Cystatin C and Statins in HIV Disease

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Persons living with human immunodeficiency virus (HIV) remain at increased risk for cardiovascular disease despite suppressive antiretroviral therapy [1]. Oxidative stress and inflammation may be important mechanisms underlying this morbidity [2]. Statins reduce the risk of cardiovascular disease in association with their lipid-lowering effects, but they also have broad immunomodulatory effects that may contribute to their effectiveness [3].

Kidney disease is an independent risk factor for cardiovascular disease. Albuminuria and lower glomerular filtration rates (GFRs) were robust predictors of cardiovascular events, as demonstrated in population-based studies and large cohort studies of persons living with HIV [4–6]. Cystatin C is a low-molecular-weight protein that is constitutively produced by nucleated cells and freely filtered by glomeruli [7]. It has been proposed as an alternative or complementary GFR marker to creatinine because it varies less by race, sex, or body composition than does creatinine. In population-based studies, cystatin C levels or cystatin C–based GFR estimates predicted cardiovascular disease outcomes, which in the latter case were superior to creatinine-based estimates [8, 9]. In these studies, cystatin C levels also were correlated with several markers of inflammation (including plasma C-reactive protein [CRP], interleukin 6, tumor necrosis factor alpha [TNF-α], and fibrinogen) [9].

In this issue of Clinical Infectious Diseases, Longenecker and colleagues report an analysis of cystatin C levels and their relationship to an array of subclinical vascular and immune activation markers within a prospective randomized, placebo-controlled, double-blind, single-center trial of a statin, rosuvastatin [10]. Participants were receiving stable, suppressive antiretroviral therapy and had fasting low-density lipoprotein cholesterol levels ≤130 mg/dL with elevated high-sensitivity CRP levels (≥2 mg/dL) or heightened T-cell activation (determined by HLA-DR/CD38 expression on CD8 cells ≥75th percentile for HIV-uninfected controls from a previous study); they had normal kidney function and no prior history of myocardial infarction.

Only 13 of 202 (6%) of the individuals who were screened for this study were ineligible because of activation levels below these thresholds [10]. With the exception of a larger proportion of African Americans (68% of study participants), the 147 subjects who enrolled in this study were demographically similar to persons living with HIV in the United States [11]. They found significant, positive associations between cystatin C levels and common carotid artery intima-media thickness (IMT), an independent predictor of cardiovascular disease risk in population-based studies [12], and epicardial fat, a novel correlate of atherosclerosis that these investigators previously associated with coronary calcium from this study [13]. Cystatin C levels also were positively associated with endovascular dysfunction as determined by a prespecified, ordinal classification of vascular phenotypes that they derived from tests for atherosclerosis and vascular endothelial function. Furthermore, these levels were positively associated with inflammation (soluble TNF receptors [sTNFRs] I and II), endothelial activation (soluble intracellular adhesion molecule 1), systolic blood pressure, and protease inhibitor use. After 24 weeks, cystatin C levels fell compared with baseline in the rosuvastatin arm but not in the placebo arm, which was associated with sTNFR-II declines. GFR (using creatinine-based estimates) fell in the placebo arm (by 3.08 mL/minute/1.73 m²), but increased (by 1.61 mL/minute/1.73 m²) in the rosuvastatin arm for an absolute difference from baseline of −4.69 mL/minute/1.73 m² between these respective arms.

This study identifies cystatin C as a potential biomarker for endovascular...
dysfunction in HIV disease. As with most current biomarkers for cardiovascular disease, however, it is unlikely to be clinically useful as a sole marker for individual patients because of the low strengths of association that they also observed. Recent guidelines from Kidney Disease Improving Global Outcomes recommend using cystatin C–based GFR estimates to improve the specificity of a chronic kidney disease (CKD) diagnosis, particularly in circumstances when creatinine-based GFR estimates are less accurate such as in cases with extremes in muscle mass or dietary protein intake, or when tubular secretion of creatinine may be affected by drugs including cobicistat, trimethoprim, fenofibrate, and cimetidine [14].

A previous analysis from this study identified associations between vascular disease and monocyte activation, including soluble CD14 [10]. Other studies among persons living with HIV have identified associations between arterial wall inflammation and soluble CD163 [15], between carotid artery stiffness with markers of T-cell senescence and cytomegalovirus immunoglobulin G levels [16, 17], and between internal carotid IMT with plasma TNF-α, vascular cell adhesion molecule I, and myeloperoxidase [18]. Of note, these associations were not evident among the HIV-uninfected population. However, it is likely to be clinically useful as a sole marker for individual patients because of the low strengths of association that they also observed. Recent guidelines from Kidney Disease Improving Global Outcomes recommend using cystatin C–based GFR estimates to improve the specificity of a chronic kidney disease (CKD) diagnosis, particularly in circumstances when creatinine-based GFR estimates are less accurate such as in cases with extremes in muscle mass or dietary protein intake, or when tubular secretion of creatinine may be affected by drugs including cobicistat, trimethoprim, fenofibrate, and cimetidine [14].

The associations between cystatin C and inflammation in the present study are consistent with previous studies in the general population, however [9]. In HIV disease, cystatin C levels also were positively associated with plasma HIV RNA levels, and elevated HIV RNA levels or heightened T-cell activation significantly reduced the accuracy of cystatin C–based GFR estimates, compared with directly measured GFR or creatinine-based estimates [19–21]. As acknowledged by the authors, because GFR was not measured in the present study it was not possible to distinguish the contributions by changes in GFR vs inflammation to the cystatin C changes that they observed.

Most intriguing in this randomized clinical trial was the apparent renal protection that was associated with rosuvastatin. Just as in the general population, HIV-infected persons of African descent have a disproportionate risk for severe kidney disease [22], so the increased representation of African Americans in the present study may correspond with an increased risk of kidney disease in this study population, despite normal baseline kidney function. Although the magnitude of renal protection was modest in the present study, the importance of preserving kidney function is strongly supported by inverse associations between GFR and cardiovascular outcomes from population-based studies, which were approximately linear for GFR <90 mL/minute/1.73 m² using cystatin C–based estimates [5, 8]. Furthermore, creatinine-based GFR estimates are included in the Veterans Aging Cohort Study Index, a risk score that predicted mortality in diverse HIV-infected patient populations [23].

The effects of statins on kidney function are difficult to discern from studies in the general population, which included heterogeneous patient groups that differed according to the presence or absence of diabetes, cardiovascular disease, or renal disease. Some studies have associated slower rates of GFR decline with statin use (approximately 0.2–1.9 mL/minute/1.73 m² slower decline per year with statins) [24–27]. Other studies, particularly in persons with CKD, did not detect significant renal protection with statins [28, 29]. As suggested by the authors, it is possible that renal benefits by statins may be more pronounced in settings of heightened inflammation such as in HIV disease [27].

Data from longer follow-up are eagerly anticipated to assess the magnitude and durability of this renal protection. High-quality data from studies such as this will better inform the use of statins and other attempts to modify cardiovascular risk in HIV disease.

Notes

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