Rationale and Design of the Medical Research

Abstracts

A2

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3

RATIONALE AND DESIGN OF THE MEDICAL RESEARCH COUNCIL PRECISION MEDICINE WITH ZIBOTENTAN IN MICROVASCULAR ANGINA (PRIZE) TRIAL MRI SUB-STUDY

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Introduction Microvascular angina is caused by cardiac small vessel disease and dysregulation of the endothelin system is implicated. The chronic elevation of circulating ET-1 in microvascular angina may be influenced by genetic factors. The minor G allele of the non-coding single nucleotide polymorphism (SNP) rs9349379 enhances expression of the endothelin 1 gene in human vascular cells, increasing circulating concentrations of ET-1. The prevalence of this allele is higher in patients with microvascular angina. Zibotentan is a potent, selective inhibitor of the ETA receptor. We have identified zibotentan as a potential disease-modifying therapy for patients with microvascular angina.

The Precision medicine with Zibotentan in microvascular angina (PRIZE) trial is a prospective, randomized, double-blind, placebo-controlled, sequential cross-over trial. We will assess the efficacy and safety of adjunctive treatment with oral zibotentan (10 mg daily) in patients with microvascular angina and assess whether rs9349379 (minor G allele; population prevalence ~36%) acts as a theragnostic biomarker of the response to treatment with zibotentan. The participants will receive a single-blind placebo run-in followed by treatment with either 10 mg of zibotentan daily for 12 weeks then placebo for 12 weeks, or vice versa, in random order.

After randomisation in PRIZE, subjects will be invited to participate in the cardiac MRI sub-study. Myocardial perfusion is generally impaired in patients with microvascular angina. The rationale for undertaking this MRI sub-study is to determine whether, compared with placebo, treatment with zibotentan improves myocardial blood flow.

Methods Patients will undergo multiparametric CMR at three points (baseline prior to therapy and after each 12 week treatment phase). At each scan they will have assessments of myocardial blood flow (both rest and stress using the Kellman quantitative perfusion method), left ventricular function and mass, aortic stiffness assessment and tissue characterisation (T1 mapping (MOLLI and ShMOLLI), T2 mapping and late gadolinium enhancement imaging).

Conclusion PRIZE invokes precision medicine in microvascular angina. Should our hypotheses be confirmed, this developmental trial will inform the rationale and design for undertaking a larger multicentre trial. The MRI sub-study contributes to this study by providing vital mechanistic and safety information.