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Oral presentation

Role of the sGC activator ataciguat sodium (HMR1766) in cardiovascular disease

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Background

Soluble guanylate cyclase (sGC), the key transducer of nitric oxide (NO) signaling, exists in two redox forms: the NO sensitive ferrous heme iron (Fe(II)) form and a NO insensitive oxidized form containing the ferric heme iron (Fe(III)). Ataciguat sodium (further named ataciguat) predominantly stimulates the oxidized form of sGC. To further define the therapeutic potential of ataciguat in cardiovascular disease, we investigated its effect in various in vivo models of: platelet aggregation, atherosclerosis and peripheral arterial occlusive disease.

Platelet activation

Thrombus formation in a coronary artery is the acute event in most unstable ischemic coronary syndromes. Ataciguat, which induced no hemodynamic effects, significantly reduced the number of cycles (the readout of thrombus formation) in a canine model of coronary thrombosis (Folts model). In contrast to aspirin, the effect of ataciguat was not abolished by epinephrine, suggesting that ataciguat will be effective under conditions of increased sympathetic tone.

Diabetes mellitus is associated with an increased thromboembolic risk via activation of circulating platelets as well as the development of endothelial and vascular dysfunction. Both effects have been attributed to a lack of nitric oxide (NO) bioavailability and/or reduced sensitivity of sGC for NO. A single intravenous injection of streptozotocine (STZ) to rats induced type I diabetes and attenuated NO-stimulated sGC activity isolated from aorta as compared to the placebo injected control group, while the ataciguat stimulated sGC activity was not different between both groups. Chronic treatment of STZ diabetic rats with ataciguat normalized platelet activation as measured by a reduction of P-selectin expression and an increase in platelet vasodilator stimulated phosphoprotein (VASP) phosphorylation. Activation of sGC by ataciguat normalized vascular function and restored endothelium dependent relaxation in isolated aortic rings from control and placebo treated STZ rats.

Atherosclerosis and endothelial function

An impairment of NO signaling has been shown to be involved in the development of endothelial dysfunction and atherosclerosis. We therefore investigated the effects of ataciguat in a mouse model of atherosclerosis. Apolipoprotein E-deficient (ApoE-/-) mice were fed a high-fat high-cholesterol diet, or the respective diets supplemented with ataciguat. At the end of the treatment periods, there were no significant differences in plasma cholesterol concentrations or blood pressure between the groups. Compared to wild-type mice, placebo-treated ApoE-/- mice developed profound endothelial dysfunction, as indicated by an impaired endothelium-dependent vasodilatation, and severe atherosclerotic lesion forma-

tion in the aortic root and the ascending aorta. In contrast, ataciguat treatment significantly reduced atherosclerotic plaque formation and markedly improved endothelium-dependent vasodilatation. Treatment with ataciguat had no effect on endothelium-independent vasorelaxation or vasoconstriction. Aortic release of reactive oxygen species was increased in ApoE-/- mice as compared to wild-type mice, but was not affected by treatment. Ataciguat led to increased expression of vascular P-VASP, a downstream target of sGC, did not alter eNOS and sGC expression, and reduced vascular VCAM-1 expression.

Peripheral arterial occlusive disease

The main characteristic of stage II peripheral arterial occlusive disease is exercise-induced muscle fatigue. The effect of placebo, ataciguat, cilostazol, and a combination of both treatments was studied in Zucker Diabetic Fatty (ZDF) rats with unilateral hind limb ischemia.

Placebo-treated animals showed marked signs of exercise-induced muscle fatigue, with a mildly reduced contraction force, moderately reduced contraction velocity, severely reduced relaxation velocity, and markedly prolonged time to recovery after 10 min of continuous contractions (80/min). All of these parameters significantly improved to a similar extent in animals treated with either ataciguat, or cilostazol alone. The combination of both treatments showed an even more pronounced reduction of muscle fatigue.

Conclusion

The sGC activator ataciguat inhibits platelet activation in an acute model of coronary thrombosis, normalizes platelet activation and restores endothelial and vascular function in type-I diabetic rats, improves endothelial function and reduces atherosclerosis in ApoE deficient mice, and improves ischemia-induced muscle fatigue in a rat model of peripheral arterial occlusive disease. Based on these data the ACCELA Trial, a 6 months randomized, double-blind, placebo-controlled dose-ranging trial of ataciguat for patients with intermittent claudication, has been initiated.