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PHARMACOGENETIC STRATIFICATION OF METHOTREXATE-INDUCED LIVER INJURY RISK IN RHEUMATOID ARTHRITIS PATIENTS

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Background

Methotrexate (MTX) is the recommended first-line conventional synthetic disease-modifying antirheumatic drug for rheumatoid arthritis (RA), endorsed by current ACR and EULAR guidelines as the anchor agent for both monotherapy and combination regimens [2, 5]. Despite proven efficacy, MTX therapy is limited by hepatotoxicity, occurring in 15–25% of patients and necessitating dose reduction or discontinuation in 5–10% of cases. The CYP2C9 enzyme participates in oxidative metabolism of various drugs including MTX metabolites and concomitant nonsteroidal anti-inflammatory drugs. The CYP2C9*2 polymorphism (Arg144Cys, rs1799853) is a common loss-of-function variant reducing enzymatic activity by 30–50% [1, 3]. The Clinical Pharmacogenetics Implementation Consortium has published guidelines for CYP2C9 genotype-guided drug dosing [6]. Population-specific data on CYP2C9*2 frequency and clinical impact in Central Asian populations remain limited [7].

Keywords: rheumatoid arthritis, CYP2C9*2, rs1799853, pharmacogenetics, methotrexate, hepatotoxicity, personalized dosing, Uzbek population.



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Aim

To investigate the association of CYP2C9*2 polymorphism with rheumatoid arthritis susceptibility and methotrexate-induced hepatotoxicity in an Uzbek population of the Fergana Valley region.

Materials and methods

100 patients with verified RA based on ACR/EULAR 2010 criteria and 73 ethnically-matched healthy controls were enrolled. Of 100 RA patients, 68 received methotrexate therapy at standard doses (15–25 mg/week) for at least 6 months. Hepatotoxicity was defined as elevation of ALT or AST above 2-fold the upper limit of normal (40 U/L) on at least two consecutive measurements at least 4 weeks apart, in the absence of other causes. CYP2C9*2 (rs1799853) genotyping was performed by real-time PCR with TaqMan probes. Multivariable logistic regression was applied to identify independent predictors of hepatotoxicity.

Results

CYP2C9*2 polymorphism showed no significant association with RA risk in the overall sample (OR=1.46; 95% CI: 0.83–2.57; $p=0.195$). Among 68 MTX-treated patients, 13 (19.1%) developed hepatotoxicity, in line with reported rates from international cohorts [4]. Carriers of unfavorable CT+TT genotypes accounted for 61.5% of hepatotoxicity cases vs 25.5% in the no-hepatotoxicity group (OR=4.67; 95% CI: 1.42–15.3; $p=0.012$; AUC=0.71). Mean ALT levels were 28.4 ± 3.8 U/L in CC homozygotes, 48.2 ± 5.4 U/L in CT heterozygotes and 72.6 ± 9.8 U/L in TT homozygotes ($p < 0.001$ for trend). The CYP2C9*2 T allele frequency in the Uzbek control group (13.0%) occupies an intermediate position between European (10–14%) and East Asian (0–4%) populations [7]. Multivariable logistic regression confirmed CYP2C9*2 CT+TT genotype as the



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strongest independent predictor of MTX hepatotoxicity (adjusted OR=4.86; 95% CI: 1.38–17.1; $p=0.014$) after adjustment for age, BMI, baseline liver enzymes and MTX dose. Modeling of genotype-guided dose modification (25–50% reduction in CT+TT carriers) demonstrated potential reduction of hepatotoxicity rates from 25.0% to 5.4% in this subgroup, representing a 78% relative risk reduction.

Conclusion

CYP2C9*2 polymorphism is not associated with rheumatoid arthritis susceptibility but represents a strong pharmacogenetic predictor of methotrexate-induced hepatotoxicity in an Uzbek population. Pretreatment CYP2C9*2 genotyping enables identification of patients requiring dose reduction and intensified hepatic monitoring. Implementation of genotype-guided MTX dosing aligns with international pharmacogenetic principles and may substantially reduce hepatotoxicity rates in carriers of unfavorable variants.

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