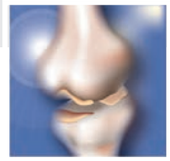
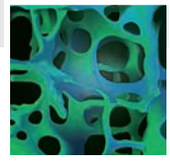




Bulletin Board

Allopurinol may improve prognosis of heart failure patients suffering from gout

A recent study has demonstrated that gout significantly increases the risk of death or rehospitalization in patients suffering from heart failure. The study also found that long-term use of the drug allopurinol can significantly ameliorate the risks of recurrent cardiac events in heart failure patients suffering from gout.

The study was presented at the recent American Heart Association annual meeting by George Thanassoulis of Boston University, MA, USA, and the Framingham Heart Study. The analysis used administrative and health records from Quebec, incorporating data from more than 150,000 heart failure patients over the age of 65 years.

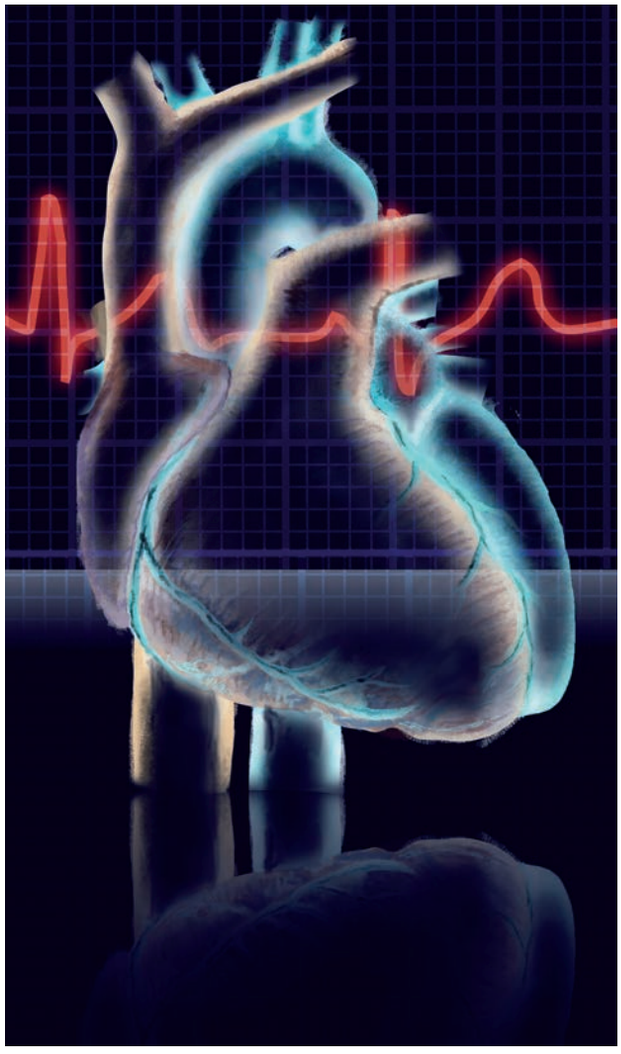
During the 2-year follow-up, the incidence of death or readmission to hospital with heart failure was significantly higher in patients with gout and heart failure (6%) compared with patients being treated for heart failure alone. The analysis was controlled to account for several demographic and clinical variables that could have acted as confounding factors. These included age, sex, comorbidities and medication. The risk of death or heart failure hospitalization was even greater in patients who had acute gout – defined as hospitalization or the need of a home visit from a physician for gout within 60 days of the index heart failure event – with a twofold higher risk in adjusted analysis.

The long-term use of allopurinol, defined as more than 30 days of treatment, by patients suffering from gout proved to significantly reduce the risk of gout by 1% compared with those patients with gout who were not on long-term allopurinol treatment. There was no link between allopruinol treatment and outcomes for the entire population, suggesting allopurinol is only beneficial for heart patients concurrently suffering with gout.

Thanassoulis hypothesises that allopurinol exerts its beneficial effect on patients suffering from heart failure and gout by inhibiting xanthine oxidase, thereby preventing endothelial dysfunction caused by oxidative stress. He urges continued effort and research: "The next steps are to assess the relationship between heart failure, gout and allopurinol treatment in a prospective, controlled study."

In a commentary in *Rheumatology News*, Janet Maynard and Alan Baer, both of John Hopkins University in Baltimore, MD, USA, urge caution in extrapolation of results from this study, whilst supporting the need for further research into the area. They note that "patients who take allopurinol may differ from patients who do not take allopurinol. Thus, findings may reflect confounders, such as healthcare utilization patterns and medication adherence, rather than a direct effect of allopurinol on outcomes. This study does remind all rheumatologists of the importance of cardiovascular risk factor modification in patients with gout. In addition, it suggests that future work should evaluate whether treatment of hyperuricemia in patients with and without gout leads to improved cardiovascular outcomes."

Source: Rheumatology News: www.rheumatologynews.com/article/PIIS154198001070066/fulltext



in the news...

Antidepressants show promise in rheumatoid arthritis therapy

A recent study has demonstrated the potential of selective serotonin reuptake inhibitors (SSRIs) to treat rheumatoid arthritis (RA). Encouragingly, the study demonstrates the ability of SSRIs to reduce clinical manifestations of the disease in mouse models, as well as reducing cytokine levels in an *in vitro* human model. However, the doses required to treat RA in humans would be prohibitively high to allow these SSRIs to progress into clinical trials. The authors highlight new avenues of research in light of these findings.

> "Fluoxetine was found to best inhibit Toll-like receptors, which play a key role in innate immune response..."

