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A Pilot Trial of Pentoxifylline on Endothelial Function and Inflammation in HIV-infected Patients Initiating Antiretroviral Therapy

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Systemic and vascular inflammation are thought to be key mechanisms underlying the increased risk of cardiovascular disease (CVD) in those with HIV-infection [1, 2]. Antiretroviral therapy (ART) reduces, but does not necessarily normalize, systemic inflammation [3]. As such, adjunctive strategies to further reduce inflammation may be helpful in mitigating the risk of CVD in HIV.

In a single-arm, open-label, eight week, pilot study, we reported that pentoxifylline (PTX) reduced circulating levels of interferon-γ-induced protein 10 (IP-10) and soluble vascular cell adhesion molecule-1 (sVCAM-1) and improved endothelial function (measured as flow-mediated dilation (FMD) of the brachial artery) in HIV-infected patients not receiving ART [4]. However, in a randomized, placebo-controlled trial of PTX in a similarly untreated population, we did not confirm that PTX reduced inflammation or improved endothelial function [5]. In fact, PTX unexpectedly led to significantly increased circulating soluble tumor necrosis factor-1 (sTNFR1) levels compared to placebo in this trial. However, the potential effects of PTX on FMD and inflammation in a population initiating ART are unknown. Thus, we conducted a randomized, placebo-controlled, single-center pilot trial of PTX 400mg thrice daily given for 48 weeks in patients concurrently initiating ART (ClinicalTrials.gov NCT00864916).

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Study conception and design: Gupta, Dubé, Stein, Liu
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The eligibility criteria, procedures, and methods in the current study were similar to our previous trial in patients not receiving ART [5]. Participants were instructed to start ART, as chosen by the primary HIV provider, and the study drug together at study entry. Study visits occurred at Weeks 0, 8, 24, and 48. No restrictions were made on the ART components or initial CD4 cell count. The primary endpoint was change in brachial artery FMD was measured using B-mode ultrasound after 5 minutes of forearm cuff occlusion to a supra-systolic pressure, as previously described [5]. All scans were performed by a certified sonographer and read at the University of Wisconsin, the brachial artery reactivity testing reading center for the NHLBI HIV-CVD collaborative, by a single reader [5]. This trial was approved by the Indiana University Institutional Review Board; all participants provided written, informed consent. The use of pentoxifylline for the purpose of reducing inflammation and improving endothelial function is unlabeled and considered investigational.

Linear mixed-effects models were constructed to evaluate changes in FMD and the circulating biomarkers both between groups and over time. Additional models were constructed to evaluate the effects of individual biomarkers (listed in Table 1), baseline brachial artery diameter, CD4 cell count, and HIV-1 RNA levels on changes in FMD. We also constructed linear mixed effects models assessing treatment group by week interactions and including HIV-1 RNA levels at each study visit as a covariate. Two-sided P-values <0.05 were considered statistically significant.

We enrolled 19 participants (10 in the PTX group, 9 in the placebo group). At weeks 8, 24, and 48, the numbers of participants remaining in the PTX and placebo arms were, respectively, 9 and 7, 8 and 6, and 4 and 5. The baseline characteristics of the enrolled participants are shown in Table 1. The two study groups were balanced. The majority of the study participants were black men with over half being current smokers. Table 1 shows the baseline brachial artery diameter, FMD, and nitroglycerin-mediated dilation (NTGMD) values at each time point. The changes in FMD (SD) in the PTX vs. the placebo groups at weeks 8, 24, and 48 were, respectively, −3.60% (2.54) vs. 1.91% (2.46), 0.72% (3.71) vs. 1.07% (1.77), and 0.01 (3.22) vs. 2.23 (1.42). In all models constructed comparing these changes in FMD, even after adjustment for changes in HIV-1 RNA levels, we did not find significant differences between the PTX and placebo groups at any time point. There were also no significant changes between groups or over time in all models for nitroglycerin-mediated dilation (NTGMD).

In our models assessing the changes in the circulating biomarkers, we found smaller declines from baseline in the PTX group vs. the placebo group in levels of monocyte chemoattractant protein-1 (MCP-1, pg/mL) [week 8: −68.18 (83.61) vs. −242.64 (180.66), P=0.01; week 24: −30.04 (129.17) vs. −225.71 (181.28), P=0.027; and week 48: −61.90 (113.69) vs. −202.02 (185.62), P=0.077] and interleukin-6 (IL-6, pg/mL) [week 8: −1.27 (1.57) vs. −2.73 (3.91), P=0.30; week 24: −0.29 (2.23) vs. −2.28 (3.46), P=0.033; and week 48: −0.12 (0.41) vs. −3.13 (3.26) (P=0.045) but trends towards greater declines in levels of asymmetric dimethylarginine (ADMA, μmol/L) in the PTX group compared to the placebo group [week 8: −0.27 (0.17) vs. −0.16 (0.12), P=0.12; week 24: −0.31 (0.19) vs. −0.15

(0.07), P=0.03; and week 48: −0.35 (0.25) vs. −0.18 (0.15), P=0.06]. There were no significant changes between groups in the other biomarkers assessed at any time point.

