A new study demonstrates how the drug anakinra can improve the symptoms of a rare, but debilitating disease found in young adults

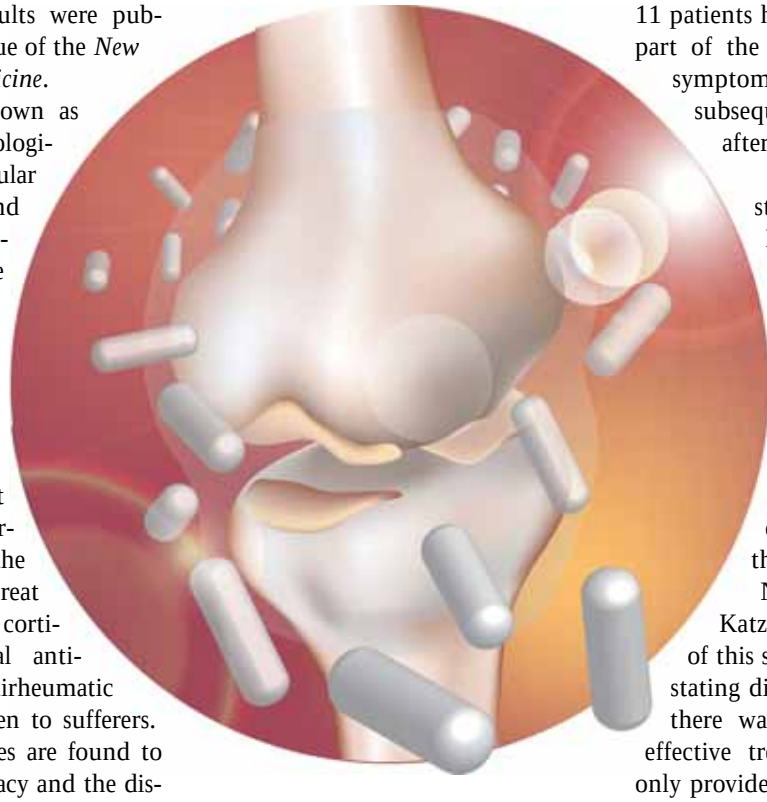
Arthritis drug in multisystem inflammatory disease breakthrough

Researchers investigating neonatal-onset multisystem inflammatory disease (NOMID) have found that the drug anakinra can help alleviate the symptoms and inflammation underlying this rare disease, which is typically found in children and young adults. The study was carried out at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the results were published in the August issue of the *New England Journal of Medicine*.

NOMID is also known as chronic infantile neurological cutaneous articular (CINCA) syndrome, and is classified as an auto-inflammatory disease due to the unprovoked incidences of inflammation. The disease affects several organs and systems of the body and can cause fever, meningitis, joint damage and mental retardation. To control the inflammation and treat NOMID, high doses of corticosteroids, nonsteroidal anti-inflammatory and antirheumatic drugs are normally given to sufferers. However, these therapies are found to be limited in their efficacy and the disease remains progressive and often fatal, with approximately 20% of affected children not surviving to adulthood.

Despite the process by which the disease functions remaining unclear, it has been found that mutations in the gene *CIAS1* occur in 60% of sufferers. This gene encodes cryopyrin, which is part of a group of proteins that regulate inflammation and cell death. The consequences of these mutations include imbalances of interleukin (IL)-1, which encourages the development of inflammation.

Anakinra is a biological agent that is used to treat rheumatoid arthritis and works by blocking the action of IL-β, which has been found to be important in the pathogenesis of related diseases.



As part of the study, the NIAMS scientists tested the consequences of using the drug on NOMID patients. A total of 18 subjects aged between 4–32 years of age and suffering from NOMID were given a daily dose of anakinra. Of these patients, 12 had clear *CIAS1* mutations. A rapid clinical response to the drug was observed in all the people tested. A rash and conjunctivitis observed in NOMID sufferers had cleared up within a few days from the start of treatment. A reduction in headaches and central nervous system lesions, as well as remission of inflammation in more than half of subjects by 6 months, was observed by the researchers. By 3 months, erythrocyte sedimentation rate, C-reactive protein and serum amyloid A protein (all measures of inflammation) had improved. When 11 patients had anakinra withdrawn as part of the investigation, the disease symptoms began to develop, which subsequently disappeared again after restarting treatment.

The lead author of the study, Raphaela Goldbach-Mansky, explained the significance of these findings; "This study demonstrates the efficacy of anakinra in improving major organ manifestations and helps confirm the role of IL-1β in many features of the disease; most importantly, the central nervous system." NIAMS Director, Stephen Katz, reiterates the importance of this study; "NOMID is a devastating disease for which previously there was little understanding or effective treatment. This study not only provides hope – in the way of an already available agent – but it also provides a better understanding of the mechanism of the disease's damaging effects."

