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Impact of rosuvastatin on pulse-wave velocity in men with HIV at moderate cardiovascular risk

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This single-centre substudy of a double-blind, randomized, placebo-controlled trial aimed to determine the effect of 96 weeks of rosuvastatin on pulse wave velocity (PWV) in men ($n = 55$, 54 years) with HIV at moderate cardiovascular risk (Framingham risk score 10–15%). PWV increased in both rosuvastatin [0.54 m/s standard error of difference (SED) 0.26] and placebo [0.50 m/s (SED 0.26), $P = 0.896$] arms, leading to no difference in PWV at week 96 [rosuvastatin 9.40 m/s (SE 0.31); placebo 9.21 m/s (SE0.31), $P = 0.676$].

Introduction

Statins reduce cardiovascular disease (CVD) in people with HIV (PWH) [1].

Pulse wave velocity (PWV) is a validated, reproducible measure of arterial stiffness which occurs early in CVD and is a strong predictor of cardiovascular events and all-cause mortality [2]. Each 1 m/s increase in PWV is associated with a 12% increased risk for CVD [3]. PWV may thus be able to detect which individuals will benefit from statins.

This substudy aimed to determine the effect of rosuvastatin on PWV in PWH at moderate CVD risk.

Methods

Study design

A single-centre sub-study within a previously described multicentre, double-blind, randomized, placebo-controlled trial [4] was performed to determine the impact of 96 weeks of rosuvastatin on PWV in PWH at moderate cardiovascular risk (Framingham risk score of 10–15%. [5]).

Participants

Participants were those recruited from the Australian site, who had the capacity to measure PWV. All were men with HIV on antiretroviral therapy with a HIV viral load of less than 200 copies/ml for at least 6 months. Exclusion criteria included, guideline recommendation for a statin [5], carotid artery stenosis or more than 50% occlusion of the carotid artery due to plaque, or recent lipid-lowering therapy, antiplatelets or a contraindication to statin, creatinine clearance less than 50 ml/min, transaminases three times the upper limit of normal or greater than Childs B cirrhosis.

Ethical approval

Ethics approval (#491-12). All participants provided written informed consent.

Intervention

Participants were randomized 1 : 1 to rosuvastatin (20 mg) or identical placebo. Participants who were taking ritonavir or cobicistat ($n = 11$) received dose-reduced rosuvastatin (10 mg).

Outcomes

Assessments occurred at weeks 0, 12, 24, 48, 72, and 96 and included safety bloods and HIV viral load and $CD4^+$ T-cell count. Plasma lipids and glucose levels were assessed following an overnight fast at screening, weeks 0, 24, 48 and 96.

PWV was recorded at weeks 0, 48 and 96. Continuous pulse-pressure wave signals were recorded simultaneously with two tonometers (Millar Micro-tip, spt-301), positioned at both the base of the right common carotid artery and femoral artery. PWV from aortic arch to femoral artery was then calculated as previously described [6]. A high PWV was defined as at least 10 m/s.

The primary outcome was the change in PWV from weeks 0 to 96 with rosuvastatin versus placebo.

Assuming a 1 m/s increase in PWV over 96 weeks with placebo and reduction of 0.8 m/s with rosuvastatin [7], with 55 participants (27/28 per arm) this study has 82% power to detect a 1.8 m/s (SD 3.5 m/s) difference in PWV.

Statistical methods

The intention-to-treat population was defined as all individuals who received a dose of study medication. The per-protocol set was participants without a major protocol deviation.

The primary outcome was assessed using linear mixed models fitted via restricted maximum likelihood (REML) method with fixed effects for treatment allocation, time of assessment (baseline, 48, 96 weeks), and their two-way interactions. These analyses were further adjusted for

baseline cardiovascular risk (age, smoking status, and SBP). Statistical significance was set at a two-sided P value of 0.05. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Participants were men, 54 years old (42–68 years) and predominantly Caucasian (91%) (see Table 1).

In the intention-to-treat population, there was a small increase in PWV from weeks 0 to 96 in each arm. This reached statistical significance in the rosuvastatin ($P = 0.044$) but not the placebo arm (0.058). However, there was no difference in the amount of change in PWV between rosuvastatin [0.54 m/s (standard error of difference (SED) 0.26)] and placebo [0.50 m/s (SED 0.26), $P = 0.896$] at 96 weeks, leading to no difference in PWV between groups at the completion of follow-up [rosuvastatin 9.40 m/s (SE 0.31); placebo 9.21 m/s (SE 0.31), $P = 0.676$]. These results were unchanged when adjusted for cardiovascular risk (see Supplementary Table 1, http://links.lww.com/QAD/D222), and when restricted to the per-protocol set. There were 12 individuals with a high PWV ($\geq$10 m/s) at baseline, 6 from each arm. This increased to 26 participants at week 96, evenly distributed across arms.

Participants were largely normotensive, with no difference in blood pressure between arms at week 96 [rosuvastatin mean SBP 120 mmHg; interquartile range (IQR 112–130), placebo 125 mmHg (IQR 120–130), $P = 0.210$]. Antihypertensive use was rare at baseline ($n = 5$) with another three starting during the study (all on placebo).

