GENETIC MARKERS OF SULPHASALAZINE ADVERSE REACTIONS IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Adverse drug reactions (ADR) associated with sulphasalazine (SS) use and leading to its withdrawal occur in 20-30% of rheumatoid arthritis (RA) patients treated with SS and include dose-dependent (gastrointestinal and central nervous system abnormalities) and immunomediated (vasculitis, pneumonitis, hepatitis, leucopenia, agranulocytosis, haemolytic and aplastic anemia) events [1,2].

Objectives: To reveal genetic markers associated with SS 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 SS was used in 11.6% (58/500) of patients. SS withdrawal due to the adverse reactions was registered in 43.1% (25/58; CI_{95} 31.2-55.9%) of them. This level of ADR frequency associated with SS use was considered as SS adverse reactions pretest probability (P_{pre}). Association between SS ADR and a number of genetic markers (erythrocytic antigens of AB0 and Rh_0 blood groups and leucocyte antigens of A, B, C, DR, DQ locuses of major histocompatibility complex) was investigated. All markers were dichotomic ($marker^+$, $marker^-$). Statistical significance of the revealed association was estimated by Fisher exact test. Likelihood ratio of positive (LR^+) and negative (LR^-) tests and prognostic odds ratio (pOR) as well as post-test probability (P_{post}) of SS adverse reactions were calculated.

Results: Gastrointestinal ADR were registered in 20.7% (12/58) of patients, mucocutaneous ADR in 8.6%, urine analysis abnormalities in 8.6%, and haematological abnormalities in 5.2% of patients. The rates of SS adverse events were significantly higher in the case of following phenotypes:

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HLA-$A1^+$ vs HLA-$A1^-$: 80.0% (8/10) and 35.5% (11/31), $p_{2\text{-}t}$=0.0265;

HLA-$A2^-$ vs HLA-$A2^+$: 64.0% (16/25) and 18.8% (3/16), $p_{2\text{-}t}$=0.0092;

HLA-$B8^+$ vs HLA-$B8^-$: 87.5% (7/8) and 36.4% (13/33), $p_{2\text{-}t}$=0.0157;

HLA-$B15^-$ vs HLA-15^+: 54.5% (18/33) and 12.5% (1/8), $p_{2\text{-}t}$=0.0268.

On the basis of these findings operational parameters of the revealed markers were determined as predictors of A_1 outcome (SS ADR^+) and A_2 outcome (SS ADR^-):

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HLA-A1: pOR=7.3; $A1^+$: LR^+=4.6, P_{post}=77.7%; $A1^-$: LR^-=0.64, P_{post}= 32.6%;

HLA-A2: pOR=7.7; $A2^-$: LR^+=2.1, P_{post}=61.4%; $A2^+$: LR^-=0.27, P_{post}= 17.0%;

HLA-B8: pOR=12.3; $B8^+$: LR^+=8.1, P_{post}=86.0%; $B8^-$: LR^-=0.66, P_{post}= 33.3%;

HLA-B15: pOR=8.4; $B15^-$: LR^+=1.4, P_{post}=51.5%; $B15^+$: LR^-=0.17, P_{post}= 11.4%.

Conclusions: Revealed phenotypes are useful as supplementary predictors of SS adverse reactions in RA patients in the case of uncertain prognosis (outcome A_3, 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:

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