There was one serious adverse event in the PTX group (suicidal ideation with overdose of a non-study drug which did not result in death) but none in the placebo group. There was a non-significantly higher number of gastrointestinal adverse events (nausea, flatus, diarrhea) with PTX (6 of 10 participants) compared to placebo (2 of 9 participants), none of which were treatment-limiting.

In this pilot, randomized, placebo-controlled trial, we did not find that PTX improved endothelial function in HIV-infected patients over the first year of ART. These results are in line with our previous trial in patients not receiving ART. However, in the current trial, we found that PTX may attenuate reductions in MCP-1 and IL-6 and possibly greater reductions in ADMA compared to placebo. We did not find any significant effects of PTX on sTNFR1 as we had in our previous trial of PTX in patients not receiving ART. To our knowledge, these potential effects of PTX on the proatherogenic molecules MCP-1, IL-6, and ADMA have not previously been described. Although we cannot fully explain these latter results, these data add to our previous trial in those not receiving ART that PTX may have mixed and potentially adverse effects on inflammatory and endothelial activation pathways. Our results are limited by the small sample size, so they must be considered exploratory as we cannot exclude the possibility a larger, longer study or one that involved patients chronically treated with ART may have found an effect of PTX on vascular function. We acknowledge that the numbers of statistical tests performed may have led to false positive findings, especially in regards to the biomarker comparisons.

Because PTX is considered safe and very well-tolerated [5–7], it has been considered an ideal anti-inflammatory agent for chronic inflammatory conditions. For this reason, it is currently being studied in trials in HIV-uninfected patients for non-alcoholic steatohepatitis, irritable bowel syndrome, chronic kidney disease, and congestive heart failure (ClinicalTrials.gov). However, the lack of improvement in endothelial function and the potentially worrisome effects on several proatherogenic inflammatory molecules in our trials should be considered before using PTX in future trials in HIV-infected patients.

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REFERENCES

1. Duprez DA, Neuhaus J, Kuller LH, Tracy R, Belloso W, De Wit S, et al. Inflammation, Coagulation and Cardiovascular Disease in HIV-Infected Individuals. PLoS ONE. 2012; 7:e44454. [PubMed: 22970224]
2. Subramanian S, Tawakol A, Burdo TH, Abbara S, Wei J, Vijayakumar J, et al. Arterial inflammation in patients with HIV. JAMA. 2012; 308:379–386. [PubMed: 22820791]
3. Wolf K, Tsakiris DA, Weber R, Erb P, Battegay M. Antiretroviral therapy reduces markers of endothelial and coagulation activation in patients infected with human immunodeficiency virus type 1. J Infect Dis. 2002; 185:456–462. [PubMed: 11865397]
4. Gupta SK, Johnson RM, Mather KJ, Clauss M, Rehman J, Saha C, et al. Anti-inflammatory treatment with pentoxifylline improves HIV-related endothelial dysfunction: a pilot study. AIDS. 2010; 24:1377–1380. [PubMed: 20559042]
5. Gupta SK, Mi D, Dube MP, Saha CK, Johnson RM, Stein JH, et al. Pentoxifylline, inflammation, and endothelial function in HIV-infected persons: a randomized, placebo-controlled trial. PLoS One. 2013; 8:e60852. [PubMed: 23593327]
6. Dezube BJ, Pardee AB, Chapman B, Beckett LA, Korvick JA, Novick WJ, et al. Pentoxifylline decreases tumor necrosis factor expression and serum triglycerides in people with AIDS. NIAID AIDS Clinical Trials Group. J Acquir Immune Defic Syndr. 1993; 6:787–794. [PubMed: 8099612]
7. Sliwa K, Woodiwiss A, Kone VN, Candy G, Badenhorst D, Norton G, et al. Therapy of ischemic cardiomyopathy with the immunomodulating agent pentoxifylline: results of a randomized study. Circulation. 2004; 109:750–755. [PubMed: 14970111]

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Table 1

Baseline (Week 0) characteristics of the study groups and vascular measures during the trial.

