Pharmacogenetic determinants of response to methotrexate in juvenile idiopathic arthritis

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Juvenile idiopathic arthritis (JIA) is the most common rheumatic chronic disease in children with a frequency of 1 in 1000 and is an important cause of disability. Methotrexate (MTX) is the first choice disease modifying antirheumatic agent in JIA and its efficacy has greatly improved the prognosis of children with this disease. However, one third of patients does not respond to MTX and the delay in the identification of the optimal therapeutic approach for each patient can be crucial in determining the outcome of JIA, in terms of worsening of the disease and even of permanent damage to joints. Identification of molecular determinants predictive of MTX response would be an important progress for the treatment of JIA. Recent studies have evaluated comprehensively the effect of genetic variants in candidate genes involved in MTX pharmacokinetics and pharmacodynamics on the response to the medication in children with JIA or in adults with rheumatoid arthritis. These studies seem to indicate that the most relevant variants to predict MTX response in JIA are those in *ATIC*, *ITPA* and *SLC19A1* genes. The aim of the present study was therefore to evaluate the role of these candidate genetic factors on the response to MTX in an Italian cohort of children with JIA. Patients with JIA treated with MTX were enrolled by the Pediatric Clinic of Burlo Garofolo Hospital in Trieste; clinical data was collected retrospectively from patients' charts. Response to MTX was evaluated by the American College of Rheumatology (ACR) pediatric score, which integrates six response variables. The most relevant functional SNP for each gene considered were characterized by Taqman (rs2372536 in *ATIC*, rs1127354 in *ITPA*) or PCR-RFLP (rs1051266 in *SLC19A1*) assays on patients' DNA extracted from peripheral blood. Seventy three children with JIA were enrolled and considered in the present analysis; one patient was excluded because of systemic disease and three patients because of confounding treatment with etanercept. Complete analysis was performed on the remaining 69 patients. Of these, 76.8% were female, median age at MTX start was 8 years (range 1–22). JIA presentation was oligoarticular in 63.7%, poliarticular in 33.3% and enthesitic/psoriatic in 2%. At the beginning of MTX therapy, disease had been lasting for a median of 1 year (range 0–19); MTX was administered at a median dose of 15 mg/m^2 (range 10 - 20), subcutaneously in 62.3% of patients and orally in the rest. Genotyping showed minor allele frequencies of 36.2% for rs2372536, 5.1% for rs1127354 and 49.3% for rs1051266, consistent with previous reports in Europeans. Assessment of response to MTX after 6 months of therapy showed that 20.3% of patients did not respond and did not reach the lowest efficacy grade (ACR30, i.e., around 30% of improvement in disease symptoms); on the other hand, 52.2% of patients reached the best response grade (ACR70). No statistically significant effect of the demographic and clinical covariates was found on MTX response. However, genotyping analysis identified a significant association between the homozygous variant of *ATIC* rs2372536 and improved response to therapy: frequency of this genotype was 20% among patients with optimal response and 0 among non responders (p=0.020). For the AA variant of *ITPA* rs1127354, a trend was present in the opposite direction, however given the low frequency of the allele it should be further examined in a larger patients' population. Preliminary analysis of *SLC19A1* rs1051266 revealed an association with disease activity, independent from the effects of MTX treatment (p=0.017). This is the first study evaluating the effect of pharmacogenetic variants on response to MTX in Italian patients with JIA, showing relevant significant associations. This report supports the utility of genotyping candidate genes to predict MTX response in children with JIA and should be further validated clinically by larger and prospective studies.