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POLYMORPHISM OF GENES INVOLVED IN METHOTREXATE RESPONSE IN SAUDI PATIENTS WITH RHEUMATOID ARTHRITIS

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Introduction: Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease which is considered genetically complex, leading cause of bone loss and chronic inflammation of the joints in populations. The aim of the present study was to investigate whether single nucleotide polymorphisms (SNPs) of dihydrofolate reductase gene (DHFR) responsible for the methotrexate (MTX) metabolism and ATP-binding cassette subfamily B member 1 (ABCB1) which is responsible for MTX transportation will affect its efficacy and/or toxicity in Saudi patients with RA.

Objective: The objectives were to measure the efficacy of MTX in treating RA by counting the number of tender, swollen joints, scoring the visual analogue scale (VAS), scoring modified Health Assessment Questionnaire (mHAQ) and to determine the effect of SNPs of SLC19A1 G80A on MTX by measuring the MTX polyglutamate (MTXPG) level in RBCs by high-performance liquid chromatography.

Patients & Methods: A total of hundred patients with RA who received low-dose MTX therapy for at least six months were selected, clinical and demographic characteristics were collected, red blood cell MTX PG concentration were measured and common polymorphisms in reduced folate carrier (RFC-1/SLC191A1G80A) was performed through genotyping procedure.

Results: The allelic frequencies for rs1045642 were 76.8 % for C, 6.0% for T, and 17.2 % for C/T, while, the allelic frequencies for rs1232027 were 50.9 for G/A, 32.5 % for G, 16.6 % for A. The allelic discrimination plot of ABCB1 (rs1045642) SNP and DHFR gene (rs1232027) SNP illustrated the allelic distribution of both SNPs in the RA individuals of the current study. The study did not reveal any association between the polymorphism in ABCB1 gene and toxicity or efficacy of MTX, while revealed an association between C677T polymorphism in the DHFR gene and related toxicities, nausea, photosensitivity, lung infection, skin nodules, menstrual irregularities in patients with RA. We also investigated whether an association exists between drug dose and plasma MTX levels, however, ABCB1 (rs1045642) and DHFR Gene (rs1232027) polymorphism were not associated with the risk of delayed elimination of MTX as MTX plasma level is a usual approach to predict toxicities related to MTX especially when taken in high doses. The current study demonstrated that MTX plasma level was not correlated with toxicities detected in patients on MTX.

Conclusion & Recommendation: The ABCB1 and DHFR genes polymorphisms could be predictive of toxicity and efficacy of MTX treatment in RA patients receiving folate supplementation. In agreement with other studies that the DHFR gene polymorphism is a reliable predictor of toxicity to MTX treatment in RA patients, further studies are needed to determine polymorphisms in other enzymes that might be responsible for the MTX variability in clinical response and toxicity

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