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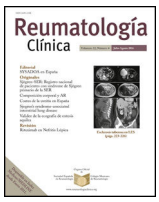

Letters to the Editor

A Step Forward in Methotrexate Pharmacogenetics☆

Farmacogenética del metotrexato. Un paso adelante

To the Editor,

We found it very interesting to read the original article recently published in the on-line version of Reumatología Clínica entitled "Impact of genetic variants of ATP binding cassette B1, AICAR transformylase/IMP cyclohydrolase, folylpolyglutamatesynthetase, and methylenetetrahydrofolatereductase on methotrexate toxicity". First, because it is a very timely subject and, on the other hand, because it is one of the areas in which we are working.[1,2] The excellent manuscript reaffirms the growing idea that pharmacogenetics constitutes a great advance in the individualized treatment of chronic inflammatory diseases. In medical specialties, like oncology, it is a diagnostic tool that enables the design of a personalized approach and has revolutionized the specialty, whereas in rheumatology, reports of this type offer novel perspectives and open new avenues for research, although we still have a long way to cover.

The reason for the present letter is to compare the results with those that we have recently published in 2 original articles along the same line of study: to establish the association between polymorphisms in genes related to the mechanism of action and transport of methotrexate (MTX) with its toxicity and/or efficacy in patients with rheumatoid arthritis (RA).[3,4] Like Sala-Icardo et al., we studied the rs1801131 and rs1801133 polymorphisms of the *MTHFR* gene and found no statistically significant results with respect to the toxicity of MTX. However, when investigating the association of the efficacy of MTX, our results showed that 2 polymorphisms (rs17421511 and rs1476413) of the *MTHFR* gene show statistical significance. With respect to the genes related to transport, in contrast to the authors of the manuscript, we observed no association between rs1045642 of the *ABCB1* gene and MTX toxicity. In this case, we studied other polymorphisms in this same gene (rs1858123, rs10280623 and rs868755) with statistically significant results.

Finally, *FPGS* is a gene related to the activation of MTX within the cells. Sala-Icardo et al. describe a significant association between MTX toxicity and rs1544105 in *FPGS*. In our work, we selected other polymorphisms of the same gene that also showed statistical significance, but they were related to survival of the drug.

Overall, the conclusions of Sala-Icardo et al. coincide with ours: there is an association between polymorphisms in genes related to transport and activation of MTX and its toxicity in RA patients. Nevertheless, we wish to point out that, regardless of the growing interest in pharmacogenetics and an increase in publications that examine genes related to the mechanism of action and transport of MTX in RA, the majority continue to offer contradictory results. The disparity among the results obtained by different groups may be due to a number of reasons: selection bias of the candidate genes, variability in the clinical definition of toxicity and/or efficacy and choice of the variables. Likewise, we consider that we should continue to advance in the design of these studies and evaluate the different polymorphisms in larger population samples and improve the strategy for selecting the implicated transmembrane or intracellular enzymes in order to achieve applicability in clinical practice of our findings in the laboratory.[5]

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