

Test May Flag Psoriasis' Response to Methotrexate

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ZURICH — The goal of individualized methotrexate therapy for psoriasis has drawn a big step closer as a consequence of a large pharmacogenetic study that identified polymorphisms in key genes in the drug's metabolic pathway that are associated with increased likelihood of favorable response or toxicity.

"By combining screening for some of these polymorphisms in the pathway, we may get a sort of pharmacogenetic index—a simple number that conveys the likelihood of efficacy or toxicity. That's



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DR. WARREN

certainly one of our aims," Dr. Richard B. Warren explained at the annual meeting of the European Society for Dermatological Research.

The ability to predict a patient's likely response to methotrexate (MTX) would breathe new life into an old but still useful and attractively priced drug. A year's worth of MTX for psoriasis costs about 90 euros (\$120), compared with more than 13,000 euros (\$17,500) for many biologic agents, noted Dr. Warren of the University of Manchester (U.K.).

In general, 20%-30% of psoriasis patients have moderate to severe disease. Many of these patients will require systemic therapy, and MTX will remain a first-line option for the foreseeable future. But the drug's utility has been limited until now by a less than stellar risk-benefit ratio. MTX is effective in about 60% of treated patients, while 30% develop significant toxicities. There has been no way to predict who would benefit or be harmed—until the recent arrival of the pharmacogenetic era, the dermatologist said.

Dr. Warren presented retrospective data on 378 chronic plaque psoriasis patients treated with MTX. He and his coworkers analyzed a large number of single-nucleotide polymorphisms in enzymes coded by nine genes prominent in the MTX metabolic pathway. Then they studied how these genetic variants were distributed among patients with different clinical outcomes. MTX was considered effective in a patient who achieved a (psoriasis area severity index) PASI 75 score. To be classified as a nonresponder, a patient had to be on at least 15 mg/week for 3 months without attaining PASI 50.

Only a single polymorphism was strongly associated with MTX efficacy. It was located on ABCC1, the efflux carrier gene, which codes for a protein serving as a pump that removes MTX from the cell. Carriage of two copies of the most common genotype of the polymorphism was associated with a 2.2-fold increased likelihood of a positive response to MTX, probably because it

codes for a less active pump and consequently higher intracellular drug levels.

Three polymorphisms located elsewhere on ABCC1 were associated with MTX toxicity. The most potent of the three, known as rs246240, conferred a 2.2-fold increased risk of MTX-related adverse events and was strongly associated with GI toxicity in particular.

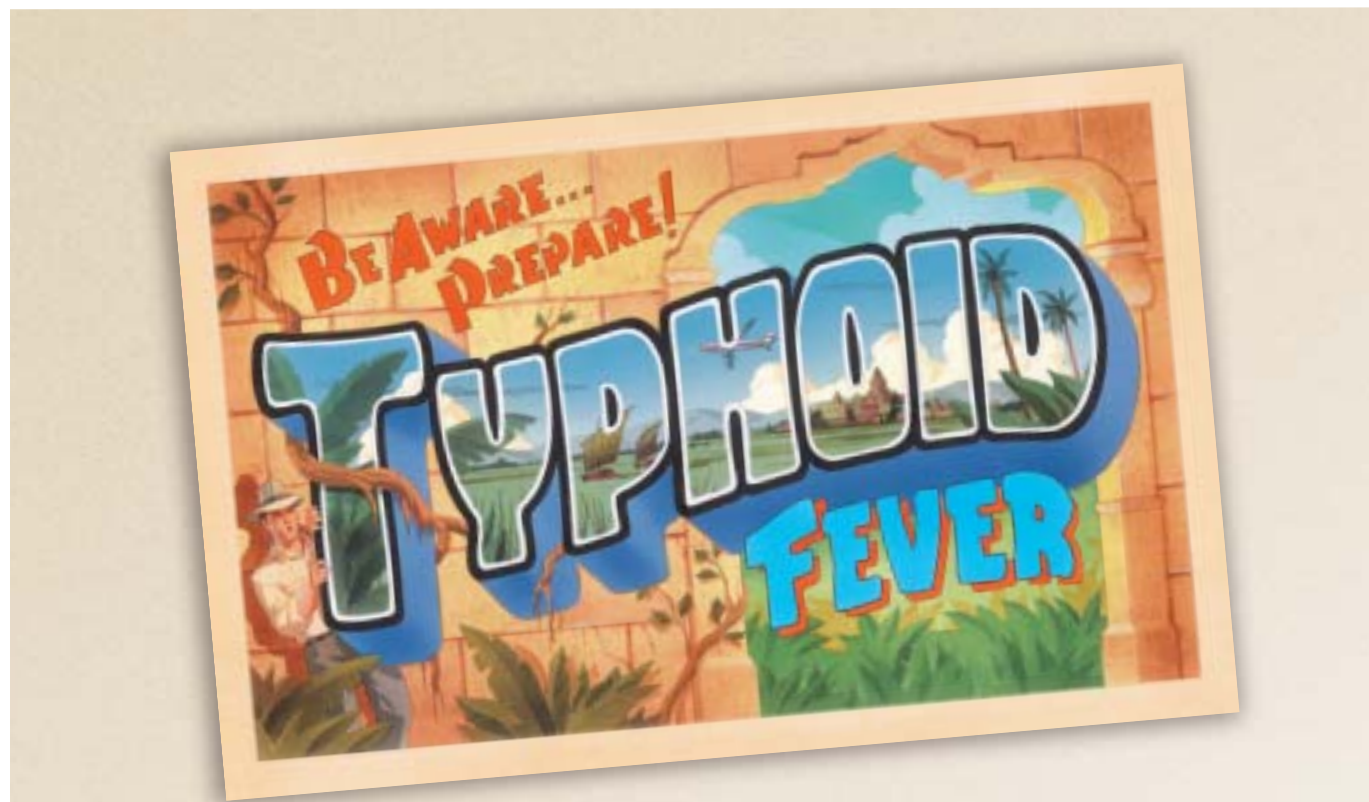
No associations were found between patient outcomes and the genes coding for glutamate enzymes, which convert MTX

from a prodrug to its active form within target cells. Nor were outcomes associated with variations in the gene coding for the adenosine A2 receptor, which helps mediate the drug's anti-inflammatory effects.

Similarly, polymorphisms found in the 5, 10-methylenetetrahydrofolate reductase (MTHFR) gene were unrelated to outcomes. This was surprising, Dr. Warren said, because other researchers had linked two polymorphisms on MTHFR with MTX efficacy and toxicity in rheumatoid

arthritis patients. "In this bigger cohort, we were unable to replicate that finding."

Audience members, quick to grasp the potential clinical import of Dr. Warren's findings, wanted to know if they can start sending him blood samples from psoriasis patients being considered for systemic therapy. Not yet, he replied. Although this was one of the largest-ever pharmacogenetic studies of MTX metabolism, it was retrospective and requires confirmation in an independent patient cohort, he said. ■



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