Despite the small study sample size, the significant and rapid response to the drug, as well as the lack of side effects observed during the study, may mean that anakinra may prove to be an important factor in the treatment of NOMID in the future.

Priority Paper Alerts

Thromboembolism complicating the treatment of lupus anticoagulant hypoprothrombinemia syndrome.

Vinet E, Rich E, Senecal JL: *J. Rheumatol.* Epub ahead of print (2006).

In this study, the authors report on a patient with systemic lupus erythematosus, lupus anticoagulant hypoprothrombinemia syndrome (LAHPS) and severe Factor II deficiency. The subject was successfully treated for central nervous system bleeding, but also experienced a major thromboembolic complication. After analysis of two other patients with this complication and Factor II deficiency, it was suggested that the deficiency compensates for the prothrombotic effect of lupus anticoagulant in LAHPS, and correcting this may promote thromboembolism.

Spontaneous recovery of sudden sensorineural hearing loss: possible association with autoimmune disorders.

Digiovanni JJ, Nair P: *J. Am. Acad. Audiol.* 17(7), 498–505 (2006).

A 46-year-old male with systemic lupus erythematosus and antiphospholipid syndrome experienced a sudden loss of hearing in the right ear. After audiological testing was performed, a sensorineural hearing loss this ear was observed. The patient was then retested twice after experiencing improvement in his condition, and these tests revealed normal hearing in both ears. The authors discuss the reasons for these observations, and conclude that they were consistent with a transient ischemic attack affecting the right cochlea in the stria vascularis. This resulted in a temporary, sensorineural hearing loss, but no residual effects were seen.

Effects of Stanger bath therapy on fibromyalgia.

Eksioglu E, Yazar D, Bal A, Usan HD: *Clin. Rheumatol.* Epub ahead of print (2006).

A total of 50 women with fibromyalgia were divided into two groups in order to examine the efficacy of Stanger bath therapy. The first group (n = 25) was treated with amitriptyline and Stanger bath, 20 min daily for ten sessions. The second group (n = 25) were prescribed only amitriptyline. The assessment parameters were measured before (t1), at the end (t2) and 2 months after hydrotherapy (t3) in the first group. In the second group, the parameters were observed before and 2 months after therapy. Significant improvements in the number of tender points between t1 and t2, and t1 and t3 were observed in Stanger bath group.

Estradiol levels and knee osteoarthritis

Knee osteoarthritis is linked to low serum levels of estradiol and related urinary metabolites, suggests a report published in *Arthritis and Rheumatism*.

MaryFran Sowers and colleagues, University of Michigan (MI, USA) investigated 842 African–American and white women at a mean age of 42.3 years and with a body mass index of 28.5, with 75% being premenopausal. Over a period of 3 years, the test subjects had annual x-rays of both knees, and their blood and urine levels of estradiol and the metabolites 2-hydroxyesterone and 16a-hydroxyesterone were measured, respectively. The baseline occurrence of knee osteoarthritis was measured at 11% with a yearly frequency of 3.2%.

The researchers found that serum levels of estradiol were 15% lower in women with knee osteoarthritis than in those without. Furthermore, women with the lowest levels of 2-hydroxyesterone and the highest ratio of 16a-hydroxyesterone to 2-hydroxyesterone (both of which are estradiol metabolites) were at a higher risk of developing the disease.

The scientists explain that the estrogen metabolites have a significant function in the metabolism of arachidonic acid, which is required for the synthesis of proinflammatory leukotrienes, and may contribute to the inflammation and pain accompanied with osteoarthritis.

The team acknowledge the need for further investigations into this topic and believe that if other studies support their findings, "Then considering alternative lifestyle and therapeutic pathways to influence these metabolites becomes increasingly

Rapid action saves kidneys in lupus nephritis

A new study suggests a quick, clinical response to the first indication of kidney involvement in systemic lupus erythematosus (SLE) can prevent renal failure.

Mikkel Faurschou and colleagues, the National University of Copenhagen, Denmark, evaluated the efficacy of renal biopsies and the clinical findings of 91 patients with both SLE and nephritis. The end-stage renal disease (ESRD) incidence was continually monitored and found to be 3.5% after 1 year, 15% after 5 years, and 17% after 10 years.

