The Journal of Infectious Diseases

EDITORIAL COMMENTARY

All About the Albumin? Prognostic Capacity of Serum Albumin in Patients With Treated HIV Infection

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(See the major article by Ronit et al, on pages 405–12.)

Keywords. HIV/AIDS; inflammation; cardiovascular disease; risk prediction; albumin.

While immediate as compared to delayed initiation of antiretroviral therapy (ART) was shown to decrease morbidity in individuals with early stage human immunodeficiency virus (HIV) infection in 2 large randomized controlled trials, even those who initiate ART at high CD4+ T-cell counts appear to be at increased risk of infectious and neoplastic complications, compared with the general population [1, 2]. As the HIV epidemic ages globally, other age-associated morbidities may also become more prevalent in the treated population. Since the HIV-associated inflammatory state persists despite ART-mediated viral suppression—even among those who initiate ART at the earliest stages [3]—and strongly predicts many of these morbidities [4], a major research effort is underway to develop immune-based interventions to further improve health in this setting. As not all HIV-infected individuals have persistently high levels of immune activation and, thus, may be at low risk of morbidity [5], the field will eventually need biomarkers to stratify individuals at the greatest risk of disease, once safe and scalable immune-based therapies are shown to reduce morbidity and mortality in this population. For example, while the recently published findings from the Canakinumab Antiinflammatory Thrombosis Outcomes Study have proven for the first time that a pure antiinflammatory intervention (in this case, an interleukin 1β inhibitor) reduces the risk of death from cardiovascular and neoplastic causes in HIV-uninfected individuals with cardiovascular disease [6], ongoing studies will need to determine whether this strategy can safely be used in the context of treated HIV infection. Even if proven safe in the context of HIV, such a strategy would only be used for those at the highest risk of disease. Statins are also now being tested in a large clinical outcomes trial in treated HIV infection to see if its antiinflammatory properties reduce cardiovascular and other non-AIDS morbidities, but even a safer intervention like this would only be given to those at highest risk, particularly in resource-constrained settings. Thus, it is likely that biomarkers that can stratify individuals with treated HIV infection according to morbidity risk will be needed in the future for the provision of antiinflammatory interventions. Since the majority of HIV-infected individuals around the world live in resource-limited settings, it will also be important for such biomarkers to be measured easily and at low cost.

In this issue of *The Journal of Infectious Diseases*, Ronit et al assessed whether the serum albumin level might be used as a low-cost biomarker to predict the risk of future morbidity in individuals initiating ART during early stage HIV infection [7]. They conducted an analysis using data from >4500 participants of the Strategic Timing of Antiretroviral Treatment study [8], which randomly assigned people with symptomatic HIV infection and a CD4+ T-cell count >500 cells/μL to immediate versus delayed ART initiation (until the CD4 count declined to <350 cells/μL or an AIDS defining event occurred). They demonstrate that serum albumin levels in the population predict future non–AIDS-related events and hospitalizations. Each increase of approximately 1 mg/dL in the albumin level was associated with a 75% decreased hazard of an event, largely comprising non–AIDS-related cancers or cardiovascular disease events. This finding was independent of other prognostic indicators, including both traditional cardiovascular disease risk factors (eg, age, hemoglobin level, lipid levels, and blood pressure), HIV-specific risk indices (eg, CD4+ T-cell count and HIV-1 RNA load), and correlates of hypoproteinemia (eg, urinary protein and alanine aminotransferase levels). Whereas an association between serum albumin levels and subsequent clinical events has been demonstrated previously in treated HIV infection [9, 10], this study is unique in that it focuses on a relatively healthy study population with early stage HIV infection, broadening the generalizability of these findings, and used rigorous methods to collect outcome data in the

Received 30 August 2017; editorial decision 30 August 2017; accepted 20 September 2017; published online December 13, 2017.

