

Article Title: Gene expression profiling identifies classifier of methotrexate non-response and pathways relevant to treatment outcome in patients with rheumatoid arthritis.

Plant et al, Arthritis and rheumatology 2019

Plain English title: Using gene profiling at 4 weeks to identify people unlikely to benefit from methotrexate therapy

Affecting over 400,000 adults in the UK, rheumatoid arthritis (RA) is a common disease that causes pain, swelling and damage in the joints. Once a patient develops RA symptoms, treatment typically begins with low dose methotrexate (MTX) to control inflammation. However, MTX fails to reduce RA symptoms in approximately 30-40% of patients who receive this drug. Depression, disability, a high number of tender joints and a positive serum rheumatoid factor test result are all associated with poor response to MTX. However, these factors are not sufficiently predictive to be useful in a clinical setting.

Not all genes are switched on (expressed) all of the time and some may become active only in specific situations, such as in the presence of inflammation. We can assess whether genes are active or not by performing gene expression studies that measure the amount of gene product. The aim of the current study was to develop a test based on levels of gene expression present in the blood that is predictive of MTX non-response. The study included patients recruited to the Rheumatoid Arthritis Medication Study (RAMS). We measured levels of over 20 thousand genes in the blood of 85 RA patients about to receive MTX, and again following 4-weeks on treatment. Next we used state-of-the-art machine learning statistical methods to assess how well gene expression levels predicted clinical response to MTX, measured following 6-months on drug.

By taking the difference in gene expression values between pre-treatment and 4-weeks we were able to develop a highly predictive test, which was able to identify patients unlikely to respond to MTX with an accuracy that could be clinically useful. If these findings are confirmed in a separate set of patient samples, it would provide an early indicator (at 4 weeks) of response to MTX by 6 months. Patients unlikely to respond based on testing at 4 weeks could be switched quickly to an alternative treatment. These data also show how machine learning* approaches can help to identify signatures of treatment response in inflammatory diseases.

* Machine learning – this is a method of analysis where computers learn from the data to using artificial intelligence (AI) to become more accurate in predicting clinical outcomes.

<https://doi.org/10.1002/art.40810>