LbPeB9018

A PROSPECTIVE, MULTICENTER, RANDOMIZED TRIAL COMPARING THE EFFICACY AND SAFETY OF FENOFIBRATE VERSUS PRAVASTATIN IN HIV-INFECTED SUBJECTS WITH LIPID ABNORMALITIES: ACTG 5087

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Background: There is growing concern that the metabolic complications associated with HIV and antiretroviral therapy may lead to accelerated coronary artery disease. In addition to non-reversible risk factors such as male sex, age > 40, and family history of premature coronary heart disease (CHD), other traditional cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and visceral fat accumulation are increasingly seen in HIV patients on HAART. These patients may also be smokers and have a sedentary lifestyle, both of which predispose to significant CHD. Current studies examining CHD risk in HIV patients are limited by their retrospective nature, short duration, and confounding factors. It seems prudent to treat all HIV infected individuals as the general population per the recommendations of the National Cholesterol Education Program (NCEP). NCEP currently recommends that the optimum LDL should be less than 100 mg/dL and triglycerides (TG) less than 200 mg/dL. In addition, NCEP recommends intensive therapeutic changes for individuals with the "metabolic syndrome", a condition defined as the presence of 3 or more of the following: abdominal obesity, hypertriglyceridemia (TG > 150 mg/dL), hypertension (> 130/85 mmHg), glucose intolerance (FBS > 110 mg/dL) and prothrombotic states. Statins are the preferred lipid-lowering drug of choice for lowering LDL, whereas fibrates are the drug of choice for lowering TG. Combination therapy has been recommended for those who fail to respond to either class of medication alone. The safety and efficacy of these approaches in persons with HIV infection, particularly those taking potent antiretroviral therapy, are not known. Therefore, a randomized trial comparing the NCEP-recommended approaches was warranted in persons with HIV infection. Pravastatin and fenofibrate were chosen as the agents of choice given their lack of metabolism by the cytochrome p450 system and PK studies suggesting that these drugs would be safe and tolerable in patients on potent antiretroviral therapy.

Objective: To determine whether fenofibrate and pravastatin are equivalent with respect to clinical response and the safety of these agents in the treatment of HIV-related dyslipidemia at week 12

Methods: A randomized, open-label, 48-week clinical trial. HIV-infected persons with dyslipidemia (LDL ≥ 130 mg/dL and TG ≥ 200 mg/dL) on potent antiretroviral regimens for > 6 months were randomized to receive either pravastatin 40 mg po daily (P) or micronized fenofibrate 200 mg po (F) daily. Subjects who had failed to reach the NCEP goal (a composite of LDL, HDL, and TG levels, taking into account pre-existing CV risk factors) by week 12 received both P and F and were followed for a total of 48 weeks. Enrollment was suspended prior to targeted accrual (630) after the initial review by a DSMB concluded that, since insufficient numbers of subjects in both single-agent treatment arms met pre-specified lipid goals, all subjects should be offered dual-agent therapy.

Results: 86 subjects were randomized to receive P and 88 to receive F. See Tables 1 and 2 for baseline characteristics. 170/174 subjects had available 12-week lipid data. See Tables 3 and 4. At week 12, 4 subjects (5%) on P achieved the NCEP composite goal and 1 (1%) subject on F achieved goal. 30 (36%) of P recipients met LDL goals; 8 (9%) of F subjects met LDL goal ($p < 0.001$). 41 (49%) of subjects on P met HDL goals, whereas 57 (66%) of subjects on F met HDL goal ($p < 0.05$). 15 (18%) of subjects on P met TG goal, whereas 42 (48%) of subjects on F met TG goal ($p < 0.001$). Median changes in LDL/HDL/TG were –30/0/–27 and +13/+4/–118 mg/dL in subjects receiving P and F, respectively (p-values for treatment difference were all significant). 136 subjects subsequently went on dual therapy. Four subjects (3F, 1P) discontinued therapy due to protocol-defined toxicities in the first 12 weeks. There were no reports of rhabdomyolysis.

Table 1: Baseline Characteristics by Treatment, Demographics

	Total	%	Fenofibrate	%	Pravastatin	%	p-value
Gender							1
Male	159	91	80	91	79	92	
Female	15	9	8	9	7	8	
Race/Ethnicity							0.765
White	114	66	55	63	59	69	
Black	18	10	10	11	8	9	
Hispanic	38	22	20	23	18	21	
Asian	2	1	2	2	0	0	
American Indian	2	1	1	1	1	1	
IV drug history							0.793
Never	158	91	81	92	77	90	
Currently	2	1	1	1	1	1	
Previously	14	8	6	7	8	9	
Age at Baseline							0.612
< 25 years	2	1	2	2	0	0	
25-34 years	18	10	11	13	7	8	
35-44 years	90	52	43	49	47	55	
45-54 years	57	33	29	33	28	33	
over 55 years	7	4	3	3	4	5	
CD4+T-cell (cells/μL)							0.176
median	442		416		462		
range	23-1843		23-1480		91-1843		
HIV–1 RNA log copies/mL							0.563
median	1.7		1.7		1.7		
CV Risk Factor							1
< 2 Risk Factors	89	51	45	51	44	51	
≥ 2 Risk Factors	85	49	43	49	42	49	

