Assay Combo Reveals Early Joint Damage in Osteoarthritis

BY DAMIAN McNAMARA
Miami Bureau

Fort Lauderdale, Fla. — People with symptomatic osteoarthritis can be differentiated from those with only radiographic evidence of disease using a combination of biomarkers, according to a study presented at the World Congress on Osteoarthritis.

Olga V. Nemirovsky, Ph.D., a researcher at Pfizer Inc. in St. Louis, and her associates, compared a large number of biomarkers of joint matrix protein degradation and synthesis and biomarkers of inflammation using urine, serum, and plasma samples from 83 participants.

Their aim was to identify biomarkers that would indicate any initial efficacy of disease-modifying osteoarthritis drugs for future clinical trials.

Participants included 22 people with symptomatic osteoarthritis; 30 people with only radiographic evidence of disease in their hip and/or knee joints; 19 with only radiographic evidence in their hand and/or spine joints; and 12 controls with no symptoms or radiographic signs of disease.

"We tried to assess each biomarker separately. Then we evaluated combinations of two biomarkers, and then applied multivariate analyses to all biomarkers," said Dr. Nemirovsky.

Five markers contributed the most to the distinction between symptomatic patients and the others: plasma procollagen type III N-terminal propeptides (PIIINP), prostaglandin PGE2, 15-hydroxyeicosatetraenoic acid (15-HETE), collagen type II neoepitope (TIINE), and procollagen type II N-terminal propeptide (NPII). Although analysis of individual markers revealed significant differences, a combination of markers proved superior to any single assay.

Patients with symptomatic osteoarthritis had significantly higher levels of urinary C-terminal telopeptides of type II collagen (CTX-II), TIINE and collagen type III neoepitope (TIIINE) levels, osteopontin, plasma procollagen type I (PINP), prostaglandin PGE2, 15-HETE, and 3-nitrotyrosine (3-NT) compared with other groups, Dr. Nemirovsky said at the meeting, which was sponsored by the Osteoarthritis Research Society International.

On the other hand, the researchers found significantly lower levels of plasma NPII and urinary aggrecan neoepitope (Agg) in the symptomatic group.

Levels of Agg were higher for the group with radiographic disease in the hip/knee compared with the no-radiographic-evidence group or the symptomatic patients. The researchers used a model to distinguish the patients with radiographic evidence of hip/knee osteoarthritis from the radiographic hand/spine and no-radiographic-evidence groups.

The markers that contributed most to this distinction were Agg, TIINE, PIIINP, PGE2, and 15-HETE. ■

Biomarkers Independently Predict OA Progression

BY DAMIAN McNAMARA
Miami Bureau

Fort Lauderdale, Fla. — Prediction of which patients with osteoarthritis will progress has been challenging for clinicians. However, there is promise—researchers identified serum and urinary markers independently associated with 5-year radiographic progression of knee osteoarthritis in a study presented at the World Congress on Osteoarthritis.

Combined use of serum type II collagen helical peptide (Helix-II) and urinary crosslinked C-telopeptide (uCTX-II) might predict disease outcome in these patients, Dr. Patrick Garnero said. Helix-II and CTX-II are type II collagen fragments believed to reflect different osteoarthritis breakdown events from the triple helix and the telopeptide regions of knee cartilage.

Dr. Garnero and his associates previously demonstrated that high *urinary* levels of these markers were associated with highly destructive hip osteoarthritis (Ann. Rheum. Dis. 2006;65:1639-44). However, urinary markers have limitations, including wide variations in urine dilution and some difficulty obtaining precise sampling among elderly patients.

"Based on this, we launched a study to investigate a new serum-based assay," said Dr. Garnero, a researcher at Synarc Inc. in Lyon, France.

They compared standing anterior-posterior knee x-rays and Helix-II and CTX-II levels among 83 patients with knee osteoarthritis at baseline and at 2, 3, and 5 years. At baseline, mean age was 62 years and 54% were women. In terms of disease severity, the majority (77%) of patients had a baseline Kellgren-Lawrence (KL) score of 3. The remaining patients scored as follows: KL 0, 13%; KL 1, 5%; KL 2, 4%; and KL 4, 1%.

Joint space was measured on radiographs at the narrowest point. Progression was defined as a reduction in tibiofemoral joint space of 2 mm or a need for total knee replacement during follow-up. A total of 24 patients progressed and 59 did not.

"At baseline and 5 years, both markers were higher in patients with progressive disease. It was not significant at baseline, but the average over 5 years was significant," Dr. Garnero said at the meeting, sponsored by the Osteoarthritis Research Society International.

