Reply to Mandorfer et al

In their letter, Mandorfer et al [1] provide additional data to support the hypothesis that discordance between absolute CD4 count and CD4 percentage is associated with underlying liver disease and associated portal hypertension. This hypothesis was initially advanced by McGovern et al [2] in a cross-sectional analysis of human immunodeficiency virus (HIV)–negative individuals with cirrhosis, in which the majority of individuals had low absolute CD4 cell count values but had CD4 percentages that remained in the normal range. In our analysis of a cohort of 908 HIV/hepatitis C virus (HCV)–coinfected patients [3], 31% of the population was found to have evidence of discordance with higher CD4 percentages than would normally be found to correlate with the documented absolute CD4 cell count. Additionally, in multivariate analysis, factors associated with very high discordance at baseline included history of end-stage liver disease (adjusted odds ratio [AOR], 6.52; 95% confidence interval [CI], 2.27–18.67) and aspartate aminotransferase-to-platelet ratio index score >1.5 (AOR, 4.69; 95% CI, 1.64–13.35).

Similarly, in a cross-sectional analysis of 287 HIV-infected individuals with underlying hepatic fibrosis (93.7% HCV coinfected) in the Johns Hopkins ALIVE cohort, 34.4% were found to have discordant CD4 percentage/absolute CD4 cell count [4]. In multivariate analysis, and using transient elastography to further classify degree of fibrosis, the odds of having high CD4 discordance was increased in those with significant liver fibrosis (OR, 1.69; 95% CI, .95–2.96). This relationship was more pronounced when overall lymphopenia was observed [4].

In this analysis of a cohort of 97 coinfected patients in whom hepatic venous pressure gradient (HPGV) had been determined, Mandorfer and colleagues found that 18% of individuals could be classified as having high discordance using the criteria we proposed. A non-significant association of high discordance in those with higher HPGV scores was observed; however, portal pressure was modestly correlated with the absolute CD4 cell count/CD4 cell percentage ratio ($r = -0.201$, $P = .049$) [1].

One potential mechanism thought to account for the discordance between CD4 percentage and absolute CD4 cell count is the splenic sequestration of lymphocytes due to consequences of end-stage liver disease and resultant portal hypertension [2, 5]. The data presented here do support this hypothesis, linking measured portal pressures to presence of discordance. Other potential mechanisms may also need to be considered, as the data from Claassen et al did not demonstrate greater discordance in those with cirrhosis versus Metavir F2 or higher stages of fibrosis [4] and the correlation observed in with higher HPGV scores was relatively weak. For example, level of HCV viral replication itself and increased hepatic inflammation have been associated with naive CD4 T-cell lymphopenia, possibly due to chronic immune activation [6].

Clinicians should consider evaluating patients with high discordance for underlying cirrhosis, based on cumulative data that support this relationship. However, it is unclear whether the CD4 percentage would serve to better determine risk for opportunistic infections in these patients;
retrospective data from the Italian IcONA cohort would suggest the absolute CD4 count remains the more important variable [7]. Prospective evaluation of the prognostic value of CD4 percentage in those with underlying cirrhosis may be necessary. In addition, evaluating the effects of HCV therapy–related regression of fibrosis on the relationship between absolute CD4 cell count and CD4 percentage may also serve to confirm the underlying mechanisms of discordance.

Notes

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