Researchers Confirm PsA Susceptibility Allele

BY KERRI WACHTER

FROM ARTHRITIS & RHEUMATISM

European researchers have confirmed a new independent susceptibility allele for psoriatic arthritis that could possibly represent a new candidate pharmacogenetic marker for the disease.

"In this collaborative work, we replicated the association of TNF*-857T as a susceptibility allele for [psoriatic arthritis (PsA)] independent of the main PSORS1 risk allele," wrote Emiliano Giardina, Ph.D., of the University of Rome, and his colleagues in an article published online in the journal (doi:10.1002/art.30591).

VITALS

Major Finding: TNF*-857T is a susceptibility allele for PsA independent of the main PSORS1 risk allele.

Data Source: A study of 2,224 individuals.

Disclosures: The study was supported by a research grant from the Italian Association for the Defense of Psoriatic Patients, the Interdisciplinary Centre for Clinical Research at the University of Erlangen-Nuremberg (Germany), and the Bath (England) Institute for Rheumatic Diseases. Two researchers were received grants from Wyeth-Pharm GmbH (Germany).

It's long been known that the strongest and most replicated susceptibility region for psoriatic vulgaris – and by extension PsA – is within the major histocompatibility complex (MHC) region (PSORS1-psoriasis susceptibility region). "This locus maps to chromosome 6p21.3, comprising many different class I antigens associated with disease expression. Human leukocyte antigen (HLA)-C was repetitively reported as the PSORS1 gene and HLA-Cw*06:02 as the susceptibility allele," they noted.

In this study, the researchers attempted to confirm this finding by assessing allele and genotype frequencies of TNF*-857 in three independent cohorts. They included a German cohort (374 cases and 561 controls), an Italian cohort (400 cases and 400 controls), and a British cohort (135 cases and 354 controls.

The overall cohort of 2,224 individuals of European ancestry was assessed for distribution of HLA-Cw*06:02/PSORS1 risk allele and also was typed for TNF*-857T. The overall allele frequency of TNF*-857T was significantly higher in individuals with PsA (27%) than in control individuals (20%).

The researchers calculated the genotype frequencies of TNF*-857T in samples that were positive and negative for the PSORS1 risk allele, in order to verify the existence of an association independent of the PSORS1 risk allele.

"Overall, the frequency of heterozygous or homozygous carriers of TNF*-857T (TT/CT) in individuals negative for the PSORS1/HLA-C risk allele was significantly higher in PsA patients (30%) than in control subjects (21%)," they reported. This yielded an odds ratio of 1.35

"As expected, the haplotype analysis confirmed TNF*-857T as a susceptibility factor independent of the PSORS1/HLA-C risk allele," they wrote. Association of PsA to TNF*-857T was significant in individuals not carrying the PSORS1/HLA-C risk allele, with an odds ratio of 1.27.

"Although the functional role of TNF*-857T remains to be determined, previous data could show that the allele T increases the transcription of TNF-alpha."

In addition, tumor necrosis factor–alpha is known to play a pivotal role in both the activation and extravasation of T cells in the highly vascularized synovium, as well as in subchondral osteoclastogenesis promoting bone erosions. Genes encoding for TNF-alpha, along with other cytokines, could be candidate pharmacogenetic markers. ■

VIEW ON THE NEWS

Findings Confrims Earlier Research

Amost intriguing aspect of psoriasis epidemiology is that about a quarter of these patients will develop psoriatic arthritis, and this disease clusters in families with remarkably high heritability. Despite evidence for genetic factors in this disease, the search for genes associated with arthritis and not psoriasis has been challenging because almost all PsA patients also have psoriasis. PSORS-1, the MHC region that contains Cw6, the allele with the strongest association with psoriasis, is characterized by long linkage disequilibrium. One report noted an association of PsA with the TNF*-857T allele that was independent of PSORS1. In this multinational study of 909 patients and 1,315 healthy controls, the TNF*-857T allele was found at significantly higher frequency in PsA patients negative for the PSORS1 allele (30%), compared with controls (21%). This study replicates findings in the previous study and is also of note because the TNF*-867T allele increases the transcription of TNF, a pivotal cytokine in the pathogenesis of PsA. Also of possible relevance is that this allele is associated with response to etanercept in RA. The replication of this important association should catalyze additional genetic and pharmacogenetic studies to better understand the diagnostic and functional significance of this allele in psoriatic disease.