Baseline Characteristics		**Total (n=19)**	**PTX (n=10)**	**Placebo (n=9)**	**P-value**
Age, years		36 (10.6)	38 (12.1)	34 (8.8)	0.44
Male sex, n (%)		16 (84%)	9 (90%)	7 (78%)	0.58
Black race, n (%)		12 (63%)	5 (50%)	7 (78%)	0.35
Current smoker, n (%)		11 (58%)	7 (70%)	4 (44%)	0.37
Body mass index, kg/m^2		26.9 (6.3)	25.4 (4.1)	28.5 (8.1)	0.39
CD4 cell count/μL		230 (191)	208 (225)	252 (161)	0.56
CD3+CD8+CD38+HLA-DR+ cells, %		49.4 (14.8)	52.9 (9.7)	45.0 (19.2)	0.19
HIV-1 RNA log_{10}copies/mL		4.97 (0.79)	5.10 (0.91)	4.82 (0.65)	0.45
MCP-1, pg/mL		346.07 (164.31)	271.02 (101.84)	429.46 (184.97)	0.06
hsCRP, mg/mL		4.07 (9.79)	1.67 (2.26)	6.74 (13.95)	0.13
ADMA, μmol/L		0.71 (0.19)	0.78 (0.22)	0.64 (0.12)	0.24
IL-6, pg/mL		3.74 (2.9)	2.86 (1.31)	4.71 (3.86)	0.26
sVCAM-1, ng/mL		1148.8 (379.0)	1227.7 (373.7)	1061.2 (387.1)	0.35
sTNFR1, pg/mL		1074.8 (317.8)	1071.2 (394.8)	1078.9 (227.6)	0.96
sTNFR2, pg/mL		10199.3 (4001.0)	10882.2 (3956.6)	9440.5 (4144.5)	0.45
IP-10, pg/mL		609.6 (244.6)	602.6 (246.9)	617.5 (256.8)	0.93
Total cholesterol, mg/dL		135.5 (24.2)	130.7 (23.4)	140.8 (25.5)	0.36
HDL-C, mg/dL		35.8 (10.2)	36.4 (12.2)	35.2 (8.2)	0.93
LDL-C, mg/dL		77.3 (21.6)	70.9 (21.1)	84.5 (21.0)	0.18
Triglycerides, mg/dL		111.3 (66.9)	116.7 (78.6)	105.3 (55.2)	0.95
HOMA-IR		1.74 (1.06)	1.75 (0.89)	1.73 (1.32)	0.97
Urine protein/creatinine, g/g		16.96 (16.93)	9.34 (5.48)	25.43 (21.39)	0.09
Urine albumin/creatinine, mg/g		5.0 (10.0)	2.0 (2.0)	9.0 (14.0)	0.16
Estimated GFR, $mL/min/1.73^2$		89.6 (21.7)	89.2 (23.0)	90.1 (21.6)	0.93
Vascular parameters during the trial					
Brachial artery diameter, cm	Week 0	0.44 (0.06)	0.43 (0.06)	0.44 (0.06)	0.56

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Baseline Characteristics		Total (n=19)	PTX (n=10)	Placebo (n=9)	P-value
	Week 8	0.45 (0.06)	0.45 (0.08)	0.46 (0.04)	0.57
	Week 24	0.47 (0.05)	0.46 (0.07)	0.48 (0.02)	0.43
	Week 48	0.50 (0.06)	0.50 (0.10)	0.50 (0.01)	0.90
Flow-mediated dilation, %	Week 0	4.27 (3.49)	4.43 (2.58)	4.07 (4.57)	0.41
	Week 8	4.24 (2.54)	4.60 (2.71)	3.77 (2.45)	0.66
	Week 24	3.91 (3.65)	4.44 (4.65)	3.16 (1.71)	0.85
	Week 48	2.81 (2.15)	2.25 (2.92)	3.36 (1.44)	0.42
Nitroglycerin-mediated dilation, %	Week 0	18.21 (7.69)	18.40 (9.01)	17.95 (5.97)	0.90
	Week 8	16.64 (6.69)	16.03 (7.64)	17.5 (5.84)	0.71
	Week 24	15.11 (5.30)	16.25 (5.18)	13.52 (5.62)	0.41
	Week 48	14.21 (4.64)	11.54 (3.69)	16.88 (4.34)	0.18

Data presented as means (SD) or as n (%). Student's t-tests and associated P-values were used for comparison between the pentoxifylline (PTX) and placebo groups. GFR estimated using the 2012 CKD-EPI creatinine-cystatin C combined equation. At weeks 8, 24, and 48, the numbers of participants remaining in the PTX and placebo arms were, respectively, 9 and 7, 8 and 6, and 4 and 5.

MCP-1, monocyte chemoattractant protein-1; hsCRP, high sensitivity C-reactive protein; ADMA, asymmetric dimethyl arginine; IL-6, interleukin-6; sVCAM-1, soluble vascular cell adhesion molecule-1; sTNFR1, soluble tumor necrosis factor receptor 1; IP-10, interferon-gamma-inducible protein-10; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance