Predicting drug-free remission in rheumatoid arthritis – results from the Biomarkers of Remission in Rheumatoid Arthritis (BioRRA) Study

Kenneth F. Baker[1,2], Arthur G. Pratt[1,2], Andrew Skelton[1,2], Dennis Lendrem[1,2], Ben Thompson[1,2], John D. Isaacs[1,2]

1 Musculoskeletal Research Group and Arthritis Research UK Centre of Excellence in Rheumatoid Arthritis Pathogenesis, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK.

2 Newcastle NIHR Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle upon Tyne, UK.

Introduction

The use of disease-modifying anti-rheumatic drugs (DMARDs) in modern treat-to-target strategies has made remission a realistic and achievable target for many patients with rheumatoid arthritis (RA). However, DMARDs carry potential risks of serious adverse effects and require inconvenient and expensive regular safety monitoring. Recent studies have demonstrated that up to half of patients with RA in remission can stop DMARDs without a subsequent flare of arthritis - however, this currently cannot be reliably predicted. In this study, we aimed to identify biomarkers that can predict drug-free remission (DFR) and flare following withdrawal of DMARD therapy.

Methods

Patients with established RA who satisfied clinical and ultrasound remission criteria were enrolled in a six-month prospective interventional study of complete conventional synthetic DMARD cessation. The primary outcome was time-to-flare, defined as DAS28-CRP ≥ 2.4. Baseline clinical and ultrasound parameters, circulating cytokines, and peripheral CD4+ T cell transcriptional profiles were assessed for their association with time-to-flare by Cox regression modelling. Receiver-operating characteristic analysis was used to identify a baseline composite score that was predictive of future DFR and flare following DMARD cessation.

Results

Of the 44 patients who discontinued DMARDs, 23 (52%) experienced an arthritis flare at a median (IQR) of 48 (31.5 – 86.5) days following DMARD cessation. A composite score incorporating five baseline variables (three genes, one cytokine and one clinical) differentiated future flare and DFR with an area under the ROC curve of 0.96 (95% CI 0.92-1.00), sensitivity of 0.91 (0.78 – 1.00) and specificity of 0.95 (0.84 – 1.00).

Discussion

We provide proof-of-concept evidence for the existence of biomarkers of DFR in RA. The results of our study provide a unique insight in to the pathogenesis of RA flare and, if successfully validated in an external cohort, may hold promise in guiding DMARD withdrawal in patients with RA in remission.