Abstract: **P3110**

**Tyrosine kinase inhibitor nilotinib increases atherosclerosis burden in ApoE knock-out mice**

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**Topic(s):**
Basic Science - Vascular Biology and Physiology: Leukocytes, Inflammation, Immunity

**Citation:**
Background. In 2001, imatinib, the 1st generation tyrosine kinase inhibitor (TKI), dramatically improved the treatment and survival of the patients with chronic myeloid leukemia (CML). However, the emergence of imatinib-resistant patients led to the development of 2nd generation TKIs. Nilotinib demonstrated increased efficacy to control CML disease over imatinib and is now recommended as first-line therapy. But arterial occlusive adverse events (AOE) occurs in patients treated with nilotinib and not with imatinib. Mechanisms leading to AOE with nilotinib is not well understood. AOE are dominated by ischemic heart disease and lower extremity arterial disease. Moreover, we demonstrated that CML patients with cardiovascular risk factors are at high risk to rapidly develop AOE with nilotinib.

**Purpose.** To evaluate the impact of nilotinib in a pre-clinical model of atherosclerosis.

**Methods.** ApoE Knock-Out mice (8-week-old) were treated with either placebo (N=10), imatinib (IMA) 200mg/kg/day (N=10) or nilotinib (NILO) 100mg/kg/day (N=10) by daily feeding and a high-fat diet for 12 weeks. Heart and aorta were harvested after sacrifice, for histology staining and immunochemistry. Splenocytes were cultured from collected spleens, and Interleukin (IL) 12p70 and IL10 measured by ELISA.

**Results.** Mice treated with nilotinib showed an increase of atherosclerotic plaque size at the aortic sinus level: 462.1x103 µm\(^2\) vs. 344.4x103 µm\(^2\) with imatinib or 394.9x103 µm\(^2\) with placebo (p<0.05) and at the thoracoabdominal aorta level (p<0.05). Plaques had greater infiltration of macrophages: 33.0±3.4% with nilotinib vs. 7.3±1.3% with imatinib and 12.6±1.1% with placebo (p<0.001) and a larger necrotic nucleus 33.0±3.4% with nilotinib vs. 7.3±1.3% with imatinib or 12.6±1.1% with placebo (p<0.001). Nilotinib modulated the systemic immune response by increasing IL-12p70 and by decreasing IL-10 production by splenocytes after stimulation by LPS-IFN\(\gamma\) whereas IL10 increase was observed with imatinib.

**Conclusion.** Nilotinib has a pro-atherogenic effect in a pre-clinical model of atherosclerosis and increases the monocyte/macrophage pro-inflammatory response. Further experiments are required to identify pathways activated by nilotinib.
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Conclusion. Nilotinib has a pro-atherogenic effect in a pre-clinical model of atherosclerosis and increases the monocyte/macrophage pro-inflammatory response. Further experiments are required to identify pathways activated by nilotinib.