New research gives insights into a common rheumatic condition

Osteoclasts as markers in psoriatic arthritis

A collaboration between the University of Rochester and Virtual Scopics Inc. (both of NY, USA) has resulted in significant advances in the diagnostics, pathology and, potentially, treatment of erosive psoriatic arthritis (PsA). The team examined the effects of the anti-TNF treatment etanercept in 20 PsA sufferers in a bid to determine the drug's effect on osteoclast precursor cells (OCPs).

Dr Edward Schwarz, professor of orthopedics at the University of Rochester Medical Center, and his team have previously shown that PsA is associated with an increased level of OPCs in the blood. Osteoclasts are intimately involved in bone remodeling, eroding bone in a similar manner to which macrophages destroy foreign bacteria. Therefore, it is believed that in PsA, osteoclasts are overproduced, resulting in excessive erosion of the bone.

'This approach will allow far better tailoring of PsA treatment than is currently available'

Their latest research, published in the March issue of *Annals of Rheumatic Disease*, shows that the levels of OPCs in the bloodstream drops dramatically following anti-TNF treatment, providing a useful marker by which to determine a patient's responsiveness to etanercept. This approach will allow far better tailoring of PsA treatment than is currently available. "A simple blood test can determine a person's osteoclast precursor levels," Schwarz explains, "That should soon change medical practice as we can tell by OCP levels if a person has erosive disease. If those levels fail to drop immediately with anti-TNF therapy, that person is likely among the 30% of people who don't respond to etanercept. We can spare them the side effects and perhaps switch them to drugs like rituximab or abatacept, which are approved for rheumatoid arthritis patients that do not respond to anti-TNF therapy".

Furthermore, using gadolinium-enhanced magnetic resonance imaging, the team examined the effects of etanercept on bone marrow edemas, commonly found near joints affected by PsA. The team proved that the reservoirs of fluid were, in fact, pools of OPCs, and not simply water as previously thought.

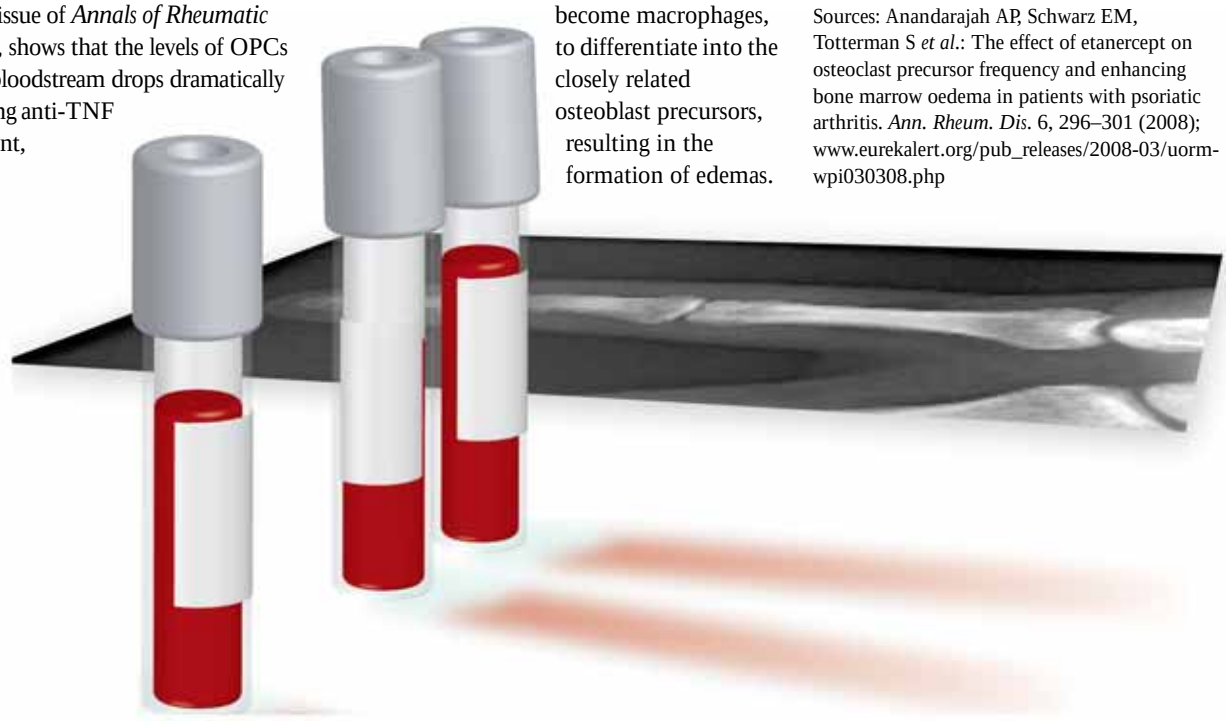
This finding suggests that there is a factor in the bone marrow of PsA sufferers that directs cells, which would otherwise become macrophages, to differentiate into the closely related osteoblast precursors, resulting in the formation of edemas. The search is now underway to identify this factor, and to elucidate its mode of action, a project that could potentially result in the development of novel treatments for the disabling condition.

