Test May Flag Psoriasis’ Response to Methotrexate

BY BRUCE JANCIN
Denver Bureau

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 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 coding for glutamate enzymes, which convert MTX to a produg to its active form within target cells. Nor were outcomes 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 produg 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.