For example, after adjustment for age, gender, and body mass index, each standard deviation increase in serum Helix-II was associated with a relative risk of 1.69 for progression. Patients with the highest quartile of serum Helix-II levels and a uCTX-II level above the median had a risk of radiologic progression 8 times higher (RR, 7.79).

"The combined measurement of serum helix-II and uCTX-II may be useful to predict disease outcome in knee osteoarthritis," Dr. Garnero said. ■

Who Knew: Knee Damage Progresses Symmetrically

BY DAMIAN McNAMARA
Miami Bureau

Fort Lauderdale, Fla. — Symmetrical bilateral progression of knee osteoarthritis was a surprising result of a genetic study of hand osteoarthritis patients and their relatives.

"The most surprising [finding] was that progression occurred in a similar manner on both sides. This indicates to me that there is probably a strong genetic factor for progression," Dr. Virginia Byers Kraus said in an interview during a poster session at the World Congress on Osteoarthritis, Osteoarthritis Research Society International.

Dr. Byers Kraus and associates studied 1,333 hand osteoarthritis patients for a median of 3.8 years. Participants whose osteoarthritis progressed in the medial compartment of one knee were significantly more likely to progress in the medial compartment of the other. The same held true for lateral compartment progressions.

"If you see these individuals [with hand OA], if they have an affected knee, the other is likely to be affected with osteoarthritis and they are likely to progress in parallel," said Dr. Byers Kraus, an internist in the division of rheumatology, Duke University Medical Center, Durham, N.C. "It's a probable prognostic factor for patients."

The cohort came from the Genetics of Generalized Osteoarthritis (GOGO) study. A total of 79% were women and the mean age was 69 years. Researchers scored baseline and follow-up radiographs for changes in Kellgren-Lawrence grade, minimal joint space, presence of osteophytes, and joint space narrowing of the medial and lateral knee compartments. They also assessed at least two affected siblings with three-joint bilateral bony enlargements in their hands to assess any genetic correlations.

"We found in a cohort with hand osteoarthritis they were more likely to have osteoarthritis [in other joints] if family members have hand osteoarthritis," Dr. Byers Kraus said. "When you have a patient with hand osteoarthritis and relatives with hand osteoarthritis, there is an increased likelihood of bilateral knee osteoarthritis."

The results may also have research implications. In studies of OA patients who don't progress, it's hard to assess the efficacy of a treatment. "This was responsible for the failure of a major trial on Actonel," said Dr. Byers Kraus. "Age, female gender, obesity—outside of these, we are not good at identifying definite progressors." ■

New Osteoarthritis Research Targeting Bone, Not Cartilage

BY BETSY BATES
Los Angeles Bureau

Beverly Hills, Calif. — New ideas about the causes of osteoarthritis may lead to targeted therapeutic advances like those currently available for rheumatoid arthritis, Dr. Steven R. Ytterberg said at the annual meeting of the American Association for Hand Surgery.

The first conceptual shift is the notion that osteoarthritis probably is not a disease, but a clinical and pathologic outcome arising from a range of disorders, explained Dr. Ytterberg, a clinical rheumatologist and researcher at the Mayo Clinic, Rochester, Minn.

He noted wide disparities in the characteristics of primary vs. secondary osteoarthritis; localized, single-joint disease vs. generalized osteoarthritis; and osteoarthritis associated with osteophyte necrosis, inflammation, or crystal deposition. Dr. Ytterberg compared, for instance, inflammatory, erosive osteoarthritis of the hands with diffuse idiopathic skeletal hyperostosis (DISH).

"Is this all the same disease? I don't know that it makes sense that it is," he said.

Another major shift is in the way researchers are studying development of osteoarthritis.

"With osteoarthritis, the focus has always been on cartilage. To begin to see frayed cartilage through the arthroscope has always been presumed to be where the action is."

Microscopic disruption of the extracellular matrix, and later, macroscopic clefts in the cartilage were seen as progressive evidence of encroaching disease.

Now, the focus has shifted, and the target of research is bone. "A large amount of information is now calling attention to what's going on in the chondrocytes: potential changes in cell-signaling pathways," he said.

Many researchers are now beginning to believe that "subchondral bone is where the problem is," with cartilage abnormalities perhaps the downstream effect of abnormal wear in response to bone changes, said Dr. Ytterberg.

Others are pursuing the hypothesis that osteoarthritis is an enthesopathy.

These theories, still in their infancy, could one day help characterize a diffusely defined symptom set that may or may not have common origins, he said. ■