OP0034 **IDENTIFICATION OF GENETIC VARIANTS ASSOCIATED WITH RESPONSE TO METHOTREXATE IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS: RESULTS FROM THE OPTIMA STUDY**

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Background: Genetic factors related to treatment response in rheumatoid arthritis (RA) have been described. International recommendations for the management of RA suggest initial therapy with synthetic DMARDs, with methotrexate (MTX) typically administered as first-line therapy. However, responses to MTX are

variable, and more than 30%[1] of patients fail to respond. Despite many studies, few genetic factors specifically associated with MTX response have been identified.

Objectives: To identify genetic variants associated with response to MTX in patients with early RA.

Methods: OPTIMA was a 78-week, multicenter, randomized, double-period, double-blind study in which patients were randomized 1:1 to combination therapy with adalimumab plus MTX or MTX alone during the initial study period (26 weeks). Enrolled patients were invited to participate in a genetic sub-study and asked to provide written, informed consent. 384 variants in genes previously shown to be associated with RA or treatment response were assayed using the Illumina BeadXpress GoldenGate Assay. Changes in the 28-joint disease activity score (DAS28) and the total Sharp score (TSS) following 26 weeks of treatment were assessed for association with allele status using genotypic tests.

Results: A total of 448 patients randomized to MTX were included in the genetic sub-study. Two SNPs in MTHFR (rs1801133 and rs1801131) and one SNP in ATIC (rs2372536)[1], previously shown to be associated with MTX response, were not associated with a change in DAS28 or TSS following MTX treatment. However, other SNPs within genes that have been associated with RA or treatment response, such as ABCB1, TNF-alpha, PTPRC, STAT4 and HLA-DRB1, did show association with MTX treatment (Table). For some genes, such as ABCB1, multiple SNPs were identified, suggesting that haplotype analysis could identify stronger associations. SNPs within ABCB1 and PTPRC were also associated with a change in TSS. In addition, a SNP within ADORA2a associated with a change in TSS. SNPs within this gene have previously been associated with MTX toxicity, however, analysis of the impact of this gene on efficacy have been more limited.

Gene	SNP	Mean change in DAS28 major allele (# subjects)	Mean change in DAS28 heterozygote (# subjects)	Mean change in DAS28 minor allele (# subjects)	DAS28 change p-value	TSS change p-value
ABCB1	rs1202184	–2.3 (87)	–1.8 (198)	–2.2 (82)	0.0071	NS
ABCB1	rs2188526	–2.2 (104)	–1.8 (187)	–2.3 (76)	0.0039	NS
ABCB1	rs4148738	–2.2 (109)	–1.8 (193)	–2.3(66)	0.011	NS
ABCB1	rs4148743	–2.2 (83)	–1.8 (202)	–2.2 (83)	0.018	0.033
PTPRC	rs2359952	–1.8 (150)	–2.2 (147)	–2.1 (38)	0.033	0.028
STAT4	rs11685878	–1.8 (142)	–2.2 (153)	–2.0 (70)	0.035	NS
STAT4	rs12327969	–1.9 (217)	–2.3 (128)	–1.8 (23)	0.025	NS
HLA-DRB1	rs4678	–2.0 (243)	–2.0 (118)	–3.4 (8)	0.016	NS

Conclusions: Genetic polymorphisms in genes such as ABCB1, TNF-alpha, PTPRC, STAT4 and HLA-DRB1 were shown to associate with MTX treatment in the OPTIMA study. These results may prove useful for the development of future diagnostic tests or personalized therapeutics for MTX treatment.

References:

[1] Malik et al. Pharmacogenomics (2013). 14(3), 305-314.

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