Rosuvastatin led to predictable decreases in total and low-density lipoprotein (LDL) cholesterol by 24 weeks, which were sustained and led to a difference between arms at 96 weeks in total cholesterol [−1.18 mmol/l (SED 0.28), $P < 0.001$] and LDL-cholesterol [−1.05 mmol/l (SED 0.25), $P < 0.001$].

Thirty-one participants had 87 adverse events. Most, 79 (90.8%) were mild but were more common in the rosuvastatin arm (66 versus 21). Of the eight serious adverse events, seven occurred with rosuvastatin. These included two myocardial infarctions, one instance of heart failure, a fatal cerebrovascular event, new type two diabetes, creatinine kinase of 9043 U/l, and a grade 3 increase in liver enzymes, the last three deemed possibly related to study medication.

Discussion

In this study, there was no reduction in the progression of PWV with 96 weeks of rosuvastatin therapy in PWH who were at moderate cardiovascular risk.

Table 1. Baseline participant demographics.

	Total ($n = 55$)	Rosuvastatin ($n = 28$)	Placebo ($n = 27$)	P value
Age (years)	54.0 (51.0–58.0)	54.0 (50.5–58.0)	55.0 (52.0–58.0)	0.96
Male	55 (100.0%)	28 (100.0%)	27 (100.0%)	1.00
Race				0.37
Caucasian	50 (90.9%)	25 (89.3%)	25 (92.6%)	
Asian	4 (7.3%)	3 (10.7%)	1 (3.7%)	
African	1 (1.8%)	0 (0.0%)	1 (3.7%)	
Current smoker	17 (30.9%)	9 (32.1%)	8 (29.6%)	0.79
Hypertension	13 (23.6%)	5 (17.9%)	8 (29.6%)	0.30
FHx heart disease	23 (41.8%)	11 (39.3%)	12 (44.4%)	0.70
BMI (kg/m^2)	26.1 (24.5–28.4)	25.7 (24.5–27.5)	26.6 (24.5–28.9)	0.52
SBP (mmHg)	130 (120–135)	127 (120–135)	130 (125–135)	0.52
DBP (mmHg)	85 (80–90)	85 (80–90)	85 (80–90)	0.31
Fasting lipids (mmol/l)				
Total cholesterol	5.3 (4.7–5.8)	5.4 (4.5–5.8)	5.3 (4.7–5.7)	0.87
HDL-cholesterol	1.1 (1.0–1.3)	1.1 (0.9–1.4)	1.2 (1.0–1.3)	0.69
LDL-cholesterol	3.4 (2.8–3.7)	3.3 (2.7–3.7)	3.5 (3.0–3.9)	0.43
Triglycerides	1.5 (1.1–2.0)	1.5 (1.1–2.1)	1.4 (1.1–2.0)	0.53
HIV-specific variables				
HIV duration (years	13.2 (8.3–20.9)	18.9 (10.5–22.2)	10.5 (7.7–20.5)	0.11
CD4$^+$ cell count (cell/μl)	588 (402–761)	655 (430–772)	483 (380–722)	0.19
Undetectable viral load	55 (100)	28 (100)	27 (100)	1.00
CD4$^+$ nadir (cell/μl)	152 (72–294)	152 (102–292)	148 (31–294)	0.27
Current antiretroviral regimen				
Protease inhibitor	23 (41.8)	11 (39.3)	12 (44.4)	0.70
Integrase inhibitor	19 (34.5)	9 (32.1)	10 (37.0)	0.70
NNRTI	28 (50.9)	14 (50.0)	14 (51.9)	0.89
Pulse-wave velocity (m/s)	8.6 (7.5–9.5)	8.8 (7.8–9.5)	8.3 (7.5–9.6)	0.75

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures. BP, blood pressure; FHx, Family History; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; NNRTI, nonnucleoside reverse transcriptase inhibitor; VL, viral load.

Previous studies investigating the effect of statins on PWV have demonstrated conflicting results with some showing modest reductions [7], but others, similar to our findings, demonstrated ongoing progression despite statin therapy [8]. Perhaps, reflecting that aortic stiffness is more closely correlated with age and hypertension, rather than dyslipidaemia [9]. After the age of 50 years, there is near linear progression of PWV, with individuals with hypertension having a more rapid progression [10].

Individuals classified by PWV as 'high risk' have an 80% increased risk for CVD compared with low-risk individuals [3]. It is thus concerning to note that nearly half of participants in our study who, were all at moderate risk at study entry, progressed into a high-risk category within 96 weeks. In this study, statin therapy did not affect the rate at which individuals crossed over this threshold suggesting that composite strategies to reduce CVD risk in PWH at the highest risk are needed.

Although predominantly mild, rosuvastatin was associated with a significant number of adverse events, similar to those reported in other rosuvastatin trials [4,11], highlighting the need for judicious use of these medications to minimize unintentional harm.

This study is limited by its homogeneous participant population and small sample size. Use of a different statin, dose, or participant population may have identified an effect on PWV that we were unable to.

In conclusion, rosuvastatin therapy for 96 weeks did not affect progression of PWV in PWH at moderate cardiovascular risk.

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Conflicts of interest

J.M.T.'s institution has received honoraria from Gilead Health Sciences and ViivV for speaker responsibilities and advisory board participation unrelated to this project. J.F.H.'s institution has received reimbursement for her participation in Advisory Boards for Gilead Sciences, ViiV Healthcare and MSD. There are no conflicts of interest for the remaining authors.

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