Fenofibrate Induces Plaque Regression in Hypercholesteremic Atherosclerotic Rabbits: In Vivo Demonstration by High-Resolution Magnetic Resource Imaging

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Introduction: Fenofibrate has shown to reduce major cardiovascular events and slow angiographic progression of coronary atherosclerosis. Its postulate mechanism of action is through activation of peroxisomal proliferator-activated receptor-alpha, a nuclear transcrption factor that controls a variety of cellular functions. We investigated the antiatherogenic effects of fenofibrate on previously established experimental atherosclerotic (AT) lesions.

Method AT-lesions were induced in NZW rabbits (n=24) by a combination of double balloon-injury and 9-month hypercholesterolemic (HC) diet. At the end of the AT-induction period all rabbits underwent MRI and 7 of them were sacrificed, processed for histology, and served as AT-control. The remaining animals were randomized into 3 groups: [1] resuming standard chow (n=5), [2] HC-diet-placebo (n=6) and [3] HC-diet-fenofibrate (n=6). Rabbits underwent an additional MRI after 6 months of treatment, and then were sacrificed for histopathology analysis.

Results MRI showed that all groups had similar vessel wall area (VWA) at randomization. Significant increase in VWA was seen in the HC-diet-placebo group (15%±4%, p=0.007 vs. baseline). In the group resuming standard chow, progression was abolished (-2.5±3%, p=0.37 vs. baseline). The fenofibrate group had significant plaque regression (-11±4%, p=0.041) despite maintained HC-diet. Plasma lipid levels were normalized in standard chow group, whereas they remained elevated in both, the HC-diet-placebo and HC-diet-fenofibrate groups. Histopathologic analysis, to define vascular biology of the different treatment groups, is under investigation.

Conclusion Our data indicate that normalization of plasma lipid levels abolishes athero-sclerotic progression. Fenofibrate allodates regression of atherosclerotic lesions independently of the plasma lipid levels. These observations support the lipid-independent mechanism of action and the anti-atherogenic benefits of fenofibrate, supporting the potential antiatherotrophic effect of PPAR-alpha agonists.

E-Selectin and P-Selectin Are Markers of Aortic Plaque Burden as Measured by Transesophageal Magnetic Resource Imaging

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Background: Cytokine expression is a major factor in the progression of atherosclerotic plaque formation. We hypothesized that serum levels of CAMS are directly related to atherosclerotic plaque burden and change in conjunction with a reduction in aortic plaque burden induced by statin therapy.

Methods: Baseline and 6 month atherosclerotic plaque volume in the thoracic aorta was measured by combined transesophageal and surface MRI (TEmRI) in 24 patients treated with simvastatin 20-60 mg daily. Lipid levels, serum inflammatory markers [C-reactive protein (CRP)], interleukin-6 (IL-6) and Monocyte Chemoattractant Protein-1 (MCP-1)] and CAMs [E-selectin and P-selectin] were measured at baseline and 6 months. Generalized estimating equation modeling was used to investigate the association between CAMs and aortic plaque burden in 11 patients at 6 months.

Results: Baseline TEMRI plaque volume correlated with E-selectin (r=0.49, p<0.02) and P-selectin (r=0.52, p<0.01). There was no correlation between baseline cholesterol values or serum inflammatory markers and aortic plaque volume. At 6 months, plaque volume was reduced by 13% from 3.5 ± 0.3 cm³ at baseline to 3.0 ± 0.3 cm³ (p<0.02). Total cholesterol and LDL values decreased at 6 months (total cholesterol 210.6 ± 10.2 to 174.1 ± 7.9 mg/dL and LDL 131.7 ± 4.0 to 104.1 ± 6.1 mg/dL, p<0.001 for both). At 6 months the changes in E-selectin and P-selectin were strongly correlated with the decrease in aortic plaque volume (p<0.01).

Conclusions: Baseline aortic atherosclerotic plaque burden by TEMRI correlated better with serum levels of E-selectin and P-selectin than with serum inflammatory markers or cholesterol values. After 6 months of statin therapy, changes in P-selectin and E-selectin were strongly correlated with the reduction in aortic plaque volume as measured by TEMRI.