Nephritis was found to be most influenced by several risk factors: duration of nephritis symptoms of more than 6 months before biopsy; diffuse glomerulonephritis; serum creatinine level above 140 mmols/l; and tubular atrophy. Subsequent hazard-ratio calculations of these risk factors ranged from 9.3 for longer durations of nephritis symptoms to 3.1 with tubular atrophy.

Faurschou explained further; "Our data show that doctors tend to delay prescription of intensive immunosuppressive treatment until the presence of nephritis has been documented through kidney biopsy. Therefore, our findings underscore the need for close medical monitoring of SLE patients, and patients with SLE should be subjected to a renal biopsy as soon as clinical signs of nephritis are evident. This approach will decrease the risk of terminal renal failure in patients with lupus nephritis."

The team conclude by emphasising the importance of immunosuppressive treatment and the risks associated with a delay in diagnosis and subsequent treatment.

NSAIDs and the risk of congenital defects in babies

Taking nonsteroidal anti-inflammatory drugs (NSAIDs) early in pregnancy may lead to babies being born with congenital defects, a report suggests from the journal *Birth Defects Research Part B*.

Up to 15% of women take over-the-counter versions of NSAIDs (e.g., aspirin and ibuprofen) in addition to others who are prescribed the drugs during their first trimester. Whilst the dangers (including circulatory problems) of taking these drug during the late stages of gestation are well known, the consequences of their use during the early phases of pregnancy have been less thoroughly studied. With this in mind, Anick Berard and colleagues, St Justine Hospital in Montreal, Canada, studied information given by 36,387 pregnant women from three administrative centers in Quebec. From these databases, the researchers concluded who had been prescribed NSAIDs during their first trimester and who had babies diagnosed with a congenital abnormality, particularly cardiac septal defects, in the first year of life. Several statistical analyses were performed to determine any links between the presence of congenital abnormalities and the use of NSAIDs.

"Women who fill prescriptions for NSAIDs in the first trimester of pregnancy may be at greater risk of having children with congenital anomalies."

It was found that, of 35,331 women who did not have prescriptions for NSAIDs, 7% gave birth to babies with congenital anomalies. This is compared with the 1056 women prescribed NSAIDs early in their pregnancy, 8.8% of whom had babies with congenital anomalies. Similarly, 16.1% of women taking the drugs had babies with multiple congenital anomalies, compared with 14.2% of subjects who had children with the same condition, but did not take NSAIDs.

The authors went on to explain the significance of their study, as well as the need for further, related tests to be performed; "Our analysis of data from the Medication and Pregnancy registry suggests that women who fill prescriptions for NSAIDs in the first trimester of pregnancy may be at greater risk of having children with congenital anomalies, particularly those related to cardiac septal closure. This is in accordance with previous findings, but needs to be replicated in other study populations."

Gout linked to risk of myocardial infarction

Scientists from the University of Pittsburgh (PA, USA) have found that hyperuricemia and gouty arthritis are independently associated with the risk of developing acute myocardial infarctions (MIs) in men at high risk of coronary artery disease. The report, published in *Arthritis and Rheumatism*, also found that this link remained in patients without diabetes mellitus, obesity or the metabolic syndrome and those who used diuretics, aspirin or alcohol.

The links between hyperuricemia and gout were analyzed using data gathered from the Multiple Risk Factor Intervention trial and included men at high risk of developing coronary events. In total, 12,866 men were evaluated.

Patients were deemed to have hyperuricemia if they had a serum uric acid concentration of 7.0 mg/dl or more. Symptoms of gout included joint pain, swelling, heat lasting up to 2 weeks and a complete alleviation of symptoms thereafter.

"The odds ratio associated with gout was the third largest among categorical variables."

After a follow-up period of 6.5 years, 1108 men were found to have had an acute MI. At the start of the study, gout and hyperuricemia occurred in 8.7 and 41.5% of the subjects, and the serum uric acid concentration was higher in men with gout compared with those without the disease. Gout was not related to cholesterol levels, the use of aspirin, family history of acute MI, or occurrence of diabetes. Although the rate of acute MIs did not alter in the presence of hyperuricemia, gout demonstrated a link with MI.

However, these levels differed in the multivariable logistic regression model, in which the demographics, lifestyle, outcomes of clinical testing, the use of aspirin, diuretics, alcohol and other potential confounders were taken into account. In this model, the occurrence of acute MI was greater in those with hyperuricemia (odds ratio: 1.11; $p < 0.001$) and in those with gout (odds ratio = 1.26; $p < 0.001$).

Although the risk associated with gout was not high, the team concluded that, "The odds ratio associated with gout was the third largest among categorical variables, after smoking and family history of acute MI."