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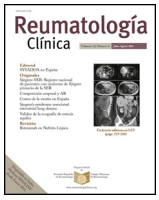

Original Article

Impact of Genetic Variants of ATP Binding Cassette B1, AICAR Transformylase/IMP Cyclohydrolase, Folyl-polyglutamate Synthetase, and Methylenetetrahydrofolate Reductase on Methotrexate Toxicity☆

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ABSTRACT

Objective: To analyze the effect of single nucleotide polymorphisms (SNPs) with well-known functional impact of methylenetetrahydrofolate reductase (MTHFR; rs1801131 and rs1801133), the membrane transporter ABCB1 (rs1045642), the AICAR transformylase/IMP cyclohydrolase (ATIC; rs2372536) and folyl-polyglutamate synthetase (FPGS; rs1544105), on liver and bone marrow toxicity of methotrexate (MTX).

Patients and methods: We analyzed 1415 visits from 350 patients of the PEARL (Princesa Early Arthritis Register Longitudinal) study: (732 with MTX, 683 without MTX). The different SNPs were genotyped using specific TaqMan probes (Applied Biosystems). Multivariate analyzes were performed using generalized linear models in which the dependent variables were the levels of serum alanine aminotransferase (liver toxicity), leukocytes, platelets or hemoglobin (hematologic toxicity) and adjusted for clinical variables (disease activity, etc.), analytical (renal function, etc.), sociodemographic (age, sex, etc.) and genetic variants of MTHFR, ABCB1, ATIC and FPGS. The effect of these variables on the MTX doses prescribed throughout follow-up was also analyzed through multivariate analysis nested by visit and patient.

Results: When taking MTX, those patients carrying the CC genotype of rs1045642 in ABCB1 showed significantly higher GPT levels (7.1 ± 2.0 U/L; $P < .001$). Carrying at least one G allele of rs1544105 in FPGS was associated with lower leukocyte (-0.67 ± 0.32; 0.038), hemoglobin (-0.34 ± 0.11 g/dL; $P = .002$), and platelet (-11.8 ± 4.7; $P = .012$) levels. The presence of the G allele of rs1544105 in FPGS, and the T allele of rs1801133 in MTHFR, was significantly associated with the use of lower doses of MTX.

Discussion: Our data suggest that genotyping functional variants in FGPS and MTHFR enzymes and the transporter ABCB1 could help to identify patients with increased risk of MTX toxicity.

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Impacto de variantes genéticas del transportador de membrana que une ATP B1, la aicar transformilasa/IMP ciclohidrolasa, la folilpoliglutamatosintetasa y la metilen-tetrahidrofolatorreductasa en la toxicidad de metotrexato

Palabras clave:
Artritis reumatoide
Metotrexato
Toxicidad
Polimorfismos de nucleótido único

RESUMEN

Objetivo: Analizar el efecto de polimorfismos de nucleótido único (SNPs) de la metilen-tetrahidrofolatorreductasa (MTHFR; rs1801131 y rs1801133), el transportador de membrana que une ATP B1 (ABCB1; rs1045642), la aicartransformilasa/IMP ciclohidrolasa (ATIC; rs2372536) y la folilpoliglutamatosintetasa (FPGS; rs1544105) en la toxicidad hepática y medular de metotrexato (MTX).

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Pacientes y métodos: Se analizaron 1.415 visitas (732 con MTX, 683 sin MTX) de 350 pacientes del *Princesa Early Arthritis Register Longytudinal study*. El genotipo de los diferentes SNP se determinó mediante sondas TaqMan (Applied Biosystems). Se realizaron análisis multivariables mediante modelos lineales generalizados en los que las variables dependientes fueron los niveles séricos de transaminasa glutámico-pirúvica (toxicidad hepática), leucocitos, plaquetas o hemoglobina (toxicidad hematológica) y se ajustaron por variables clínicas (actividad de la enfermedad, etc.), analíticas (función renal, etc.), sociodemográficas (edad, sexo, etc.) y las variantes genéticas de MTHFR, ABCB1, ATIC y FPGS. También se analizaron las variables que influyeron en las dosis de MTX administradas a lo largo del seguimiento.
Resultados: Cuando recibían MTX los portadores del genotipo CC del SNP rs1045642 de ABCB1 presentaron niveles significativamente mayores de GPT (7,1 ± 2,0 U/l; p < 0,001). Los portadores de al menos un alelo G de rs1544105 en FPGS presentaron niveles significativamente menores de leucocitos (−0,67 ± 0,32; 0,038), hemoglobina (−0,34 ± 0,11 g/dl; p = 0,002) y de plaquetas (−11,8 ± 4,7; p = 0,012). La presencia del alelo G de rs1544105 (FPGS) y T de rs1801133 (MTHFR) se asoció, de forma aditiva y significativa, al uso de menores dosis de MTX.
Discusión: Nuestros datos sugieren que variantes genéticas de las enzimas FGPS y MTHFR, y del transportador ABCB1, podrían ayudar a detectar pacientes con mayor riesgo de toxicidad por MTX.
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Introduction