CHRISTOPHER T. RITCHLIN, M.D., *is professor of medicine, allergy/immunology, and rheumatology at the University of Rochester (N.Y.) He reported having no conflicts of interest that are relevant to this piece.*

New Protein Marker Predicts Success of JIA Treatment

BY JENNIE SMITH

FROM THE 18TH EUROPEAN PEDIATRIC RHEUMATOLOGY CONGRESS

BRUGES, BELGIUM – Blood levels of an inflammatory protein have been found to be strongly predictive of how well a child with juvenile idiopathic arthritis will do on methotrexate, U.K. researchers have learned.

Children with higher serum levels of myeloid-related protein 8/14 (MRP8/14) were seen to respond considerably better.

The MRP8/14 findings came from Sparks CHARMS (Childhood Arthritis Response to Medication Study), which used a cohort of 109 previously untreated children with JIA to assess predictors of success with methotrexate. The findings represent a step toward the "ambitious goal" of personalized medicine for JIA, said Halima Moncrieffe, Ph.D., of University College London (Pediatr. Rheum. 2011;9[Suppl. 1]:O10), who presented the data on MRP8/14. Dr. Moncrieffe noted that serum MRP8/14 is "relatively easy to measure," and that samples do not require cold storage.

High levels of MRP 8/14 were shown to be the most strongly predictive factor in a JIA patient achieving an American College of Rheumatology score of 50 or higher at 6 months on methotrexate, with the likelihood of achieving ACR50 or better increasing with every 500-ng/mL serum increase. Of patients with MRP8/14 levels above 3,000 ng/mL at baseline, 96% went on to achieve an ACR50 or higher response to methotrexate. High serum levels were predictive of response to methotrexate regardless of the type of JIA or age at onset; however, patients with systemic JIA were excluded from the study.

Dr. Marieke Otten of Erasmus University Medical Center in Rotterdam (the Netherlands) presented data on clinical indicators of treatment success or failure with etanercept in a cohort of JIA patients (Pediatr. Rheum. 2011;9[Suppl 1]:O28). Ongoing research is examining the usefulness of baseline MRP levels as response predictors, she noted.

Dr. Otten and her associates enrolled 262 patients who had never been prescribed a biologic agent to control their disease before starting etanercept. The patients had been enrolled in the Dutch Arthritis and Biologicals in Children register, which since 1999 has kept data on all Dutch JIA patients using etanercept. The register is funded in part by an unconditional grant from Abbott.

They collected baseline clinical data using the physician's global assessment of disease activity and children's health assessment questionnaire scores. The investigators' goal was to identify clinical predictors of poor response to etanercept and which clinical characteristics might predict adverse events during treatment. However, the study failed to show any significant associations for adverse effects.

VITALS

Major Finding: Serum levels of the inflammatory protein MRP8/14 were elevated in 96% of children with JIA who went on to respond well to methotrexate.

Data Source: Data from a Dutch register of 109 children with JIA.

Disclosures: Dr. Moncrieffe's study was sponsored by Sparks-UK, the Big Lottery Fund, Arthritis Research U.K., and the Great Ormond Street Hospital Children's Charity.

"It has been proven that etanercept is highly effective in juvenile idiopathic arthritis, and under current treatment strategies inactive disease seems to be a realistic treatment goal," said Dr. Otten. "However, a still-substantial proportion of patients do not reach the goal of inactive disease."

About a third of the patients in Dr. Otten and colleagues' study (32%, n = 85) reached clinically inactive disease after 15 months on etanercept. Another third had an ACR50 response or better but did not reach inactive disease, and the last third (34%, n = 88) reached a poor response, defined as less than ACR50, or stopped etanercept early because of ineffectiveness or adverse effects, she said.

Children who began etanercept treatment before trying disease-modifying antirheumatic drugs improved more than those who had been on them previously. This finding was "really important," as it indicated "the earlier and more aggressively we treat, the better the patients get," she said. ■