The search continues for biomarkers of osteoarthritis progression

The search for a reliable biomarker of osteoarthritis progression has been ongoing for over 20 years. In a new study, none of the biomarkers investigated predicted progression of joint-space narrowing (JSN) over a 30-month period. There were, however, indications that one biomarker should be studied further.

In a previous trial of doxycycline, plasma samples were taken from 431 patients at baseline and at 6-month intervals for 30 months. Mazzuca *et al.* selected 60 participants from this trial who had shown osteoarthritis progression in radiographic assessments, and 60 participants who had not. They compared the concentrations of several biomarkers (i.e. the proteoglycan aggrecan epitope CS846; markers for collagenase cleavage of type II collagen, collagenase cleavage of type I and II collagens, and type II collagen synthesis; and the ratio of collagenase cleavage of type II collagen to type II collagen synthesis) in all the plasma samples of the two groups.

Mazzuca *et al.* did not find any strong evidence that these biomarkers predicted osteoarthritis progression. Neither baseline nor serial biomarker levels predicted JSN progression over the entire 30-month study period; however, an association was noted between CS846 and JSN progression in the knee over the first 16 months ($P<0.01$). The authors note that their cohort comprised patients from the extreme ends of the JSN spectrum, and recommend that further studies explore the connection between CS846 and JSN progression in a more-representative population.

Original article Mazzuca SA *et al.* (2006) Associations between joint space narrowing and molecular markers of collagen and proteoglycan turnover in patients with knee osteoarthritis. *J Rheumatol* **33:** 1147–1151

ANCA titers predict relapse in patients with anti-proteinase-3-ANCA-associated vasculitis

Although immunosuppressive treatment of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis results in a 10-year survival rate of 60–90%, a substantial number of patients suffer relapse following induction of remission. These relapses are associated with high morbidity and mortality. The identification of risk factors associated with relapse might allow for improved management of those patients at greatest risk.

In this retrospective study, the cytoplasmic ANCA (cANCA) positivity status and anti-proteinase-3 (PR3)-ANCA levels of 87 patients with PR3-ANCA-associated vasculitis were determined at diagnosis and during immunosuppressive maintenance therapy (continued cyclophosphamide and corticosteroids or switched to azathioprine). Overall actuarial relapse-free survival was 72% at 2 years and 34% at 5 years. There was no difference in relapse-free survival between patients on cyclophosphamide maintenance and those who were switched to azathioprine. A significantly lower risk of relapse was found in patients who became and stayed negative for cANCA ($P=0.01$) or PR3-ANCA ($P=0.02$) until 24 months after diagnosis, whereas positive cANCA titers at 3, 12, 18 and 24 months were strongly associated with relapse within 5 years of diagnosis. Median time to relapse was 20 months in patients who were cANCA-positive >6 months after diagnosis. PR3-ANCA levels of >10 U/ml at 18 and 24 months were predictive of relapse within 5 years. In patients who switched to azathioprine maintenance, relapse was associated with a positive cANCA titer at the time of switching.

The authors conclude that cANCA positivity and elevated PR3-ANCA titers at various time points during early follow-up can identify patients with PR3-ANCA-associated vasculitis who are at increased risk of relapse.

Original article Sanders JS *et al.* (2006) Prediction of relapses in PR3-ANCA-associated vasculitis by assessing responses of ANCA titres to treatment. *Rheumatology (Oxford)* **45:** 724–729

Reduced habituation in response to somatosensory stimulation in fibromyalgia

Recent research suggests that the chronic pain and tenderness experienced by patients with fibromyalgia might result from altered neurobiological mechanisms involved in the processing of somatosensory information. Previous studies have investigated the brain mechanisms involved in processing painful

stimuli in fibromyalgia patients, but little is known about the mechanisms involved in processing painless stimuli.

This study compared brain responses to repeated, painless somatosensory and auditory stimuli in 15 female patients with fibromyalgia and 15 healthy control individuals. Participants underwent two sessions of electroencephalographic tests, with a 2 min rest period between sessions. Each session contained 40 paired stimuli, which could be either painless and tactile (pneumatic stimulator), or auditory. Mean event-related potentials (ERPs) in response to a pair of identical stimuli (S1 and S2) were calculated over the 40 paired trials of each sensory modality. In healthy controls, ERP amplitudes in response to the somatosensory and auditory S2 stimuli were markedly lower than those in response to S1 stimuli, which indicated (as expected) habituation in response to repeated stimulation. In 15 patients with fibromyalgia, similarly marked ERP amplitude reductions from S1 to S2 stimuli were seen for auditory stimuli, but the amplitude reductions from S1 to S2 in response to somatosensory stimuli were smaller than those of healthy controls.

The authors conclude that patients with fibromyalgia lack inhibitory control to repeated, painless somatosensory stimulation during stimulus coding and cognitive evaluation.

Original article Montoya P *et al.* (2006) Reduced brain habituation to somatosensory stimulation in patients with fibromyalgia. *Arthritis Rheum* **54:** 1995–2003

Factors associated with transition from primary to secondary Raynaud's phenomenon

Patients with primary Raynaud's phenomenon have, at the time of diagnosis, no evidence of an underlying disease whereas those with secondary Raynaud's phenomenon have a wide variety of vascular and nonvascular diseases. It is unclear how often primary Raynaud's phenomenon progresses to secondary Raynaud's phenomenon, and whether prognostic factors for this transition, or for disease progression, exist.

This prospective, follow-up study assessed the rate of transition from primary to secondary Raynaud's phenomenon in 307 consecutive patients, 34 of whom had a confirmed diagnosis of secondary Raynaud's phenomenon. The initial prevalence of secondary Raynaud's phenomenon was 11%. In the remaining patients, the annual rates of transition to suspected and confirmed secondary Raynaud's phenomenon were 2% and 1%, respectively. An increased risk of transition to secondary Raynaud's phenomenon was associated with older age at onset, recent onset of Raynaud's phenomenon at enrolment, abnormal thoracic-outlet test results and antinuclear antibody titer >1:160. Overall, patients with confirmed, secondary Raynaud's phenomenon had earlier onset, and a higher number, of pathologic findings.

The authors suggest that patients with primary Raynaud's phenomenon can be divided into three subsets: those with no sign of underlying disease at presentation or during long-term follow-up (idiopathic Raynaud's phenomenon), those with rapid onset and an increased number of pathologic findings (severe course of disease), and those with late onset of pathologic findings and a relatively benign disease course, apparently unrelated to other conditions.

Original article Hirschl M *et al.* (2006) Transition from primary Raynaud's phenomenon to secondary Raynaud's phenomenon identified by diagnosis of an associated disease: results of ten years of prospective surveillance. *Arthritis Rheum* **54:** 1974–1981

Clinical symptoms of osteoarthritis are associated with MRI structural findings

The underlying cause of the knee pain experienced in osteoarthritis (OA) is unclear. It is unlikely to be related to cartilage loss given the lack of pain fibres in this tissue, but the role of damage to other structures, such as the joint capsule, periosteum, menisci and synovium, has not been clarified.

To investigate whether structural abnormalities detected by MRI in the knees of patients with OA are associated with pain and stiffness, Kornaat and colleagues performed a prospective study in 205 patients with symptomatic OA in at least two joints (hands, spine, knees and/or hips). All patients underwent MRI of the knee, and the scans were evaluated using a comprehensive score for a range of structural abnormalities, by three clinicians blinded to patient data. No associations were found between pain and stiffness of the knee and focal or diffuse cartilaginous abnormalities, subchondral cysts, bone-marrow edema, subluxation of the meniscus, meniscal