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Three gene sets could predict response to rheumatoid arthritis therapies

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Three gene expression signatures can help rheumatologists predict which patients are more likely to respond to tumor necrosis factor inhibitors (TNFi) or B-cell depletion therapies in patients with moderate to severe rheumatoid arthritis, according to new research findings presented this week at the American College of Rheumatology Annual Scientific Meeting in Washington.

Rheumatoid arthritis (RA) is a chronic disease that causes pain, stiffness, swelling, and limitation in the motion and function of multiple joints. Though joints are the principal body parts affected by RA, inflammation can develop in other organs as well. An estimated 1.3 million Americans have RA, and the disease typically affects women twice as often as men.

Drawing on data from the ORBIT study, a randomized, controlled trial of RA patients in the United Kingdom, researchers looked for gene expression markers that would help predict responses to either TNFi drugs or the B-cell therapy rituximab, or both.

The ORBIT data "showed that patients who have seropositive rheumatoid arthritis are just as likely to respond to rituximab therapy when compared to anti-TNF therapy," said Duncan Porter, MD, Honorary Associate Professor and a consultant rheumatologist at Queen Elizabeth University Hospital in Glasgow, Scotland, and one of the lead authors of the study. "However, a significant proportion of patients failed to respond to their first biologic drug, but responded when they were switched to the alternative. If we could identify markers in the

blood that predicted which drug patients were most likely to respond to, that would allow us to choose the best treatment for that patient at the start, rather than rely on a trial-and-error approach."

Dr. Porter and his fellow researchers sequenced the RNA from the peripheral blood of 241 RA patients recruited for the ORBIT study, after first depleting ribosomal and globin RNA. They used 70 percent of the samples to develop response prediction models, and reserved 30 percent for validation. Clinical response to the therapies was defined as a drop in DAS28-ESR (disease activity score) of 1.2 units between the baseline and at three months. They used multiple machine learning tools to predict general responsiveness and differential responses to TNFi and rituximab. They also used tenfold cross validation to train the models for responsiveness, and then tested these on the validation samples as well.

Using support vector machine recursive feature elimination, the researchers identified three gene expression signatures that predicted therapy responses. Eight genes predicted general responsiveness to both TNFi and rituximab, 23 genes predicted responsiveness to TNFi and 23 genes predicted responsiveness to rituximab.

The researchers also tested their prediction models on the validation set, and this resulted in ROC (receiver operating characteristic) plot points with an AUC (area under the curve) of 91.6 percent for general responsiveness, 89.7 percent for TNFi response and 85.7 percent for rituximab response.

"There are indeed gene expression markers that predict drug-specific response," said Dr. Porter. "If confirmed, this will allow stratification of patients into groups more likely to respond to one drug rather than another. This would lead to higher response rates, and reduced likelihood of receiving a trial of an ineffective drug. Because ineffective treatment is associated with pain, stiffness, disability and reduced quality of life,

this will lead to better patient care."

Confirmation of these models is the next step for research in this area, said Dr. Porter.

"The findings need to be confirmed using targeted RNA sequencing, or internal validation, and then tested in a new cohort of patients, or external validation. Ultimately, a commercial testing kit would be developed to allow clinicians to test patients before they receive treatment to guide them to the most effective treatment," he said.

Provided by American College of Rheumatology