 EFFECT OF LXR-623, ALONE OR IN COMBINATION WITH SIMVASTATIN, ON REGRESSION AND STABILIZATION OF ATHEROSCLEROTIC PLAQUES: AN MRI STUDY IN A MODEL OF ADVANCED ATHEROSCLEROSIS

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Authors: Chiara Giannarelli, Giovanni Cimmino, Thomas M. Connolly, Borja Ibanez, José M. Garcia Ruiz, Giora Feuerstein, Matilde Alique, Valentin Fuster, Juan Badimon, AtheroThrombosis Research Lab, Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY, Weyth Research, Collegeville, PA

Background: It has been postulated that LXR activation would increase the benefits of LDL-lowering interventions on cardiovascular risk. We studied the effect of LXR-623, an oral LXR agonist, on plaque progression/regression in a model of advanced atherosclerosis.

Methods: Abdominal aortic lesions (9 months 0.2% cho-diet and balloon denudation) were induced in NZW rabbits (n=41). All animals underwent a MRI (baseline) to assess the severity of the induced lesions; then they were randomized to placebo, simvastatin (simva, 5mg/Kg/day), LXR (1.5 and 5 mg/Kg/day) or LXR-623 (1.5 mg/kg) + simva combination. The effect of the treatments was expressed as % change in MRI-plaque burden after 6 months of treatment vs baseline. Plaque composition (macrophages and SMC) was studied by immunostaining.

Results: Simva significantly reduced plaque progression vs placebo. LXR-623 alone induced a similar effect on plaque progression without altering plasma lipids. Preliminary data showed a significant lesion regression by LXR-623+simva combination (Fig 1). Macrophages were significantly (p<0.05) reduced by simva (20%) as well as LXR 5 (18%) and combination (22%) vs placebo. SMC density was unchanged by all treatments.

Conclusions: LXR-623 inhibits lesion progression similar to simvastatin. Of interest, LXR-623+simva combination showed a synergism that regressed previously induced lesions. Our data suggest that LXR-623 is a promising antiatherosclerotic agent, especially when combined with statins.

![Image of MRI plaque progression/regression](image_url)

Figure 1. Effect of LXR-623 on plaque progression/regression
A) Box plots represent the percentage of variation of vessel wall area (VWA, plaque) between the end of the study and pretreatment baseline MRI.
B) Representative MRI images of plaque at baseline and after the combination treatment with LXR-623 and simvastatin. Note the severity of atherosclerotic burden identified by the red surface at baseline and the significant plaque regression after six months of treatment with LXR-623/simvastatin.