ABC Transporter Genes and Methotrexate Response in Rheumatoid Arthritis

To the Editor:

In a recent issue, de Rotte, *et al*¹ reported that 3 single-nucleotide polymorphisms (SNP) in 3 key methotrexate (MTX) transporter genes were determinants of response to MTX in patients with juvenile idiopathic arthritis (JIA). These investigators are to be commended for their efforts in a field, juvenile arthritis, where there is a relative scarcity of data on MTX pharmacogenetics, compared to adult rheumatoid arthritis (RA). Their study examined the association between 21 SNP in 13 genes involved in MTX cellular transport and polyglutamation, and found 3 SNP in *SLC19A1*, *ABCB1*, and *ABCC3*, all 3 transporter genes, were associated with MTX efficacy in a cohort of 287 patients with JIA.

Our study in adult patients with RA² using a retrospective cross-validation approach demonstrated that 4 SNP, one in *ABCB1* and 3 in *ABCC2*, were associated with an increased risk of MTX toxicity in our training cohort. These SNP were predictors of individual toxicities such as alopecia and gastrointestinal and hepatic toxicity, except the *ABCB1* SNP, which was a marker of overall toxicity. These associations differed by race, with unique genetic markers in whites and African Americans with RA. In our validation cohort, one of the *ABCC2* SNP (an intronic SNP) influenced MTX toxicity-related time to discontinuation or dose decrease; again, this was race-specific, and this effect was seen only in white patients with RA².

It would be interesting to know whether similar associations were found in the cohort studied by de Rotte, *et al*. Because that was a prospective, longitudinal cohort followed for 1 year, data on any associations (or lack thereof) between the transporter gene SNP and MTX toxicity would be valuable, if ascertainable. Because it appears that laboratory measurements and reasons for discontinuation of MTX in the cohort were documented, the question of whether there were any associations between these SNP and MTX toxicity and toxicity-related discontinuation could be

answered. It is important to note that this was a pediatric cohort, and such data, if available, will give important insights into whether MTX pharmacogenetic associations are comparable in pediatric and adult RA populations, a subject on which there is a paucity of data to date³. Unfortunately, the effect of race on such associations cannot be determined using this cohort, as it was racially homogeneous.

ABC transporter gene SNP appear to determine MTX response both in adult RA and in JIA, but affect different outcomes, i.e., toxicity in adult RA and efficacy in JIA. This is an area of MTX pharmacogenetics that needs further investigation.

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