Interestingly, the metabolic enzymes FPGS and GGH were significantly up-regulated in the MTX⁻ RA group compared to the healthy control group (HC group), whereas GART expression was markedly down-regulated. Following MTX treatment, these alterations in expression levels were normalised to those observed in the HC group. Furthermore, the MTX-efflux transporters multidrug resistance protein-2 (MRP2) and MRP3 showed an increased expression in the MTX⁺ group compared to the MTX⁻ group and the HC group, suggesting that cellular extrusion may contribute to a diminished MTX response in the MTX⁺ group.

Conclusions Collectively, these results indicate that, under inflammatory conditions, basal folate metabolism is altered in blood cells of RA patients versus HC. Treatment with MTX restores expression of these genes to the levels within the range of the HC group. Finally, our results provide the first indication that multidrug resistance protein efflux transporters could contribute to an attenuated MTX response in MTX-based RA treatment.

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5 GENE EXPRESSION PROFILING OF FOLATE PATHWAY RELATED GENES IN METHOTREXATE NAÏVE- AND METHOTREXATE-TREATED RHEUMATOID ARTHRITIS PATIENTS

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Background and objectives The folate antagonist methotrexate (MTX) is an anchor drug in the treatment of rheumatoid arthritis (RA). Many attempts have been undertaken to predict response to MTX treatment, in particular by evaluating possible correlations with polymorphic variations of methotrexate/folate-related genes. Thus far, however, many of these studies were not elusive in providing robust predictive markers. The aim of this study was to explore whether analysis of expression of methotrexate/folate-related genes provide information on the pharmacodynamics and (non)responsiveness of RA patients for MTX therapy.

Methods Gene expression profiling was performed on peripheral blood from 25 MTX-treated (MTX⁺) and 10 untreated (MTX⁻) RA patients, and 15 healthy controls (HC). Statistical analysis was performed for 25 genes involved in the methotrexate/folate pathway using student's t test or Mann-Whitney U test, p values of ≤ 0.05 were considered to be statistically significant.

Results Several folate/MTX-related genes were markedly and significantly altered between the three study groups.