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The Journal of Infectious Diseases® 2018;217:347–9

DOI: 10.1093/infdis/jix463

setting of a clinical trial, which strongly enhances the validity of the findings.

One key remaining question that emerges from the work of Ronit el al is whether the serum albumin level truly has sufficient prognostic capacity to inform clinical decisions, particularly in resource-limited settings where more-expensive biomarker testing may be impractical. Indeed, predicting clinical outcomes in the context of a large cohort study is much easier than predicting risk for an individual. Notwithstanding the robust and independent predictive value of the albumin level for significant clinical outcomes, its role as a clinical biomarker remains uncertain. This is partly due to the absolute effect size demonstrated in this study. Although the relative hazard of non–AIDS-related events was quite large, only approximately 1.5% of participants in this cohort had a non–AIDS-related event, and the crude absolute risk difference between those with an intermediate albumin level (ie, 4.2–4.5 mg/dL) and a low albumin level (ie, <4.2 mg/dL) appears to be <1% over 5 years of observation. Similarly, the area under the curve of the receiver operator characteristic curve was only 0.64, suggesting imperfect sensitivity and specificity to predict events in individual patients. It is also important to recognize that, in this analysis of relatively healthy people with HIV, albumin levels were not predictive of AIDS-related events (particularly tuberculosis, a major concern in resource-limited settings), which still occurred in approximately 1% of those randomly assigned to the immediate ART arm. As such, the albumin level does not appear to have sufficient prognostic capacity (at least not on its own) for clinical events to be used to effectively stratify individuals according to the risk of morbidity due to immune-based interventions in this setting.

Another important question emerging from this work is why low serum albumin levels strongly predict clinical events. One possibility is that a low albumin level is simply a marker for the persistent inflammatory state. Indeed, low serum albumin levels were strongly associated with higher levels of the inflammatory marker interleukin 6 (IL-6) in this study. Nevertheless, although the prognostic capacity of the serum albumin level was attenuated slightly by adjustment for the IL-6 level, it remained a statistically significant predictor of non–AIDS-related events in these adjusted models. This may mean that a low serum albumin level is predicting disease via pathways that are largely independent of inflammation. If this were the case, the albumin level might not necessarily be the best biomarker to stratify individuals on the basis of their risk of morbidity due to antiinflammatory interventions, as the pathways by which low albumin levels predict disease may not be the same ones ameliorated by the intervention. On the other hand, as the authors suggest, a low albumin level might be a consequence of other pathways of immune activation that may be less directly associated with the inflammatory marker IL-6, like microbial translocation. It is also possible that the lack of complete attenuation of the albumin level's prognostic capacity with adjustment for the IL-6 level may simply reflect the high degree of within-subject variability in IL-6 levels (ie, noise in the measurement), all exacerbated by a relatively small number of clinical events in the analysis. It is also possible that the albumin level—a putative measure of end-organ function—may be a more proximal measure of end-organ disease than the IL-6 level itself, resulting in a significant relationship persisting after adjustment for the IL-6 level, even if they were on the same causal pathway. A similar phenomenon likely applies to other indices of end-organ function that strongly predict mortality after adjustment for inflammatory biomarker levels in treated HIV infection, like the VACS index [11]. Along these lines, it would be interesting to see how the prognostic capacity of the serum albumin level compares to that of other indices of end-organ function, like the VACS index, and whether the addition of albumin level to the VACS index improves the prognostic capacity of the index.

Nevertheless, the fact that the serum albumin level is a strong and independent predictor of the risk of non–AIDS-related events in individuals initiating ART during the very early stage HIV infection is a striking finding. It suggests that low-level organ dysfunction may persist even in individuals with early stage HIV infection. While the serum albumin level might not yet be ready for adoption as a screening test for risk stratification, its association with subsequent morbidity underscores the fact that we still have work to do to improve the health of people living with HIV, even when ART is started during early disease stages.

Note

Potential conflicts of interest. Both authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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