Precision Medicine in Rheumatoid Arthritis

James Bluett, MBBS, PhD[a,*], Anne Barton, FRCP, PhD[a,b]

KEYWORDS

• Methotrexate • Anti-TNF • Anti-TNF response • Genetic • Genomic
• Rheumatoid arthritis • Pharmacogenomics

KEY POINTS

- Treatment of rheumatoid arthritis (RA) has improved in recent years but response is not universal.
- Clinical predictors of response alone are not sufficiently predictive to aid treatment decisions.
- Understanding the pharmacogenomics of RA would allow more personalized health care.

INTRODUCTION

Rheumatoid arthritis (RA) is a heterogenous disease and can range from a mild, self-limiting arthritis to rapidly progressive joint damage. Treatment is based on controlling inflammation, and early effective therapy reduces disability, joint damage, and mortality.[1] A range of treatment options are available but none are universally effective, so treatment selection is based on a "trial-and-error" approach, trying different therapies until a drug that induces low disease activity or remission is identified.[2] Time on multiple ineffective medications affects the patient's quality of life, may lead to irreversible joint damage,[3] exposes the patient to potential adverse events, and is a waste of health care resources. Therefore, considerable research effort has been applied to identifying predictors of drug response to allow more rational prescribing of the drug most likely to be effective in individual patients, an approach known as precision (or stratified) medicine.

Methotrexate (MTX) is the first-line therapy for RA,[2] whereas biologic therapies target specific molecular pathways, including the tumor necrosis factor (TNF),

Disclosure Statement: The authors have nothing to disclose.

[a] Division of Musculoskeletal and Dermal Sciences, Arthritis Research UK Centre for Genetics and Genomics, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University of Manchester, Room 2.607, Stopford Building, Oxford Road, Manchester M13 9PT, UK; [b] NIHR Manchester Biomedical Research Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester M139WU, UK
* Corresponding author.
E-mail address: james.bluett@manchester.ac.uk

Rheum Dis Clin N Am 43 (2017) 377–387
http://dx.doi.org/10.1016/j.rdc.2017.04.008 rheumatic.theclinics.com
0889-857X/17/© 2017 Elsevier Inc. All rights reserved.

interleukin-6, B-cell and T-cell costimulation pathways. The biologic drugs are typically reserved for those with an inadequate response to nonbiologic disease-modifying antirheumatic drugs,[2] but there is currently no guidance on which biologic agent to use first.[4] Each drug has a significant failure rate; for example, TNF inhibitors (TNFi) are ineffective in up to 30% patients,[5] yet remain the most commonly prescribed first-line biologic. As most research has investigated biomarkers predictive of response to MTX and TNFi biologics, the current review limits the focus to these drug classes.

Treatment response is likely to be multifactorial and influenced by clinical, psychological, and biological factors. For example, robust clinical predictors of TNFi response include disease severity, smoking status, concomitant MTX, and patient disability, but account for a small proportion ($r^2 = 0.17$) of the variance in response and so, alone, are not useful in informing therapy selection decisions.[6] There is, therefore, a need for accurate predictors (biomarkers) of response to RA therapies to enable precision medicine, defined by National Academy of Sciences as the use of genomic, epigenomic, exposure, and other data to define individual patterns of disease, potentially leading to better individual treatment.[7]

The use of genomic variants as predictors of response has several theoretic advantages. Genetic variants are stable and will not change because of the environment, unlike epigenetics or expression profiling. Genetic variants that are associated with response are likely to be involved in key molecular pathways and can therefore provide insight into the mechanisms of nonresponse. Whole-genome genotyping is now economically viable, and the assays are standardized, enabling their use in the clinical setting. Indeed, genetic biomarkers are already being used to personalize health care. In cystic fibrosis, for example, ivacaftor, a drug that targets the CFTR molecule, is recommended in the 4% of patients with the G551D mutation[8] whereas in rheumatology, screening for the enzyme TPMT, responsible for the metabolism of 6-mercaptopurine and related compounds, is recommended to identify the 13% of the population with reduced activity and who are at increased risk of toxicity to azathioprine.[9] There are currently more than 200 examples of US Food and Drug Administration–approved drugs that contain information on genomic biomarkers that may be used to inform treatment decisions.[10] Although many of these are not commonly used in clinical practice, TPMT screening is frequently in the United Kingdom.

STUDIES INVESTIGATING GENOMIC PREDICTORS OF METHOTREXATE

Given that MTX remains the treatment of choice for patients with newly diagnosed RA, several studies have investigated genes involved in the key molecular pathways affecting MTX absorption, metabolism, or its target enzymes as predictive biomarkers of response (**Fig. 1**).

The most consistent evidence for association is for the solute carrier family 19 member 1 (SLC19A1) gene, one of several transport carriers that allow MTX to enter cells. Studies have reported that the rs1051266 variant associates with intracellular MTX-polyglutamate levels and a recent meta-analysis of 12 studies (n = 2049) reported an association with MTX treatment response (odds ratio [OR] = 1.49 of AA genotype, $P = .001$).[11,12] Methylene tetrahydrofolate reductase is another key enzyme in the MTX pathway and has also been extensively investigated with several studies reporting associations with efficacy and toxicity. However, a meta-analysis including 17 previous studies revealed no association with either outcome,[13] and this finding has been replicated in 2 subsequent meta-analyses.[14,15] MTX is thought to exert an

Download English Version:

https://daneshyari.com/en/article/8743653

Download Persian Version:

https://daneshyari.com/article/8743653

Daneshyari.com