Background: Methotrexate (MTX) is the DMARD of choice in the treatment of rheumatoid arthritis (RA). Despite an acceptable efficacy, its use is limited by side effects. The most known adverse events (AE) are gastrointestinal, hepatic, and haematological.

Objectives: To study the effect of clinical characteristics and of different genetic single nucleotide polymorphisms (SNPs) related to the transport and metabolic pathways of MTX, on the toxicity of this compound, in a cohort of RA patients treated with MTX in monotherapy.

Methods: Observational study. Toxicity was defined as the occurrence of AE, global and of haematological, hepatic, and gastrointestinal nature. Factors under study: SNPs of transport (ABCB1 C3435T), glutation (GGH T16C and FPSG G278R2A), transmethylation (MTHFR C677T and MTHFR A1298C) and adenosine (AMPD1 C314T, ADA A534G, ITPA C94A). The association between SNPs and MTX toxicity was analysed using logistic regression models, assessing allele independence (Hardy-Weinberg equilibrium) and interaction with sex. Different models of inheritance of SNPs were analysed. The models were adjusted by the characteristics of the patient, of disease and of treatment. The haplotypes of the MTHFR SNPs (C677T and A1298C) were also analysed.

Results: Bivariate analysis showed that AE, globally considered, are related to lower age at diagnosis (OR=0.98), female sex (OR=1.95), disease activity (OR=1.38), extra-articular manifestations (OR=1.84) and comorbidity (OR=1.14). For the SNPs, the A/G genotype of the ADA A534G decreases the probability of AE (OR=0.55); the G/G of the ADA A534G increases the hepatic AE (OR=10.1) and the genotypes C/T and T/T of the ABCB1 C3435T decrease the risk of haematological AE.

According to the adjusted analysis, the probability of global AE increased with the C/T genotype of MTHFR C677T (OR=1.85) and C/C of MTHFR A1298C (OR=1.53), and decreased with the A/G of ADA A534G (OR=0.49). Gastrointestinal AEs were less frequent in patients with A/G genotype of ADA A534G (OR=0.49) and in men with G/A of FPSG C2782G (OR=0.29). The G/G genotype of the SNP ADA S34A was associated with a significant increase in hepatic AE (OR=12.7), which was also observed in men with the MTHFR A1298C (OR=8.34). The T allele of the ABCB1 C3435T decreases the probability of haematological AE, especially in women (OR=0.06). All the effects were independent of the characteristics of patient, disease and treatment. The C/C haplotype of the combination MTHFR C677T and MTHFR A1298C increases the probability of global (OR=4.35) and hepatic AE (OR=1.19) in men, but not in women.

Conclusions: SNPs related to the transport and metabolism of MTX are associated with liver toxicity of MTX.