Will Statins Be an Effective Anti-inflammatory Intervention for Prevention of Cardiovascular Disease in Patients With HIV?

Michael P. Dubé
Department of Medicine and Division of Infectious Diseases, University of Southern California Keck School of Medicine, Los Angeles, California

(See the major article by Eckard et al on pages 1156–64.)

Keywords. HIV; inflammation; immune activation; HMG-CoA reductase inhibitors; rosuvastatin; lipids.

The JUPITER trial [1] established that an anti-inflammatory intervention using a statin (rosuvastatin) prevented primary cardiovascular disease (CVD) events among individuals with elevated levels of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) but who had levels of low-density lipoprotein cholesterol (LDL-C) that were below the target for primary prevention that were in place at the time (<130 mg/dL) [2]. Men >50 years and women >60 years were enrolled. The trial was stopped after a Data Safety Monitoring Board recommendation at a median follow-up of 1.9 years, when clear evidence of superiority for rosuvastatin was shown. Although the number needed to treat for prevention of a single CVD event was relatively high, for example, 95 individuals treated with high-dose rosuvastatin in order to prevent 1 CVD event in 2 years’ time [3], JUPITER was encouraging, given that the relative risk reduction with 20 mg/day of rosuvastatin was approximately 50% for myocardial infarction, stroke, or need for arterial revascularization, and also demonstrated a 20% mortality benefit. These results persisted even among those participants with no other CVD risk factors, as well as across ages, gender, and race. Given this degree of benefit, might statins be even more effective when intervening in a population with a chronic disease characterized by greater inflammation and immune activation such as human immunodeficiency virus (HIV) infection?

Although the underlying reasons are unclear, among many well-treated virologically suppressed patients with HIV infection, there is evidence of persistent immune activation and inflammation [4, 5]. These abnormalities are felt to contribute to the greater incidence of end-organ disease in this population, such as myocardial infarction (MI). Population-based studies suggest that increased levels of hsCRP are more common among HIV-infected patients compared to controls [6] and are associated with increased risk of MI [6] and mortality [4, 7]. Thus, an anti-inflammatory intervention such as a statin might have particular CVD benefit for people living with HIV. To begin to address this question, in this issue of the Journal of Infectious Diseases, Eckard and colleagues report a rigorously performed, short-term 24-week study of the effects of rosuvastatin, 10 mg/day, on circulating biomarkers [8]. SATURN-HIV included subjects who were receiving stable antiretroviral therapy and had LDL-cholesterol ≤130 mg/dL, in addition to evidence of increased inflammation, either by an hsCRP level ≥2 mg/L or evidence of increased CD8+ T-cell activation measured by flow cytometry. Nearly 2/3 of subjects had an elevated hsCRP level at entry.

In spite of including subjects that might receive particular benefit from the intervention, the general lack of effect on inflammatory and coagulation markers relevant to HIV-related CVD in SATURN-HIV is disappointing. Among the markers related to CVD risk that were reported, hsCRP, interleukin 6, and D-dimer did not change significantly with rosuvastatin. In contrast, hsCRP levels were 37% lower at 1 year with rosvuastatin in JUPITER (P < .001 compared to placebo) [1]. Similarly, the magnitude of LDL-C reduction appeared to be much less in SATURN-HIV (28% reduction) as compared to JUPITER, where at 1 year, rosvuastatin recipients had 50% lower levels of LDL-C. In JUPITER, lowering of LDL-C and of hsCRP each had significant independent benefits on incident CVD events [3]. LDL-C and hsCRP reductions did not correlate well...
monocyte/macrophage activation in the not particularly effective at reducing CVD events in HIV-infected persons may not be great. Thus, if statins such as rosuvastatin are correspondingly limited. Additional mechanistic studies will be needed to address this latter issue. Interestingly, there were significant reductions in circulating lipoprotein-associated phospholipase A2 (Lp-PLA2) mass with rosuvastatin. Lp-PLA2 is potentially directly implicated in atherogenesis. Enthusiasm about the observed lowering of Lp-PLA2 in isolation, however, is greatly limited by a trial recently reported as a press release by the sponsor. STABILITY is a placebo controlled phase III trial to evaluate the Lp-PLA2 inhibitor darapladib in 15,550 subjects with stable coronary heart disease [11]. No benefit was reported for the primary endpoint of time to first major CVD event (GSK announces top-line results from pivotal Phase III study of darapladib in chronic coronary heart disease. http://www.gsk.com/media/press-releases/2013/gsk-announces-top-line-results-from-pivotal-phase-iii-study-of-d.html Issued: Tuesday 12 November 2013, London UK).

Ultimately, the potential for statins to yield CVD benefit in patients with HIV infection who would not normally require statin therapy will need to be evaluated during long-term trials involving placebo. Both event-driven trials and the use of CVD surrogate imaging techniques are needed. For example, subclinical atherosclerosis progression will be evaluated in SATURN-HIV by carotid ultrasound up to a planned 96 weeks of treatment (http://clinicaltrials.gov/ct2/show/NCT01218802). Ultimately, the potential for statins to yield CVD benefit in patients with HIV infection who would not normally require statin therapy will need to be evaluated during long-term trials involving placebo. Both event-driven trials and the use of CVD surrogate imaging techniques are needed. For example, subclinical atherosclerosis progression will be evaluated in SATURN-HIV by carotid ultrasound up to a planned 96 weeks of treatment (http://clinicaltrials.gov/ct2/show/NCT01218802).

Note
Potential conflicts of interest. The author has served as a consultant to AstraZeneca on mexitrelent and receive research grants from ViVi Healthcare, Gilead Sciences, and Serono. Author certifies no potential conflicts of interest.

The author has 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.

References

1150 • JID 2014:209 (15 April) • EDITORIAL COMMENTARY