Aside from opening up new avenues of research, the characterization of the edemas may prove to be an important diagnostic tool, as there is currently no way to identify which joints will be affected by PsA.

'... [the findings] could potentially result in the development of novel treatments for the disabling condition'

"While the blood test can tell you if you have PsA, it cannot tell which joints are affected. That feat has been achieved in this study for the first time with new MRI technology, which shows which joints have pre-erosive, osteoclast precursor lesions forming in the nearby bone marrow. These two tests, done in serial fashion, should allow for earlier diagnosis and more precise treatment of psoriatic erosive arthritis." Schwartz said.

Sources: Anandarajah AP, Schwarz EM, Totterman S *et al.*: The effect of etanercept on osteoclast precursor frequency and enhancing bone marrow oedema in patients with psoriatic arthritis. *Ann. Rheum. Dis.* 6, 296–301 (2008); www.eurekalert.org/pub_releases/2008-03/uorm-wpi030308.php



Priority Paper Alerts

Effects of postmenopausal hormone therapy on rheumatoid arthritis: the Women's Health Initiative randomized controlled trials.

Walitt B, Pettinger M, Weinstein A *et al.*: *Arthritis Care Res.* 59(3), 302–310 (2008).

This study aimed to establish the effects of postmenopausal hormone therapy on the incidence and severity of rheumatoid arthritis (RA). RA is far more prevalent in women than in men, which has led to the suggestion that female hormones may play a key role. Randomized controlled trials compared the effects of estrogen alone, estrogen and progestin, and placebo on the severity of RA in postmenopausal women. Cox proportional hazard regression model was used to asses the risk of developing RA in 27,347 participants. No statistically significant difference in the number of new RA cases over a period of 5–6 years were found between those receiving PHT and those taking a placebo. Furthermore, those that already had signs of RA at the beginning of the trials reported no change in severity of disease symptoms. The study is the only placebo-controlled trial to evaluate the effect of hormone replacement therapy on developing RA.

Effect of glucosamine sulfate on hip osteoarthritis.

Rozendaal RM, Koes BW, van Osch GJVM *et al.*: *Ann. Intern. Med.* 148(4), 268–277 (2008).

In order to assess the effectiveness of glucosamine sulfate treatment for osteoarthritis of the hip, 222 primary-care patients from the Netherlands, who met the American College of Rheumatology clinical criteria for hip osteoarthritis, were assigned to either a daily dose of 1500 mg of glucosamine sulfate or a placebo, for 2 years. All physicians, patients and researchers were blinded, there was a high completion rate (93%) and the study was conducted without drug company funding to ensure a reliable, unbiased result. The outcome of treatment was measured using Western Ontario and McMaster Universities (WOMAC) pain and function subscales and joint space narrowing over 24 months. The results showed no statistically significant difference in pain, function or joint space narrowing between the glucosamine sulfate and control groups. This finding calls the efficacy of glucosamine sulfate treatment for hip osteoarthritis into question, an important finding considering its widespread use.

Statins linked to rheumatic complications

A study led by led by Dr Catherine Noblet, of Rouen University Hospital (France) has demonstrated a link, albeit rather weak, between statins and tendon impairment.

In a retrospective study, in which 96 cases of tendon complications associated with statin treatment were identified, researchers found that 2% of side-effects caused by statin treatment were tendon-related. This finding appears to be quite robust; the symptoms appeared only following commencement of statin treatment, disappeared following cessation of treatment and reoccurred in all those who restarted statin therapy. This provides the first nonanecdotal evidence for a connection between the common cholesterol-lowering treatment and tendon problems. Tendon problems were linked to a number of statins, including atorvastatin, simvastatin, pravastatin, fluvastatin and rosuvastatin.

The reason for the link is unknown, but a number of hypotheses have been ventured. By blocking cholesterol synthesis, the tendon cell membranes become unstable, making them more prone to swell and rupture. Alternatively, statins may have adverse effects on tendon cell maintenance or cause the destruction of vascular smooth muscle cells.

> "Patients who are at risk of developing statin-associated tendon manifestations and who require statins [should] be routinely questioned about symptoms consistent with tendon involvement."

As a consequence of their results the authors suggest that greater communication between physicians and their patients is vital if harmful side-effects are to be avoided. "Patients who are at risk of developing statin-associated tendon manifestations and who require statins [should] be routinely questioned about symptoms consistent with tendon involvement".

Sources: www.sciencedaily.com/releases/2008/02/080228080539.htm; Marie I, Delafenêtre H, Massy N, Thuillez C, Noblet C: Tendinous disorders attributed to statins: a study on ninety-six spontaneous reports in the period 1990–2005 and review of the literature. *Arthritis Care Res.* 59(3), 367–372 (2008).

