Gene profiling can help predict treatment response and could save money in RA

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Two new studies presented at the European League Against Rheumatism Annual Congress (EULAR 2016) have shown that the use of gene profiling designed to predict a positive response to treatment in rheumatoid arthritis (RA) patients is following the lead from its use in cancer treatment. Prompt identification of those RA patients not responding to treatment supports timely switching to alternative treatment, reducing the chance of long-term joint damage and avoiding money being wasted on ineffective drugs.

The latest innovations in developing personalised medicine for RA patients come from two gene profiling studies, which identified early predictors of response to treatment from blood samples as follows:

- A distinctive pattern of changes in gene expression occurs in those RA patients who have a good-response to a TNF inhibitor at three months, but not in non-responders
- A specific genetic marker influences response to therapy in the early stages of RA; a link thought to be due to the gene activating a cell-signalling protein involved in the inflammatory disease process.

Faced with an increasing choice of different biologic therapies, rheumatologists have a critical need for better tools to inform their management of RA. Despite the revolutionary impact of anti-TNF treatments on RA patients, good disease control is only achieved in 30% of patients. The ability to identify those patients unlikely to respond to

first-line biologic anti-TNF therapies prior to their treatment would allow these patients to be prescribed alternative therapies, providing faster relief of symptoms and reducing the risk of future complications.

There is now a large body of information about the genetic basis of RA, and it seems likely that genetic variation will become useful in predicting treatment response, with the ultimate aim of developing diagnostic and prognostic gene tests that achieve clinical validation, regulatory approval and widespread adoption.5

Genomic profiling identifies responders to adalimumab

According to lead author Mr James Oliver of the Arthritis Research UK, Centre for Genetics and Genomics, Centre for Musculoskeletal Research, University of Manchester, UK, "in current clinical practice, RA drugs are administered on a trial and error basis; there are no clinical biomarkers of response to guide treatment decisions. While non-responding patients can be switched to alternative therapies at three months, many remain on ineffective therapy for longer periods.

"Having a blood-based biomarker for good-response to anti-TNF treatment at three months would support timely switching in patients whose disease activity is not controlled by a particular drug, reducing the impact of long-term joint damage and facilitating more responsible spending on RA drug treatment. Gene expression biomarkers are being successfully used to guide therapy decisions in the field of cancer. Therefore gene expression analysis should be explored and included in future efforts to personalise therapy in RA," Mr Oliver concluded.

Gene expression profiling was performed on blood samples taken from 70 RA patients: 50 of whom had shown a good response to the anti-TNF

biologic treatment adalimumab, 20 of whom had shown no response to this drug. The samples were taken at the start of treatment (baseline) and three months later; treatment response was assessed using ACR/EULAR criteria.

Evaluation of the levels of gene expression in these blood samples showed a distinct change in RA patients who had responded to treatment. However, there were no significant differences in gene expression between baseline and three months in the non-responders. Further analysis of the genes that had been stimulated in the responders revealed that they were involved in immune cell function relevant to the inflammatory disease process in RA.

RA patients with specific genetic marker less likely to respond to treatment

"Our findings show that a specific genetic marker (known as allele*2 of the HS1,2A enhancer region) influences not just disease activity in RA patients, but also response to therapy in the early stages of their disease," said lead investigator Dr Gabriele Di Sante of the Institute of Rheumatology and Related Sciences, Catholic University of the Sacred Heart, Rome, Italy. This genetic biomarker should be further tested as a possible contributor to personalised therapy in RA," he added.

Previous research has identified the role of the HS1,2A enhancer genetic marker in several autoimmune chronic inflammatory diseases. , Interest in its potential role as a predictor of disease activity and treatment response was heightened by the demonstration that one specific gene (allele*2) in the HS1,2A enhancer region has a binding site for the cell-signalling protein known as NF-kB, which is not present in an alternative gene (allele*1) in this region. NF-kB is known to be involved in the inflammatory disease process in RA.

Genotyping of a population of 329 patients with early RA revealed just over one-quarter had the allele*2 HS1,2A enhancer, and one in 10 the allele*1 HS1,2A enhancer, which is comparable with previously published data.7 Patients with the allele*2 genotype had more active disease at the start of treatment and were significantly less likely to achieve a good response and/or remission after three months treatment than those patients with the allele*1 genotype.

Moreover, at six months follow-up, a higher percentage of subjects carrying the allele*2 genotype needed an additional TNF-blocker compared to patients without the allele*2 genotype.

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