ABSTRACT

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Title of Doctoral Thesis:	Selected aspects of methotrexate treatment in patients with rheumatoid arthritis

Introduction and objectives

Rheumatoid arthritis (RA) is an autoimmune disease typically connected with chronic inflammation of the joints, causing their swelling and pain. The prevalence of RA is about 1% in the general population. A crucial role in higher morbidity and mortality in RA patients has been associated with increased inflammatory activity. Methotrexate (MTX), a drug with immunosuppressive activity, is the most frequent drug of choice used in RA therapy. It seems that main anti-inflammatory effect is mediated via release of purine nucleoside adenosine. The status of patients with inflammatory diseases is influenced by activation of A2a and A3 adenosine receptors. High caffeine (adenosine receptor antagonist) consumption may therefore lead to alteration of MTX treatment efficacy. **1)** The aim of first study was to determine whether RA patients who had discontinued methotrexate treatment before the study enrolment (MTX 0) were at a higher risk of CVD than patients treated with methotrexate at the time of the data collection (MTX 1). **2)** The aim of second study was to determine influence of caffeine consumption on the therapeutic effect of methotrexate (MTX) in patients with rheumatoid arthritis (RA) sorted according to ADORA2A genotypes.

Methods

1) A total of 125 patients were enrolled in the study. Medical documentation as well as information taken in patient examinations during regular rheumatologist visits was used to obtain the required data. **2)** 82 RA patients were dichotomized into groups according to caffeine/week intake with a threshold of 700 mg.

Patients were genotyped using qPCR allelic discrimination for adenosine receptor ADORA2A and its polymorphisms *rs2298383*, *rs3761422*, *rs2267076* and *rs2236624* genotypes.

Results

1) The composite of any CVD occurred less frequently in patients in the MTX 1 group than in MTX 0 group (18.8% vs. 40.0%, OR 0.35, 95% CI 0.15 to 0.83; P=0.017) with slightly non-significant trend after adjustment analysis (P=0.054). Significant difference was found for the reduction of myocardial infarction in the MTX 1 compared to the MTX 0 group (3.5% vs. 14.3%, OR 0.22, 95% CI 0.05 to 0,97; P=0.046. There were 4 deaths (4.7%) in the MTX 1 group as compared with 7 (20.0%) in the MTX 0 group (OR 0.20, 95% CI 0,05 to 0,73; P=0.015). **2)** We found significantly higher disease activity in MTX naïve patients with higher caffeine intake and the CT genotype of ADOARA2A *rs2298383*, *rs3761422* and *rs2267076* SNPs (OR 5.0; 95% CI 1.13-22.05, p=0.03, OR 5.0; 95% CI 1.13-22.05, p=0.03 and OR 6.94; 95% CI 1.29-37.49, p=0.02 respectively). We found significantly higher disease activity in patients from low caffeine intake group treated with MTX and having the CC genotype of ADORA2A *rs2236624* SNP (OR 12.94; 95% CI 1.51-110.74, p=0.019).

Conclusion

1) Our results demonstrate that patients, who discontinued methotrexate treatment are at a significantly higher risk of CVD and all-cause mortality. Based on our findings, we recommend stricter control of CVD in cases of methotrexate discontinuation. **2)** We found that caffeine consumption may affect RA disease activity as well as MTX treatment response in patients with specific genotypes for adenosine receptor ADORA2A. Further studies with more patients are needed for confirmation of our findings.