Gene Analysis Ties Variant to Psoriatic Arthritis

BY BRUCE K. DIXON
Chicago Bureau

Canadian researchers have taken an important step in the long-running process of identifying genetic causes of psoriatic arthritis.

The analysis, which targeted polymorphisms in the tumor necrosis factor–α (TNF-α) gene in two psoriatic arthritis populations, suggests that the –238(A) variant is a significant risk factor for this disease (Ann. Rheum. Dis. 2006;65:919-23).

The study involved 237 psoriatic arthritis patients and 103 controls from Newfoundland and 203 patients and 101 controls from Toronto. The mean age of patients in both groups was 50 years. With respect to the subtype of psoriatic arthritis in the two populations, 61% had the polyarticular pattern, 27% had the oligoarticular pattern, 5% had isolated spondyloarthropathy, and 7% had assorted other patterns, explained Dr. Proton Rahman and colleagues at St. Clare's Mercy Hospital in St. Johns, Newfoundland.

'Before our study, a significant association for [tumor necrosis factor–α] and psoriatic arthritis was noted only in German populations.'

"Before our study, a significant association for TNF-α and psoriatic arthritis was noted only in German populations. We examined five common variants with the TNF-α promoter gene, including –238 and –308. We noted a significant association between –238 variant and psoriatic arthritis," explained the investigators, who took the additional step of conducting a pooled analysis of nine cohorts from eight studies (including their own two Canadian cohorts). Again, the –238(A) gene polymorphism was a significant risk factor, though the six outside studies each used fewer than 150 probands and may have been underpowered.

"We acknowledge that population stratification was not entirely avoided as family-based controls were not used in these studies," the authors said, adding that publication bias may exist in the metaanalysis, because small, negative association studies often are not published. "As demonstrated in our study, because metaanalysis of association studies in complex diseases [is] helpful in estimating population-wide genetic effects, further efforts must be made to track all association data for a given polymorphism," they wrote.

The targeting of the TNF-α gene is supported by studies noting significantly higher serum, synovial fluid, and synovial membrane levels of TNF-α in patients with psoriatic arthritis, compared with either patients with osteoarthritis or healthy controls, the investigators point out. "The importance of TNF-α in psoriatic arthritis is further strengthened by the marked clinical response of TNF-α blockade."

However, genetic studies have produced conflicting results, with inconsistencies that may reflect insufficient sample sizes, differences in populations, the presence of linkage disequilibrium, or multiple testing, the authors said. ■

Phase II Efficacy Seen With New TNF Blocking Agent

BY NANCY WALSH
New York Bureau

AMSTERDAM — The therapeutic options for patients with rheumatoid arthritis who do not respond to methotrexate alone continue to expand, with a new tumor necrosis factor–α blocker showing efficacy in a phase II trial.

In preclinical studies, the human monoclonal antibody golimumab was shown to be more effective at neutralizing tumor necrosis factor–α (TNF-α) than the other currently available biologic agents, Dr. Jonathan Kay wrote in a poster session at the annual European Congress of Rheumatology.

At week 16, 62% of patients receiving golimumab plus methotrexate achieved an ACR 20 response, compared with 37% of those receiving placebo plus methotrexate.

And while golimumab must be given subcutaneously, the dosing interval is once every 4 weeks rather than twice weekly as is the case with etanercept, or every other week as with adalimumab. Because the drug can be given once a month, it may provide a convenient alternative for patients, Dr. Kay told RHEUMATOLOGY NEWS in an interview.

The investigators randomly assigned 172 patients with rheumatoid arthritis (RA) of at least 3 months' duration to placebo or treatment with golimumab with one of four dosages: 50 mg every 2 weeks, 50 mg every 4 weeks, 100 mg every 2 weeks, or 100 mg every 4 weeks. All patients also were on stable doses of methotrexate.

At week 16, 62% of patients who were receiving golimumab plus methotrexate achieved an American College of Rheumatology 20 response, which was the primary end point, compared with 37% of those patients who were receiving placebo plus stable doses of methotrexate, according to Dr. Kay of the rheumatology unit at Massachusetts General Hospital, Boston.

