Published in final edited form as:

Ann Rheum Dis. 2014 April 1; 73(4): 785–786. doi:10.1136/annrheumdis-2013-204263.

Gene-body mass index interactions are associated with methotrexate toxicity in rheumatoid arthritis

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Keywords

Gene polymorphism; methotrexate; rheumatoid arthritis

Despite the introduction of multiple biologic agents for the treatment of rheumatoid arthritis (RA), methotrexate (MTX) remains the initial drug of choice.[1]Response to MTX therapy is highly heterogeneous between individuals. An extensive body of work illustrates the complexity of MTX response architecture, which includes genetic polymorphisms, environmental factors, and gene-gene interactions.[2] Among environmental contributors, elevated body mass index (BMI) has emerged as an important predictor of MTX toxicity.[3] Using data from the Treatment of Aggressive Rheumatoid Arthritis (TEAR) trial,[4] we present first evidence linking the risk of MTX-associated toxicity to interactions between genotype and BMI.

The TEAR trial, described in previous publications,[4]compared two strategies (early intensive therapy versus step-up therapy) and two combinations of medications (etanercept (ETN) plus MTX versus triple therapy)in treatment of early aggressive RA. Drug toxicity was assessed every 6 weeks via laboratory measures (liver enzymes, cytopenia, platelet count) and/or self-report of adverse events. All participants received a daily 1 mg supplement of folic acid; approximately half experienced MTX toxicity over 24 weeks, with upper respiratory infections (19%) as the most common form.

Of 755 TEAR participants, 491 were successfully genotyped using a custom panel of 3,127 single nucleotide polymorphisms (SNPs), comprised of variants related to MTX metabolism pathways or RA susceptibility. The study population was randomly allocated (3:1) to discovery (n= 368) and replication (n=123). Logistic regression models tested for associations between the SNPs and MTX toxicity, adjusting for age, sex, race, treatment, active smoking (serum cotinine > 5 ng/mL), BMI, and interaction terms. Interactions with SNPs that reached nominal significance (P<0.05) were tested for replication (Table 1).

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Contributorship: SA designed the study and wrote the manuscript; JS and DR conducted the statistical analyses; LWM, JRO, JRC, and SLB conducted the parent TEAR trial and contributed to the interpretation of the findings; TRM measured smoking status of TEAR participants; DKA interpreted the findings and revised the draft paper.

Competing interests: The authors declare no competing interests.

In the overall population, BMI was not significantly associated with MTX toxicity ($P=0.22$). However, among carriers of at least one copy of the minor allele at either locus, the estimate of BMI effect was fourfold higher than in wild type individuals ($P=0.07$ for rs12651804, $P=0.09$ for rs1504582).

Both variants were associated with MTX toxicity but not efficacy. The rs12651804 variant is located in *CMYA5*, an RA susceptibility gene.[5] To our knowledge, this is the first evidence of gene-environment interactions at that locus. In contrast, the genomic region containing rs1504582 offers insights into the biological mechanisms. It is located near the gene encoding CCL2, a proinflammatory mediator upregulated in both RA [6] and obesity. [7] Our findings contribute to the evidence of synergy between obesity and autoimmune disease.

This study is limited by its broad definition of adverse events, necessitated by statistical power concerns. Future studies are warranted to confirm our findings and investigate the interplay between genes and BMI in more narrowly defined categories of MTX toxicity. Upon successful validation, our findings will inform development of more accurate and complete algorithms of MTX response prediction.

Acknowledgments

The authors have no acknowledgments.

Funding information: This analysis was funded by the National Institutes of Health (NIH P60 AR048095 and ARRA supplement 3P60AR048095-07S1; NIH R01 AR052658; 5UL1RR025777-03, 5KL2RR025776-03, 5TL1RR025775-03), while the parent TEAR trial was funded by Amgen.

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Table 1

Evidence of gene-BMI interactions in MTX toxicity.

SNP	Minor Allele Frequency	Interaction		Genetic Main Effects			
		Discovery Effect	P	Replication Effect	P	Discovery Effect	Replication Effect
rs12651804	0.24	0.08	0.005	0.14	0.04	2.44	4.03
rs1504582	0.15	0.10	0.005	0.18	0.05	3.28	6.50