Correspondence

Effect of Hepatitis C Virus Genotype on CD4+ T Cell Count in a Cohort of Antiretroviral-Naive HIV-1–Infected Individuals

To the Editor—Over the past few years, there has been substantial controversy regarding whether HIV-1/hepatitis C virus (HCV)—coinfected individuals experience more-rapid HIV-1 disease progression than do HIV-1–monoinfected individuals [1–3]. Yoo et al., in a cohort of largely untreated young HIV-1/HCV–coinfected participants with hemophilia who were followed for 7 years, observed lower CD4+ T cell counts and a higher risk of AIDS-related mortality in the participants infected with HCV genotype 1 than in the participants infected with other genotypes [4]. However, as was suggested by the authors, the peculiar characteristics of the participants make the results of the study not directly applicable to other coinfect groups.

We repeated the analysis of Yoo et al. using the CD4+ T cell counts and HIV-1 RNA loads recorded in the Italian Cohort Naive for Antiretrovirals (I.Co.N.A.) database over the period during which the patients remained untreated. The I.Co.N.A. is a multicenter, prospective, observational study cohort that includes HIV-1–infected adults who were antiretroviral naive at the time of enrollment [5]. Specifically, we created an age-adjusted random coefficient linear regression model with CD4+ T cell count as the response variable [6]. We then further adjusted for HCV RNA loads measured in plasma that had been obtained and stored before the initiation of therapy. Mean CD4+ T cell counts were compared overall across the HCV genotype groups as well as between groups by the construction of prespecified contrasts.

Our analysis focused on 302 adult patients, 72 (23.8%) of whom were female, who were tested for HCV RNA load and genotype. Of these, 153 (50.7%) were infected with genotype 1, 7 (2.3%) were infected with genotype 2, 95 (31.5%) were infected with genotype 3, and 47 (15.6%) were infected with genotype 4. The mean (± SD) numbers of CD4+ T cell counts and HIV-1 RNA loads measured during the follow-up period (stratified by genotype) were 1.80 (1.75) for genotype 1, 1.71 (0.76) for genotype 2, 2.55 (2.56) for genotype 3, and 2.64 (2.72) for genotype 4 (P = .02, Kruskal-Wallis test); the mean (±SD) follow-up period for all patients was 4.57 (8.33) months. Risk categories were injection drug use (255 [84.4%] patients), heterosexual contact (11 [3.6%] patients), and heterosexual contact (27 [8.9%] patients).

In our basic model that adjusted for age alone, absolute CD4+ T cell counts were significantly lower in the HCV genotype 1 group than in the HCV genotype 3 group and the HCV genotype 4 group (table 1). Thus, our results extend those of Yoo et al. to a more heterogeneous population, suggesting that HCV genotype 1 possibly plays a role in accelerating HIV-1 disease progression.

However, in light of other concomitant observations, it is not easy to explain just how genotype 1 may affect HIV-1 disease progression. In particular, neither our data nor those of Yoo et al. provide evidence for an association between HCV genotype and HIV-1 RNA load. In our analysis, patients infected with HCV genotype 4 tended to have lower HIV-1 RNA loads than did patients infected with genotype 1, but the association was not statistically significant (P = .07, Wilcoxon rank sum test). Recently, it has also been suggested that the differences in CD4+ T cell count observed by Yoo et al. could be explained by higher HCV RNA loads in patients infected with HCV genotype 1 than in patients infected with other genotypes [7]. However, our data do not support this hypothesis (median loads, 6.16 log_{10} IU/mL for genotype 1; 6.32 log_{10} IU/mL for genotype 2; 6.06 log_{10} IU/mL for genotype 3; and 6.08 log_{10} IU/mL for genotype 4 [P = .81, Kruskal-Wallis test]).

In addition, our analysis of the difference in CD4+ T cell count by HCV genotype remained virtually unchanged after further adjustment in the linear model for HCV RNA load (for a 35-year-old person with an HCV RNA load of 6.00 log_{10} IU/mL, 299 cells/µL for genotype 1 vs. 385 cells/µL for genotype 3 [P = .001, Wald test] and 386 cells/µL for genotype 4 [P = .009, Wald test]). Finally, both our analysis (data not shown) and that of Yoo et al. provided no evidence for a difference in the slope of the decrease in CD4+ T cell count over time by HCV genotype.

To our knowledge, in the era of potent combination antiretroviral therapy (cART), it remains unclear whether the response to therapy may substantially differ between HIV-1/HCV–coinfected and HIV-1–monoinfected individuals [5, 8, 9]. Interestingly, in another recent investigation conducted in a group of HCV-viremic coinfect patients in the I.Co.N.A. who were initiating cART, we did not find a clear association between HCV genotype and the probability of a CD4+ T cell count response to their first treatment [10]. However, even if an association between HCV genotype 1 and CD4+ T cell count decay really does exist in untreated HIV-1 populations, it is possible that the same association may not be seen when comparing the CD4+ T cell count rise after cART initiation. Further investigations aimed at better understanding the intimate mechanisms by which HCV alters HIV-1 disease progression.
progression, irrespective of the amount of circulating virus, are warranted.

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References

Reply to Antonucci et al.

To the Editor—We read with great interest the letter by Antonucci et al. [1] responding to our article describing the relationship between hepatitis C virus (HCV) genotype and HCV RNA load, CD4+ T cell count, and HIV-1 disease progression [2]. Our study, which was conducted in HIV-1/HCV–coinfected children and adolescents with hemophilia enrolled in the Hemophilia Growth and Development Study (HGDS), made the novel observation that, compared with those with HCV non–genotype 1 infection, those with HCV genotype 1 infection had lower absolute and percentage CD4+ T cell measurements. As with any new finding, confirmation in other cohorts and further study to determine whether the results can be extrapolated to other populations are vital. Antonucci et al. performed a related analysis in a cohort of 302 patients followed longitudinally in the Italian Cohort Naive for Antiretrovirals (I.Co.N.A.). This cohort was considerably different from the HGDS cohort, being an adult cohort of whom ~24% were women and ~84% had injection drug use as the primary risk factor for HIV-1 infection. In addition, the study population included a larger percentage of patients with non–genotype 1 infection than did the HGDS cohort (49% vs. 22%). Despite these differences, Antonucci et al. found the same relationship between HCV genotype and CD4+ T cell count that we reported in our study. Although follow-up of the I.Co.N.A. was limited to a mean of 4.6 months, compared with up to 7 years for the HGDS cohort, Antonucci et al. also failed to see a difference in change over time in CD4+ T cell count by HCV genotype.

In the editorial commentary by Núñez and Soriano that accompanied our article [3], it was proposed that the difference in CD4+ T cell count may have been related to the higher HCV RNA loads seen in those infected with HCV genotype 1, an