A secondary end point of the trial was the Disease Activity Score 28 response to active and placebo treatments.

This outcome measure can be calculated using either the erythrocyte sedimentation rate or C-reactive protein levels, and patients' responses to therapies are categorized as good, moderate, remission, and nonresponse.

Using the erythrocyte sedimentation rate, Disease Activity Score 28 remission plus good/moderate responses were seen in 72% and 10% of the golimumab and placebo groups, respectively, and in 74% and 27%, respectively, using C-reactive protein levels.

Serious adverse events were reported by 8% of patients receiving golimumab plus methotrexate and by 5.9% of those receiving methotrexate plus placebo.

"Clinically relevant" adverse events reported in the golimumab group included two cases of pneumonia, one case of heart failure, one case of lung cancer, and one case of cardiac tamponade, Dr. Kay reported.

There were no deaths or cases of tuberculosis or opportunistic infections, however.

The phase II study was supported by Centocor Research and Development Inc. The pharmaceutical company has initiated Phase III studies that are underway to evaluate golimumab in patients with RA, psoriatic arthritis, and ankylosing spondylitis.

The drug is being given in doses of 50 or 100 mg every 4 weeks in these trials, which will follow patients for 5 years. ■

Biomarker Predicts Joint Damage At 10 Years in Patients With RA

BY NANCY WALSH
New York Bureau

AMSTERDAM — Baseline levels of the leukocyte protein calprotectin in patients with rheumatoid arthritis correlated with clinical and radiographic outcomes at 10 years in a prospective longitudinal study, suggesting that this biomarker may be a useful predictor of joint damage, Dr. Hilde Berner Hammer reported at the annual European Congress of Rheumatology.

A cohort of 145 patients with early rheumatoid arthritis (RA) were enrolled during 1991 and 1992—before the era of biologic treatment—from the rheumatology departments of Diakonhjemmet Hospital in Oslo and University Hospital Maastricht (the Netherlands).

Baseline measurements included calprotectin levels, erythrocyte sedimentation rates (ESRs), and C-reactive protein levels. Radiographs of the hands were obtained, and modified Sharp scores were calculated. Damage was assessed according to the RA articular damage (RAAD) score and all measurements were repeated at 10 years, Dr. Berner Hammer wrote in a poster session at the meeting, sponsored by the European League Against Rheumatism.

The 88 patients with elevated levels of calprotectin (0.9 mg/L or more) at baseline and at 10 years also had high modified Sharp and RAAD scores at both time points. (See box.)

Moreover, patients who were rheumatoid factor positive had elevated calprotectin levels as well as high ESRs, modified Sharp scores, and RAAD scores, according to Dr. Berner Hammer of Diakonhjemmet Hospital.

Calprotectin is one of the calcium-binding proinflammatory S100 proteins released during cell activation. High levels of the protein have been found in the synovial fluid of RA patients. It is also upregulated in other immunopathologic conditions, particularly in the setting of acute inflammation or Th1-mediated reactions (Physiol. Res. 2004;53:245-53). An immunoassay for the detection of fecal calprotectin in patients with inflammatory bowel disease—marketed as PhiCal by Genova Diagnostics Inc.—was recently approved by the Food and Drug Administration.

This marker has also been investigated as a measure of disease activity in polymyalgia rheumatica and temporal arteritis. A group of 47 patients, 33 with polymyalgia rheumatica, 10 with temporal arteritis, and 4 with both conditions, were followed prospectively for up to 3 years. Calprotectin was highly correlated with acute phase parameters and ESRs, and levels fell significantly after the initiation of prednisone therapy (Scand. J. Rheumatol. 2005;34:125-8). ■

Mean Marker Levels and Sharp Scores

	At baseline	At 10-year follow-up
Calprotectin	3.7 mg/L	2.3 mg/L
CRP	11.7 mg/L	7.6 mg/L
ESR	25.3 mm/hr	18.0 mm/hr
Modified Sharp score	7.3	36.1

Note: Based on 88 rheumatoid arthritis patients.
Source: Dr. Hammer