Correspondence

Coinfection with HIV and Hepatitis C Virus and Immune Restoration during HAART

Sir—In the meta-analysis by Miller et al. [1], the study design, data analysis, and main conclusions seem to have substantial drawbacks and to be affected by poorly controlled clinical and statistical variables [2, 3].

Only 8 trials (5.3%) were extracted from a 152-study search, and the selected studies still had biases: only 5 were prospective, only 4 included treatment-naive patients, and subjects in the 8 trials were enrolled during the long period from 1992 to 2002 [1].

Statistics appear forced to obtain the biggest and, possibly, the most homogeneous patient samples; the authors analyzed only limited aspects of the 8 studies. These aspects tended to show a slightly lower increase of mean CD4 cell count among individuals coinfected with HIV and hepatitis C virus (HCV), and always failed to reach statistical significance. Moreover, the cumulative mean CD4 cell counts and standard deviations or mean CD4 cell counts and standard errors for the patient groups were not disclosed. Miller et al. [1] discuss the absolute “difference in CD4 cell count increase,” (p. 714) without considering that the significance of absolute differences cannot be pre-scrinded from baseline values.

From table 2 in the article by Miller et al. [1], I tried to calculate the mean increase in CD4 cell count for the patients who were HIV-positive, HCV-negative, compared with the count for the HIV-HCV–coinfected patients, by using weighted mean values from the reported but noncomparable trials (reference 5 was excluded). Even considering all the limitations of our calculations (which cannot lead to a cumulative assessment of SDs and SEs), I determined that there was a mean increase in CD4 cell count of 151.6 cells/μL for 3317 HCV-negative patients, compared with 113.8 cells/μL for 1579 HCV-positive patients (with a mean difference limited to 37.8 cells/μL). Sample sizes strongly influence crude statistical comparisons, and even minimal differences become statistically significant when sample size is increased [2, 3]. To demonstrate this, I simply doubled the number of specimens tested by Miller et al. [1] (8074 specimens from HCV-negative subjects versus 4358 specimens from HCV-positive subjects). For HCV-negative patients, I maintained the same mean increase in CD4 cell count of 151.6 cells/μL and the same conservative estimated SD of 70 cells/μL, and I obtained a minimum (but still statistically significant) P value (P = .048); the HCV-positive patient group should have had a theoretical mean CD4 cell count of 149.0 cells/μL and an estimated SD of 70 cells/μL. This last, extreme experiment shows that a mean absolute increase of 2.6 CD4 cells/μL (regardless of the baseline count) points out that there was a significantly decreased CD4 cell count among HIV-HCV–coinfected individuals, compared with the count among HIV-positive, HCV-negative individuals, when all patients were receiving (effective, I hope) HAART.

From a technical standpoint, the absolute CD4 cell count (considered alone, regardless of lymphocyte count, cell subset counts, and other immunological features) is influenced by numerous variables in a healthy subject, including circannual and circadian rhythms, sex, transient viral inflammatory disease, and limitations of laboratory assays (which account for a negligible 5% difference when specimens are double-checked in the same experimental setting) [3–5]. When I considered subjects with stable HIV infection who had blood drawn for testing 3 times per week for 2 weeks, 4 weeks apart, the median absolute difference between duplicate CD4 cell counts was 16 cells/μL, and the median range among individual patients was 119 cells/μL [5]. All of these limitations should be compared with the claimed significant difference of 33.4 cells/μL (95% CI, 23.5–43.4 cells/μL) [1]. Furthermore, the reader can imagine how many adjunctive variables should be considered when HIV-HCV–coinfected patients receiving HAART are evaluated; so a mean difference of slightly more than 30 cells/μL is academically, but not clinically, relevant [4, 5].

A moderately lower mean CD4 cell count in HCV–HIV–coinfected patients than in HIV-positive, HCV-negative patients is somewhat expected, as is the transient lymphocyte count and CD4 cell count decrease after anti-HCV therapy [6]. Other studies demonstrated that T cell response during anti-HCV therapy may be influenced by HCV genotype and patient ethnicity [7] or HIV load [6]. These variables were not considered in the meta-analysis by Miller et al. [1].

Regarding HAART for HIV-HCV–coinfected patients, no study has demonstrated that minimal differences in absolute CD4 cell count increases play any role whatsoever in the end result of HAART, so I cannot agree with the statement, “This meta-analysis shows that patients with HIV-HCV coinfection do…have less immune reconstitution, as determined by CD4 cell count after 48 weeks of HAART, than do patients with HCV infection alone” [1, p. 713]. By performing a mere analysis of data from 8 noncomparable cohorts with increased absolute mean CD4 cell counts, the au...
“Strange things I have in head”: Evidence of Prion Disease in Shakespeare’s Macbeth

Sir—The first reports of prion diseases are mid-18th-century accounts from Scotland of sheep scrapie and early-20th-century reports from Germany of human dementia with myoclonus [1]. We suggest that Shakespeare’s Macbeth [2] presents an earlier account of possible human prion disease.

Macbeth’s descent into madness often elicits psychological interpretations, but he experienced neurologic and cognitive deterioration as well. This brings into question whether a psychiatric disorder alone could fully account for his condition. Any patient today, particularly one from Scotland, presenting with a similar rapid decline in neurologic, psychiatric, and cognitive function, accompanied (as in Macbeth’s case) by involuntary movements, hallucinations, and insomnia, would require an evaluation for variant Creutzfeldt-Jakob disease [3]. In table 1, we match features of Macbeth’s illness with manifestations of variant Creutzfeldt-Jakob disease and related prion diseases.

Although we contend that Macbeth’s presentation is compatible with a spongiform encephalopathy, no evidence corroborates that this is what Shakespeare intended. Nevertheless, Shakespeare showed an uncannily prescient understanding of prion disease transmission via exposure to neural tissues: “[Once], when the brains were out, the man would die / And there an end; but now they rise again / With twenty mortal murders on their crowns” (3.4.78–80). Conceivably, Macbeth was exposed to infectious prions during an early encounter with the weird sisters, whose necromantic brews contained a variety of human and animal organs. Proclaiming, “Round about the cauldron go / In the poison’d entrails throw,” (4.1.4–5), they added, for example, a human nose and liver tissues that are capable of carrying infectious prions [4]. It is not clear that anyone consumed the witches’ brews, but if Macbeth had, that could explain the exposure. Furthermore, Shakespeare foreshadowed current prion disease epidemiology [5] by warning his audiences to “eat our meal in fear” (3.2.17) until the time when “we may again / Give to our tables meat” (3.6.33–34). (A character in Twelfth Night declares “I am a great eater of beef, and I believe that does harm to my wit” [1.3.85–86]).

Macbeth is loosely based on Holinshed’s chronicle of Macth, an 11th-century Scottish king who murdered Malcolm and fought Duncan for the throne, but we found nothing in Holinshed’s account that we could infer to be evidence of prion disease [6]. Therefore, it appears that Macbeth’s condition as portrayed in the play arose from either Shakespeare’s imagination or from his observations of human behavior around him. In either case, Macbeth himself might advise—and admit—“Do not muse at me, my most worthy, / I have a strange infirmity” (3.4.84–5).

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References