes were observed in a few cases at 24 h in both responders and nonresponders, but no consistent pattern of amino acid shifts was observed, which ruled out the possibility that IFN-α selected IFN-resistant variants. These findings show that there is no ISDR in the HCV genotype 1 NS5A protein and that the NS5A sequence does not influence the capacity of IFN-α to block viral replication. The findings do not rule out a role for NS5A in subsequent viral clearance.

Thus, it is very unlikely that the NS5A-PKR interaction plays a role in IFN-α– based treatment failure. Whether the induction of interleukin-8 by NS5A exists in vivo and plays a role in treatment outcome remains to be determined. Studies of early viral kinetics during treatment indicate that specific viral interactions with both the antiviral and the immunomodulatory effectors of IFN-α are probably involved in HCV resistance to IFN-α–ribavirin treatment [9,10]. The 3 principal findings are as follows. First, the slope of the initial viral decline on day 1 is significantly steeper for genotypes 2 and 3 than for genotypes 1 and 4, suggesting that the latter genotypes are intrinsically more resistant to the direct, nonspecific antiviral action of IFN-α. In addition, differences in the effectiveness of IFN-α blocking were observed on day 1 in different patients infected by a given genotype. Second, the vast majority of patients infected by genotypes 2 and 3 had a biphasic decline in viral load, with the second phase starting on day 2. In contrast, a significant number of responder patients infected with genotype 1 or 4 had a kinetic “shoulder” phase that preceded the second phase decline and lasted until the end of the first week of treatment. Because the second phase of viral load decline is thought to reflect clearance of infected cells by immune effectors, these findings suggest that the immune response may be delayed or otherwise altered in a viral genotype–dependent manner. Third, the slope of the second phase of viral load decline was significantly steeper in responder patients infected with genotypes 2 and 3, compared with those infected by genotypes 1 and 4. This suggests that the half-life of infected cells is longer for genotype 1 or 4 than for genotypes 2 and 3 infection and that HCV itself can modulate this half-life through direct interactions with cellular mechanisms and/or immune responses. Most importantly, rapid viral response to genotype 1 behaves as does rapid viral
response to genotypes 2 or 3 (with only 10% more patients experiencing relapse). The fact that IFN-α monotherapy cures the vast majority of patients with acute-phase HCV-1 infection, whereas it fails for approximately 50% of patients with chronic HCV-1 infection, further suggests that virus-induced modifications of the half-life of infected cells, possibly through direct intracellular interactions and/or interactions with the immune system, are probably key determinants of treatment failure.

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References

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