Scottish Government Health Directorates Chief Scientist Office

CHIEF SCIENTIST OFFICE

FOCUS ON RESEARCH

TITLE

Researchers
Dr Duncan Porter, Prof Iain McInnes, Dr Carl Goodyear, Dr Pawel Herzyk, Dr Steve Young

Aim
The aim of the project was to identify biomarkers in the blood of patients with rheumatoid arthrits (RA) that predict the response to two types of biologic therapy – rituximab (B cell depletion) and TNF inhibitor (TNFi) therapy.

Project Outline/Methodology
The ORBIT study was the first investigator-initated randomised controlled trial to compare TNFi and rituximab therapy in patients with RA. It was conducted in 35 centres across the UK, and found that rituximab is as effective as TNFi therapy. Many patients repsonded well to their first drug, but others had to be switched to the other drug because they had not responded well to the first drug. If it were possible to predict which patient would respond to which drug, this would improve the quality of care delivered to the patient, and would save the NHS money.

Metabolomics and transcriptomics are disciplines that study all the small molecules (metabolites) or gene expression products (transcripts) in a patient's blood. This study analysed the metabolome and transcriptome in baseline blood samples taken from patients who took part in the ORBIT study, and explored whether there were any patterns that predicted drug response.

The cohort of patients was split into two (70%/30%). The larger (70%) group was used to 'train' a predictive model using complex machine learning techniques. The resultant model was then tested on the smaller (30%) group to test how well the model predicted response in patient samples which had not been used to train the model.

Key Results
Three gene sets were identified that predicted 1) general responsiveness to both rituximab and TNFi therapy 2) drug-specific response to rituximab 3) drug-specific response to TNFi therapy. The gene sets predicted response with high sensitivity and specificity in the 'test' group.

Analysis of the metabolome found that metabolite levels are strongly influenced by factors surrounding sample collection. Some samples had been processed and frozen immediately after being obtained; a sub-group analysis of these samples suggested that there might be a small number of unidentified metabolites that are predictive of response, but further work will be required to confirm this.

Conclusions
In patients with RA, it is possible to predict response to rituximab, TNFi, or both using the number of transcripts derived from small sets of genes.

What does this study add to the field?
At the moment, patients and doctors must select treatments on a trial and error basis, because there is no effective way to predict patients' response to therapy – some patients respond better to one drug, and other patients respond better to another. The identification of predictive biomarkers in this study paves the way for the development of 'stratified' or 'personalised' medicine because it could be possible to tailor treatment to individual patients on the basis of their gene expression profile.

Implications for Practice or Policy
Personalisation of treatment has the potential to improve patients' quality of life, by reducing the risk of being treated with a drug that proves to be ineffective for them. It will also be more cost effective because the NHS will spend less money on ineffectve therapy.

Where to next?
The findings in this study must be replicated in other patients. If the results are confirmed, work will be needed to develop a robust, cost effective diagnostic kit that can measure the gene expression profile in patients, so that the most effective treatment for that patient can be prescribed.

Further details from:
Dr Duncan Porter duncan.porter@glasgow.ac.uk