PDE-4-Inhibitors for treatment of dyslipoproteinemia

Technology

Dyslipoproteinemia is a well-accepted risk factor for atherosclerosis. Atherosclerosis is the leading cause of vascular disease with its major manifestations ischemic heart disease, ischemic stroke and peripheral artery disease. Especially ischemic heart disease is associated with elevated levels of low density lipoprotein cholesterol (LDL-C) and lowering LDL-C has been shown to reduce mortality risk for heart attacks. The same holds true for LDL-triglyceride levels (LDL-TG) which are also associated with coronary artery disease although less research has been conducted studying LDL-TG.

We have shown that an inhibitor of the enzyme phosphodiesterase-4 (PDE-4-I) (roflumilast) lowers LDL-C and LDL-TG levels 4 weeks after initiation of treatment and LDL-C and LDL-TG reductions are maintained with treatment for 8 weeks. Therefore, PDE-4-I may be effective – among other indications - for therapy of dyslipoproteinemia.

Innovation

- New indication for phosphodiesterase-4-inhibitors (PDE-4-Is)
- Roflumilast lowered LDL-C after only 4 weeks and until 12 weeks of treatment
- Roflumilast lowered LDL-TG after only 4 weeks and until 12 weeks of treatment

Application

- PDE-4-Is for prophylaxis and treatment of dyslipoproteinemia / elevated levels of LDL-C and LDL-TG and the decrease of the ratio of LDL to high density lipoprotein (HDL).
- PDE-4-Is for diseases and medical complications related to dyslipoproteinemia (atherosclerosis and its manifestations cardiovascular disease, stroke, peripheral artery disease).

Developmental Status

Pilot study was successful: The PDE-4-I roflumilast lowers LDL-C (- ~20 mg/dl) and LDL-TC in COPD patients treated with standard dose of roflumilast. In other studies (e.g. IMPROVE-IT) additional reductions of LDL-C of 15 mg/dl have been shown to significantly reduce cardiovascular risk.
Next Steps: Validation study with increased number of subjects *ongoing*.
Validation study in animal model *intended*.

Responsible Scientist

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Patent Status

European patent application pending

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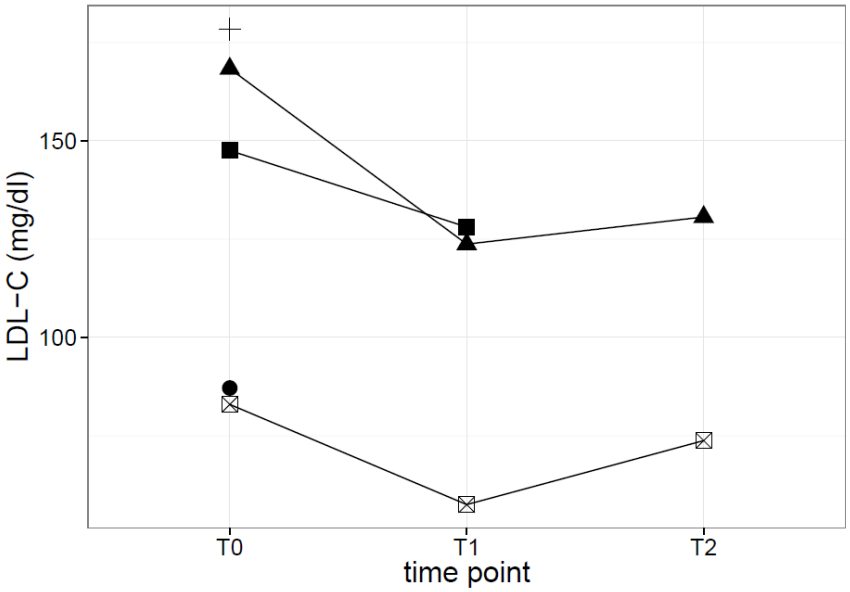
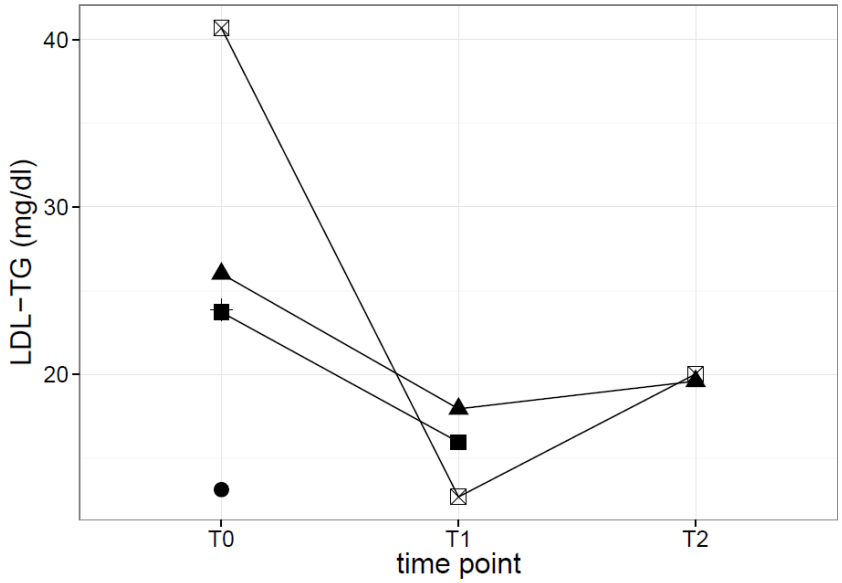
Pilot study

Treatment of 5 subjects with COPD with 500mg/roflumilast every other day until T1 (4 weeks) and 500mg/d from T1 until T2 (8 weeks) (2 dropouts)





Summary:

In this pilot study, subjects treated with PDE-4-I roflumilast had reduced values of LDL-C (- ~20mg/dl) and LDL-TG (- ~12mg/dl) already after treatment with a reduced dose (500mg every other day for 4 weeks). Remarkably, reductions in LDL-C and LDL-TG were observed in all subjects. Reductions were maintained at treatment with full dose (500mg/d) over 8 weeks. Drop-outs occurred due to side effects of roflumilast (n=2) and lost to follow up (n=1). No serious adverse events occurred throughout the course of this study.