Chromosomal loop signatures could identify poor drug response in arthritis

March 28 2018

Credit: University of Glasgow

Chromosomal loop signatures found in blood samples obtained in early rheumatoid arthritis could identify patients that will not respond adequately to 'anchor' treatment drug methotrexate.

New University of Glasgow research, published in the *Journal of Translational Medicine*, investigated whether differences in genomic architecture, as defined by a chromosome conformation signature (CCS) in blood taken pre-treatment from people with early rheumatoid arthritis

, could assist in identifying the likelihood of a response to the first line disease-modifying anti-rheumatic drug (DMARD) methotrexate (MTX).

The study successfully showed that a CCS found in the blood samples obtained in pre-treatment early rheumatoid arthritis could identify patients that will not respond adequately to MTX with a high degree of accuracy.

MTX is the anchor drug for the treatment of people with new onset rheumatoid arthritis. However, a significant proportion of patients treated with MTX do not respond to therapy. It can take at least six months to determine if a patient will not exhibit a sufficient response to MTX; this would then lead to a change in treatment.

Providing patients with the correct therapy during the early stages of rheumatoid arthritis is essential for preventing long term disability.

It is generally believed that substantial damage can occur as a result of inflammation during the early stages of rheumatoid arthritis, and damage correlates very well with future disability and loss of function. Thus, choosing the correct therapy early in the disease is very important.

The study represents collaboration between the University's Institute of Infection, Immunity and Inflammation Oxford BioDynamics and Pfizer Inc.

Professor Carl Goodyear, Professor of Translational Immunology at the Institute of Infection, Immunity and Inflammation at the University of Glasgow, said: "The study we have undertaken provides proof of concept, and demonstrates the feasibility of using EpiSwitch to predict who will or will not respond to a given therapy in rheumatoid arthritis. This ability to determine whether or not a patient will respond to their chosen medicine may have far-reaching socio-economic implications,

which would not be restricted to just healthcare costs. The sooner we achieve control of disease activity in patients, the more likely we are to decrease the risk of disability and therefore enhance the future quality of life of these patients."

Professor Iain McInnes, ARUK Professor of Rheumatology and Director of the Institute of Infection Immunity and Inflammation further added: "The field of precision medicine is moving quickly and offers exciting potential for people with immune mediated diseases such as rheumatoid arthritis. Although this study now requires to be extended and confirmed, it offers a glimpse of what is possible in this dynamic and exciting field as we seek better outcomes for our patients."

Dr. Alexandre Akoulitchev, Chief Scientific Officer of Oxford BioDynamics, commented: "There is a pressing need in rheumatoid arthritis to identify patients who will not respond to first line disease-modifying anti-rheumatic drugs. These initial results demonstrate that EpiSwitch can identify, with a high degree of specificity, those patients that will not respond to MTX. This has been one of the main challenges in rheumatoid arthritis management for over two decades. Our results provide a proof of principle that stratification of response to MTX is possible and offers the potential to provide alternative treatments for non-responders to MTX earlier in the course of the disease to improve clinical outcomes."

Dr. Claudio Carini, a member of Oxford BioDynamics's Scientific Advisory Board, said: "Despite advances in medicine, not all patients respond favourably to drugs. A proportion of patients under therapy don't benefit from their treatment, or experience adverse reactions to the medication. The identification of a predictive signature in rheumatoid arthritis creates unique opportunities in the management of the disease, helping to identify patients that are more likely to respond to a given therapy thus reducing unwanted drug side effects.

"We believe the ability to detect predictive signatures using EpiSwitch allows the identification of responders and non-responders prior to large Phase 3 clinical trials. This can have a profound effect on the size and cost of clinical trials by eliminating non-responders, and drastically reducing the number of subjects required to demonstrate effect. Our method to stratify patients may ultimately affect clinical practice not only in rheumatoid arthritis but in a wide variety of diseases, including cancer."

More information: undefined undefined et al. Chromosome conformation signatures define predictive markers of inadequate response to methotrexate in early rheumatoid arthritis, *Journal of Translational Medicine* (2018). DOI: 10.1186/s12967-018-1387-9

Provided by University of Glasgow