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology.

If you have newsworthy information, please contact:

Sean Cleghorn, Assistant Commissioning Editor,
Future Rheumatology;
Future Medicine Ltd, Unitec House, 2 Albert Place, London N3 1QB, UK
Tel.: +44 (0)20 8371 6090; Fax: +44 (0)20 8343 2313
s.cleghorn@futuremedicine.com

Rare rheumatic disorders get first drug

The US FDA has just approved the first drug treatment for a group of rare rheumatic conditions classified as cryopyrin-associated periodic syndrome (CAPS) disorders.

CAPS disorders, such as familial cold auto-inflammatory syndrome (FCAS) and Muckle–Wells syndrome (MWS), are frequently caused by a mutation in the gene *CIAS-1*, the product of which is cryopyrin. Cryopyrin is involved in the production of IL-1, a key mediator of inflammation. As such, individuals with the mutation overexpress cryopyrin, resulting in a number of symptoms including rash, fatigue, fevers and chills, and joint pain.

Regeneron Pharmaceuticals Inc. (NY, USA) have developed an IL-1 blocker, Arcalyst™, which has now been approved for use in the USA for the treatment of CAPS disorders. "Arcalyst offers new promise for this small patient population suffering disorders associated with cryopyrin-associated periodic syndromes," said Dr Curt Rosebraugh, acting director of the FDA's Office of Drug Evaluation II.

> "The Orphan Drug Act ... has been tremendously successful in delivering effective treatments to patients with extremely rare, but serious, diseases."

As CAPS disorders are rare disorders (with a prevalence of around one in 1 million), securing funding for drug research can be problematic as there is little prospect of getting a return on the money invested. In response to this problem many governments provide incentives to drugs companies to develop these so-called 'orphan' drugs. Arcalyst was one such drug.

Rosebraugh continues "The Orphan Drug Act – now in its 25th year – has been tremendously successful in delivering effective treatments to patients with extremely rare, but serious, diseases".

The approval comes following clinical trials in which patients completed a daily diary questionnaire, 47 patients rated five signs and symptoms (joint pain, rash, feeling of fever/chills, eye redness/pain and fatigue) of CAPS on a scale of zero (none/no severity) to 10 (very severe). Patients taking Arcalyst noted initial onset of relief of symptoms in their diaries within several days, compared with those taking placebo.

Sources: www.regeneron.com/arcalyst.html; www.fda.gov

Cellular suicide provides clues for lupus

A study in the February issue of *Immunity* highlights the importance of apoptosis in the development of autoimmune diseases such as systemic lupus erythematosus (SLE).

Research led by Dr Harris Perlman, associate professor of molecular microbiology and immunology at St Louis University (MO, USA) and senior author on the paper, found that antigen-presenting cells that would normally have undergone apoptosis, accumulated in patients with SLE. The presence of the cells results in the development of autoimmunity, leading to the onset of SLE.

Initially, the team took blood from 14 SLE patients and 14 healthy individuals. It was found that those with SLE produced an increased number of immune cells with abnormally high levels of antiapoptotic proteins. Based on this evidence, the team then created a strain of mice to mimic this situation.

Normally, apoptosis is triggered by two complimentary pathways: extrinsic binding to a 'death receptor' such as Fas (a member of the tumor necrosis factor receptor superfamily); or intrinsic, mitochondrial apoptosis initiated by Bim.

Perlman and his team engineered mice lacking the genes that encode both Bim and Fas (*Bcl2/11*$^{-/-}$*Fas*$^{lpr/lpr}$). These mice developed severe SLE-like disease by 16 weeks of age, unlike mice lacking only one of the genes. The antigen-presenting cells in the *Bcl2/11*$^{-/-}$*Fas*$^{lpr/lpr}$ strain were remarkably active, collecting in the kidney and lymphoid tissue in increased numbers. "We showed it in patients and reproduced the result in mice," Perlman said. "Now we can use this mouse model to do pre-clinical trials for therapies to fight lupus."

Perlman hopes that these findings will lead to the identification of molecules that inhibit the antiapoptotic proteins, restoring the balance and allowing the immune cells to die at the correct time; "We want to deliver a treatment that will target those proteins that keep these immune cells alive. This could induce a type of remission in patients. We need to tilt the balance toward the normal cells – cells that don't want to attack the body but function correctly so the patient can fight infection and have a normal life. We want to kill those cells that lead to the continuation of disease."

Sources: Hutcheson J, Scatizzi JC, AM Siddiqui *et al.*: Combined deficiency of proapoptotic regulators Bim and Fas results in the early onset of systemic autoimmunity. *Immunity* 28, 206–217 (2008); www.eurekalert.org/pub_releases/2008-02/slu-bst021108.php