Methotrexate (MTX) continues to be the cornerstone of the treatment of rheumatoid arthritis (RA), and the major guidelines for the management of that disease recommend it as the initial therapy and as a key support for treatment with biological therapies.[1–3] It is not strange that in a recent international observation study, COMORA (Comorbidities in RA), 89% of the patients received treatment with MTX or had taken it over the course of their disease.[4] In Spain, the EMECAR study (Study of the Morbidity and Clinical Expression of Rheumatoid Arthritis) or in the emAR II study, conducted within the last 10 years, revealed that MTX was the initial drug of choice in 55% of the cases, and between 60% and 64% received this disease-modifying drug, either alone or in combination.[5,6] Despite its wide use and the extensive research on this agent, the mechanism of action of MTX in RA is not fully established. Although the drug inhibits several metabolic pathways related to folic acid (Figure 1), the available data suggest that supplements with folic acid have a greater impact on the toxicity of MTX than on its efficacy.[7] It has been shown that there is a marked individual susceptibility to its immunomodulating effect as well as to its toxicity, which makes it necessary to interrupt the treatment in up to a fourth of the patients receiving it.[8] This means that, although it is the synthetic disease-modifying drug with the longest survival, less than 55% of those taking it maintain it for more than 8 years.[9]

Given that early treatment in RA has been shown to be essential to achieving an optimal control of the disease, it would be of great utility to have access to biomarkers that would enable us to predict which individuals will develop toxicity that could impede their taking full therapeutic doses of MTX. The study of genetic variants in the metabolic pathway enzymes in which folic acid participates has been a question of interest that has led to the performance of a number of studies that have attempted to predict the response to or toxicity of MTX, although the information obtained until now, in patients with an inflammatory rheumatic disease, is not conclusive.[10] The objective of this article is to analyze the effect of genetic variants of methylenetetrahydrofolate reductase (MTHFR; rs1801131 and rs1801133), the membrane transporter that binds adenosine triphosphate (ATP) B1 (ABCB1; rs1045642), 5′-phosphoribosyl-5-aminoimidazole-4-carboxamide (AICAR) transformylase/inositol monophosphate (IMP) cyclohydrolase (ATIC; rs2372536) and folyl-polyglutamate synthetase (FPGS; rs1544105), whose function is shown in the diagram in Fig. 1, in the toxicity related to the drug in patients with early RA (ERA) exposed to MTX.

ABCB1 belongs to the ATP-binding cassette superfamily that is responsible for transport toward the exterior of the cytoplasmic membrane of a number of molecules, among them those that are cytotoxic. Specifically, the single nuclide polymorphism (SNP) rs1045642 consists in the transition of a C for a T in exon 26 of the ABCB1 transporter gene.[11] This substitution provokes mRNA instability and has been associated with a decrease in the expression and, thus, in the function of ABCB1, accompanied by higher tissue levels of numerous drugs.[11] In the case of MTHFR, the SNP rs1801133 involves the transition of a C for a T in exon 4, which entails the change of an alanine for a valine in position 222 of the protein, whereas the SNP rs1801131 involves the transition of an A for a C in exon 7, provoking the change of a glutamic for an alanine in position 429 of the protein. In both cases, this results in greater thermolability of the enzyme and less functional activity. With respect to rs1544105, there is a change of a G for an A in the promotor region of the *FPGS* gene that has been related to lower mRNA levels of this enzyme.[12] The SNP rs2372536 in ATIC means a transition of a C for a G in exon 5, which brings about the change of a threonine for a serine in position 116 of the protein.[13] This information on the functional impact of these genetic variants led to their being chosen for this study, which was planned in 2008.

Patients and Methods

Patients

We utilized data from the Princesa Early Arthritis Register Longitudinal Study (PEARL), in which the patients recruited had had inflammation in 1 or more joints for at least 4 weeks and a disease duration of less than 1 year. The registry began in September 2001 and continues at the present time. The study protocol was reviewed and approved by the clinical research ethics committee of La Princesa teaching hospital in Madrid, Spain, and all of the participants provided written informed consent when they were included in the registry.

In the database, we included those patients who, after 2 years of follow-up, met the 1987 American Rheumatism Association criteria for RA[14] and those considered to have undifferentiated arthritis (UA)[15] after ruling out other causes of inflammatory arthropathy, such as crystal arthritis, septic arthritis, spondyloarthritis and other

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