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Review Article

Pharmacogenetics of methotrexate in rheumatoid arthritis: A systematic review☆

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ABSTRACT

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease characterized by inflammation of multiple joints, leading to destruction of cartilage and juxta articular bone. It eventually leads to deformity, disability, and impaired quality of life. Methotrexate (MTX) has a reported response rate of 33–65%, and this variability may be explained by genetic variations (polymorphisms) in the metabolic pathway of this drug.

To evaluate possible relationships between polymorphisms in the metabolic pathway and response to MTX in patients with RA.

Methodology: A systematic search and review of the literature was conducted. A total of 29 studies that evaluated polymorphisms in the metabolic pathway of MTX were included, due to their full text and methodological quality.

Results: Of the 29 studies, five were systematic reviews and/or meta-analyses, three of which clinical trials none was triple blind and only one was double-blind, six were cohort, seven were case–control, and eight cross sectional. The polymorphism identified were: methylene tetrahydrofolate reductase, dihydrofolate reductase, thymidylate synthase, 5-aminoimidazole-4-carboxamide ribonucleotide formyl transferase (AICAR formyltransferase), 5-aminoimidazole-4-carboxamide polymorphisms formyltransferase/IMP cyclohydrolase ribonucleotide (ATIC) identified conveyors attached to ATP cassette (ABC ATP-binding cassette), folylpoly-glutamate, glutamyl hydrolase, reduced folate carrier (RFC-SLC10A1). The dihydrofolate reductase and methylene tetrahydrofolate reductase polymorphism were shown to be associated with increased MTX toxicity. RFC and C677T polymorphisms are associated with better efficacy of MTX.

Conclusions: The polymorphisms of methylene tetrahydrofolate reductase, C677T and RFC1-G80A generate increased efficacy and toxicity in patients treated with MTX. However, for the other polymorphisms, although studies show statistically significant associations, they are not conclusive and some are contradictory. This justifies conducting multicenter studies to

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assess the presence and association with the effectiveness or toxicity in patients with RA treated with MTX.

Farmacogenética del metotrexato en artritis reumatoide. Revisión sistemática

Palabras clave:
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Polimorfismo
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RESUMEN

Antecedentes: La artritis reumatoide (AR) es una enfermedad inflamatoria de origen autoinmune, caracterizada por inflamación de múltiples articulaciones que lleva a destrucción del cartílago y del hueso yuxta articular, con el tiempo genera deformidad, discapacidad y deterioro de la calidad de vida. El metotrexato (MTX), reporta un índice de respuesta del 33 al 65%, esta variabilidad puede ser explicada por las variaciones genéticas (polimorfismos) en la ruta metabólica de este fármaco.

Objetivo: Evaluar las posibles asociaciones entre los polimorfismos de la ruta metabólica del MTX y su respuesta en pacientes con AR.

Metodología: Revisión sistemática de la literatura cualitativa (integrative review). Se realizó una búsqueda sistemática de la literatura, 29 estudios fueron incluidos por texto completo y por calidad metodológica para alcanzar el objetivo del estudio, estos estudios evaluaron polimorfismos en la ruta metabólica del MTX.

Resultados: De los 29 estudios, cinco fueron revisiones sistemáticas o metaanálisis, tres ensayos clínicos de los cuales ninguno fue triple ciego y solo uno fue doble ciego, seis fueron cohortes, siete fueron casos y controles y ocho de corte transversal. Se identificaron los polimorfismos de metiltetrahidofolato reductasa, dihidrofolato reductasa, timidilato sintetasa, 5-aminoimidazol-4-carboxamida ribonucleótido formiltransferasa (AICAR formiltransferasa), 5-aminoimidazol-4-carboxamida ribonucleótido formiltransferasa/IMP ciclohidrolasa (ATIC), transportadores de casete unidos a ATP (ABC ATP-binding cassette), folilglutamato sintetasa, glutamil hidrolasa, transportador de folato reducido (RFC-SLC10A1). Los polimorfismos metiltetrahidofolato reductasa y dihidrofolato reductasa demostraron estar asociados con un aumento en la toxicidad del MTX; los polimorfismos RFC y C677T están asociados a una mejor eficacia del MTX.

Conclusiones: Los polimorfismos de metiltetrahidofolato reductasa C677T y RFC1 - G80A generan aumento de eficacia y toxicidad en pacientes tratados con MTX. Sin embargo, para los demás polimorfismos, aunque los estudios muestran asociaciones estadísticamente significativas, no son concluyentes y algunos son contradictorios. Lo anterior justifica la realización de estudios de carácter multicéntrico, para evaluar la presencia y asociación, con la eficacia o toxicidad en los pacientes con artritis reumatoide tratados con MTX.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of autoimmune origin, characterized by inflammation of multiple joints. Over time it leads to variable degrees of destruction of the articular cartilage and the juxta-articular bone, generating progressive deformity, and thereby disability, alteration of the quality of life and a decrease in the life expectancy.[1] In the treatment are included the nonsteroidal anti-inflammatory drugs (NSAIDs), synthetic and biological disease-modifying antirheumatic drugs (DMARDs), analgesic agents and non-pharmacological measures seeking to alleviate pain, reduce the damage and preserve the joint function.[2]

DMARDs are by definition drugs associated with the reduction of the articular and bone damage caused by the disease. Among the DMARDs, methotrexate (MTX) has been the most used. This drug was discovered in 1948 and was initially indicated for the treatment of neoplastic diseases. In 1951, it was used for the first time for the treatment of psoriatic arthritis. In 1980 it started to be used for the treatment of RA, showing a good response and an adequate safety profile. Since the 1990s, MTX became the DMARD of first choice.[3,4] A significant percentage of patients do not respond clinically to treatment. Because of the limited result of monotherapy with this drug, combinations of MTX with other traditional DMARDs are used to increase the response percentage in the treatment of RA.[5]