Pharmacogenomics and Precision Medicine of Rheumatoid Arthritis

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Treatment of rheumatoid arthritis (RA), a chronic autoinflammatory condition primarily affecting the joints, is centered around controlling systemic and synovial inflammation. The antifolate agent methotrexate (MTX) is the recommended first-line disease-modifying anti-rheumatic drug (DMARD) utilized in the treatment of RA in both UK and European guidelines. MTX is a mainstay of treatment in RA, given its low cost, long-term safety profile and that many patients achieve disease control with monotherapy. However, approximately 30% of patients suffer from inadequate treatment response and approximately 20% stop MTX due to toxicity (Bluett, Sergeant et al. 2018).

RA is a heterogeneous disease and while there exists a varied armamentarium of therapies with different

mechanisms of action to treat the condition, none are universally effective. If disease activity is not adequately

controlled, this can lead to permanent joint damage and disability. Long-term studies have shown that response to the first-line DMARD predicts long-term prognosis (Farragher, Lunt et al. 2010). Hence, it is vital that baseline characteristics predictive of response to MTX are discovered to prevent long-term disability. To adequately identify clinical and biomarker baseline predictors of response and how these interact, large stratified medicine programs are required to integrate these variables into a prediction model.

Although EULAR and ACR have provided RA treatment guideline which is also accepted in the majority of Hospitals in China, more personalized treatment strategies are applied including the different combinations of DMARDs in the clinical practices. Evidences showed these extra drugs and combination regimes showed better

The use of genetic markers to predict treatment response to MTX in RA patients has huge potential, in that

genetic variability can be reliably and reproducibly measured relatively inexpensively and it has been shown to

predict treatment response in other therapeutic agents, for example, the TPMT genotype and risk of azathioprine toxicity. The ability to tell which patients are more likely to respond to MTX would lead to a more personalized approach, reducing the time to establishing effective treatment and the risk of disability in a patient. Many of the early studies of MTX pharmacogenetics focused on candidate genes, investigating those genes implicated in RA susceptibility/pathogenesis and the MTX metabolic pathway.

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