Imatinib myselate, a specific Bcr-Abl tyrosine kinase inhibitor, is used to treat chronic myelogenous leukaemia and other malignancies, although unfortunately it has been associated with several cases of left ventricular dysfunction and congestive heart failure (Kerkelä R et al., 2006). Most of the approaches used in clinical practice are recognized by clinicians to show low diagnostic sensitivity and predictive power in detecting subclinical myocardial injury. An improved translational approach to assess the extent of drug-induced cardiotoxicity is required. MicroRNAs (miRNA) have been found to play a role in responding to cellular stresses and gene changes following exposure to toxic substances.

The current study was carried out to identify the potential use of miRNA profiling methods in determining a mechanistic based assessment of early stage toxicity in vitro.

Functional parameters and infarct sizes were measured using a Langendorff system. Isolated hearts were subjected to 120 minutes of perfusion in the presence and absence of Imatinib (1µM, n=6). During the experiment haemodynamic parameters were determined and at the end of the experiment hearts were stained with Evans blue and incubated with 2,3,5-triphenyl tetrazolium chloride to determine the infarct size to risk ratio (%). Quantitative real-time PCR (qRT-PCR, Applied Biosystems 7900HT real-time PCR) was used to analyse the expression of mature miRNAs: miR-1, miR-27a, miR-133a and miR-133b relative to the U6 small nuclear RNA in myocardium which was subjected to Imatinib treatment compared to naive vehicle control myocardium over an acute time period for 120 minutes.

Infarct size to risk ratio significantly increased (p<0.05) dose dependently to Imatinib as compared to control (30nM-1000nM, 22.8±1.8% - 37.5±3.6% vs. 14.6±1.1% respectively, EC_{50} = 51nM). In response to Imatinib (1µM) treatment, three miRNAs showed significant differential expression. MiRNA-1, miRNA-27a and miRNA-133b showed significant alteration in expression compared to naive myocardium in response to Imatinib treatment: (fold change: miR-1 = 5.9; miR-27a = 4.5; miR-133b = 4.6, P<0.01,n=6)

To our knowledge this is the first study to show the differential expression signatures of miRNA-1, miRNA-27a and miRNA-133b in the myocardium following exposure to Imatinib. We are currently investigating the potential of these microRNAs for use as early translational biomarkers for drug induced cardiotoxicity.

Reference