Table 2: Distribution of Baseline Lipid Measures by Treatment

	Total (n = 174)	Fenofibrate (n = 88)	Pravastatin (n = 86)	p-value[a]
Cholesterol (mg/dL)				0.544
Mean	279.49	279.81	279.17	
Standard deviation	57.6	53.13	62.15	
Min, Max	183, 639	185, 531	183, 639	
Median	270	275.5	261.5	
IQR	246.00, 302.00	242.50, 307.50	246.00, 292.00	
LDL (mg/dL)[b]				0.184
Mean	157.18	154.49	159.93	
Standard deviation	37.59	39.06	36.05	
Min, Max	58, 291	58, 291	67, 248	
Median	154.5	149.5	162	
IQR	132, 179	132, 179	136, 179	
HDL (mg/dL)				0.43
Mean	34.62	34.08	35.17	
Standard deviation	7.62	7.97	7.25	
Min, Max	6, 54	6, 54	21, 52	
Median	34	34	34	
IQR	30, 39	30, 39	31, 39	
Triglycerides (mg/dL)				0.728
Mean	417.66	412.58	422.85	
Standard deviation	358.92	325.36	392.15	
Min, Max	118, 3,324	118, 2,516	129, 3,324	
Median	325.5	336.5	311.5	
IQR	274, 474	243, 472	251,475	
Non-HDL/HDL ratio				0.414
Mean	7.60	7.82	7.38	
Standard devi ation	3.24	3.65	2.75	
Min, Max	3.89, 29.83	3.89, 29.83	4.14,23.58	
Median	6.98	7.16	6.91	
IQR	5.95, 8.51	6.11, 8.60	5.70,8.51	

[a]Kruskal-Wallis Test
[b]measured by ultracentrifugation

Table 3: Lipid Reduction at Week 12 by Treatment

	Total	Fenofibrate	Pravastatin	p-value[a]
Change of Cholesterol				< 0.001
Mean (std dev)	-33.08 (52.95)	-18.56 (42.54)	-48.3 (58.49)	
Min, Max	-392, 141	-125,141	-392, 28	
Median	-30	-15	-41	
Change of LDL				< 0.001
Mean (std dev)	-10.22 (43.46)	9.24 (41.76)	-30.63 (35.23)	
Min, Max	-129, 97	-92, 97	-129, 55	
Median	-11	13	-30	
Change of HDL				< 0.001
Mean (std dev)	2.28 (7.18)	4.22 (7.23)	0.25 (6.58)	
Min, Max	-17, 29	-15, 29	-17, 22	
Median	2	4	0	
Change of Triglycerides				< 0.001
Mean (std dev)	-108.1 (318.34)	-138.46 (212.79)	-76.28 (399.21)	
Min, Max	-3,027, 507	-1,447, 408	-3,027, 507	
Median	-77	-118	-27	
Change of non-HDL				0.002
Mean (std dev)	-35.36 (52.63)	-22.78 (42.55)	-48.55 (58.87)	
Min, Max	-397, 133	-133, 133	-397, 36	
Median	-34	-18	-43	
Change of non-HDL/HDL Ratio				0.94
Mean (std dev)	-1.09 (3.87)	-1 (3.87)	-1.19 (3.88)	
Min, Max	-16.61, 31.17	-9.56, 31.17	-16.61, 25.58	
Median	-1.25	-1.23	-1.27	

[a]Kruskal-Wallis Test

Table 4: Response Frequency by Treatment

	Total	%	Fenofibrate	%	Pravastatin	%	p-value[a]
LDL/HDL/TG							0.203
Non-Responder	165	97	86	99	79	95	
Responder[b]	5	3	1	1	4	5	
LDL							< 0.001
Non-Responder	132	78	79	91	53	64	
Responder[c]	38	22	8	9	30	36	
HDL							0.043
Non-Responder	72	42	30	34	42	51	
Responder[d]	98	58	57	66	41	49	
Triglycerides							< 0.001
Non-Responder	113	66	45	52	68	82	
Responder[e]	57	34	42	48	15	18	

[a]Fisher's Exact Test; [b]Met all three criteria defined in footnotes c-e
[c]LDL ≤ 100 mg/dL (≥ 2 CV risk factors) or < 130 mg/dL (< 2 CV risk factors)
[d]HDL ≥ 35 mg/dL
[e]TG < 200 mg/dL (entry TG 200-800 mg/dL) or TG < 400 mg/dL (entry TG > 800 mg/dL)

Conclusion: Monotherapy with either P or F for HIV-related dyslipidemia appears safe but unlikely to achieve composite NCEP goal. P appears to be most effective in lowering LDL, while subjects receiving F had larger increases in HDL and decreases in TG. Dual therapy with P and F is being evaluated for effectiveness at achieving composite NCEP goal. Future analyses will include response rates to combination lipid-lowering therapy at weeks 28 and 48; analysis of response rates by type of background antiretroviral therapy; and safety of combined therapy. Although response rates to all three NCEP criteria were low, reductions in cholesterol, triglyceride and LDL were similar to those observed in trials of lipid-lowering therapy in non-HIV-infected persons. Treatment of HIV-infected persons with dyslipidemia should be individualized.

Acknowledgment: This research was supported by grants from the National Institutes of Allergy and Infectious Diseases AIDS Clinical Trials Group. Judith A. Aberg, MD, Washington University, 314 454-0058, jaberg@im.wustl.edu