BIOMARKERS OF METOTHREXATE ADVERSE REACTIONS IN RHEUMATOID ARTHRITIS PATIENTS

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Background: According to the recent study [1] adverse drug reactions (ADR) associated with metothrexate (MTX) use in rheumatoid arthritis (RA) patients most frequent occur in women, at a younger age, with the absence of folate supplementation, with high body mass index (BMI) and decreased creatinine clearance (<50 ml/min).

Objectives: To reveal biomarkers associated with MTX adverse reactions in RA patients and to estimate their prognostic value.

Methods: In the observational trial of RA patients (n=500: 405 women, 95 men) treated with disease modifying antirheumatic drug MTX was used in 30.6% (153/500) of patients and MTX withdrawal due to the adverse reactions occurred in 41.2% (63/153; CI_{95} 33.7-49.1%) of them. This level of ADR frequency associated with WTX use was considered as MTX adverse reactions pretest probability (P_{pre}). Association between MTX ADR and a number of biomarkers (sex, triggers and age of RA onset, variant of early RA, rheumatoid factor (RF) presence during the first year of the disease, extraarticular manifestations, rapid RA progress (systemic manifestations, joint damage or disability during the first three years of the disease), comorbidity and BMI) was investigated.

Statistical significance of revealed association was estimated by Fisher exact test. Likelihood ratio of positive (LR^+) and negative (LR^-) tests and prognostic odds ratio (pOR) were calculated and post-test probability (P_{post}) of MTX adverse reactions was determined.

Results: Gastrointestinal ADR and hepatotoxicity were registered in 13.1% (20/153) of patients, mucocutaneus ADR in 12.4%, haematological abnormalities in 10.5% and infections in 9.8% of patients. MTX ADR significantly more frequent registered in patients with RA extraarticular manifestations and a number of comorbidities preceeding MTX prescription. Operational parameters of revealed biomarkers were determined as predictors of A_1 outcome (MTX ADR^+) and A_2 outcome (MTX ADR^-):

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Sjögren's syndrome (61.9% and 37.9%, p=0.0338; LR^+=2.32, LR^-=0.87, P_{post}=61.7%);

rapid RA progress during the first three years of the disease (88.9% and 38.2%, p=0.0037; LR^+=12.95, LR^-=0.88, P_{post}=90.7%);

chronic cholecystitis (50.5% and 25.0%, p=0.0022; LR^+=1.46, LR^-=0.48, P_{post}=52.5%);

chronic hepatitis (58.8% and 36.1%, p=0.0288; LR^+=2.04, LR^-=0.81, P_{post}=60.7%);

chronic obstructive pulmonary disease (60.0% and 35.1%, p=0.0137; LR^+=2.05, LR^-=0.77, P_{post}=60.8%);

anaemia (41.4% and 8.3%, p=0.0150; LR^+=1.13, LR^-=0.13, P_{post}=46.1%);

arterial hypertension (52.1% and 31.7%, p=0.0135; LR^+=1.56, LR^-=0.66, P_{post}=54.2%);

multiple local chronic infections ≥2 (50.6% and 28.8%, p=0.0080; LR^+=2.53, LR^-=0.58, P_{post}=65.7%).

We revealed no association between MTX ADR and sex, triggers and age of RA onset, variant of early RA, RF presence in the first year of the disease, as well as BMI.

Conclusions: Presence of several independent biomarkers of MTX ADR in RA patient considerably increases the post-test probability of prediction of ADR, associated with MTX, closely approaching the threshold levels of prediction: P_{post}≥95% for the approval of the hypothesis (A_1 outcome) or P_{post}≤5% for the acceptance of the alternative hypothesis (A_2 outcome).

References:

Hoekstra M, van Ede A E, Haagsma C J et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Ann Rheum Dis 2003;62:423-426.

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