The research team from Brighton and Sussex Medical School, UK, demonstrated the antiarthritic potential of two SSRIs – fluoxetine (Prozac®) and citalopram (Celaxa®) – used primarily as antidepressants. The team, led by Sandra Sacre, explored the potential of SSRIs as antiarthritic drugs after reports of their anti-inflammatory effects. Sacre explains: "Prior studies have shown that patients with depression who respond to treatment with SSRIs display a reduction in cytokine levels, suggesting a connection between SSRIs and the immune system."

Collagen-induced arthritis (CIA) mouse models were used as the disease manifestation shares similarities with human RA, including synovitis, bone erosion and pannus formation. CIA-affected mice were treated with 10 or 25 mg/kg of fluoxetine and 25 mg/kg of citalopram daily for 7 days. Mice treated with low-dose fluoxetine showed a marked improvement in clinical indicators of arthritis, including joint redness, swelling and mobility. The higher dose of fluoxetine further halted disease progression, reducing inflamation, cartilage, bone erosion and also preserving joint structure – more so than the lower dose of fluoxetine or the high dose of citalopram.

The researchers also managed to demonstrate a reduction in cytokine production when adding the SSRIs to cultures of human RA synovial joint tissues. Fluoxetine was found to best inhibit Toll-like receptors, which play a key role in innate immune response, eventually leading to activation of the inflammation inducing cytokines.

As Sacre explains, despite such encouraging results, the current study only serves to shed light on possible future avenues of research: "Effective inhibition of RA would require levels of the drugs higher than the safe therapeutic doses – further study of the role of Toll-like receptors in chronic inflammation may uncover drugs that offer an effective treatment for RA in the future."

Source: Sacre S, Medghalchi M, Gregory B, Brennan F, Williams R: Fluoxetine and citalopram exhibit potent antiinflammatory activity in human and murine models of rheumatoid arthritis and inhibit Toll-like receptors. *Arthritis Rheum.* 62(3), 68–69 (2010).

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:

Christine Forder, Commissioning Editor,
International Journal of Clinical 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;
c.forder@futuremedicine.com

in brief...

Contrasting association of a non-synonymous leptin receptor gene polymorphism with Wegener's granulomatosis and Churg-Strauss syndrome.

Wieczorek S, Holle JU, Bremer JP *et al.*: *Rheumatology (Oxford).* (2010) (Epub ahead of print).

The study evaluates the genetic background of Wegener's granulomatosis (WG) to determine the level of involvement of the leptin/ghrelin system in T-cell regulation. Researchers screened variations in the genes encoding leptin, ghrelin and their receptors, the leptin receptor (LEPR) and the growth hormone secretagogue receptor (GHSR). Three single nucleotide polymorphisms (SNPs) in each gene region were analyzed in 460 cases and 878 matched controls. A three-SNP haplotype of GHSR was significantly associated with WG as was one nonsynonymous SNP in LEPR. In reanalysis with an independent cohort, the GHSR association was not confirmed, whilst the LEPR SNP allele frequencies were virtually identical. The LEPR 656Lys allele showed significant association with WG. Remarkably, the Lys656Asn SNP showed contrasting allele distribution between German and English cohorts diagnosed with Churg-Strauss syndrome and WG respectively. Study shows evidence for association of the LEPR Lys656Asn SNP with ANCA-associated vasculitides, resulting in opposing effects in WG and Churg-Strauss syndrome.

Visual assessment of the spine bruckel instrument, a novel status tool to reflect appearance of the spine in patients with ankylosing spondylitis.

Podbielski DW, Bruckel J, Pomeroy E *et al.*: *J. Rheumatol.* (2010) (Epub ahead of print).

The study assessed the Visual Assessment of the Spine Bruckel Instrument (VASBI) as a new tool to reflect spinal appearance in patients with ankylosing spondylitis (AS). Patients (n = 00) were asked to rate the degree of perceived spinal deformity using the VASBI. VASBI scores were compared with functional outcome, spinal mobility and radiographic spinal damage to assess VASBI construct validity. Patient VASBI scores had a moderate correlation with functional impairment ($r = 0.490$) and structural damage ($r = 0.09$) and a strong correlation with functional impairment ($r = 0.54$). Test reliability was evaluated using the k statistic, and showed to be very reliable ($k = 0.97$; $p < 0.001$). The authors conclude that VASBI has practical implications in a busy clinic owing to that fact that it is feasible, reliable and simplifies assessment of AS spinal deformity.

High-dose cyclophosphamide therapy may help systemic lupus erythematosus sufferers who do not respond to standard therapy

A recent study published in *Arthritis and Rheumatology* has demonstrated that intensive cyclophosphamide therapy may be advantageous for the treatment of systemic lupus erythematosus (SLE) patients who do not respond to the traditional lower dose therapy. No difference was found in patient responsiveness when treated with either traditional or high-dose therapy from the outset of the trial.

> "...nonresponders to monthly intravenous cyclophosphamide can sometimes be rescued by high-dose cyclophosphamide."

Researches at John Hopkins University School of Medicine, Baltimore, MD, USA, conducted a prospective randomized trial comparing the effects of a traditional cyclophosphamide regimen, with a high-dose treatment in 47 patients suffering from SLE. The traditional approach is to treat patients intravenously with 750 mg/m^2 once a month for 6 months followed by quarterly administration, while the high-dose treatment involves 50 mg/kg per day for just 4 days.

Rates of complete response – measured by the Responder Index for Lupus Erythematosus – did not vary significantly between the traditional or high-dose regimens at either 6 or 0 months. Notably, in both groups, patients with neurological manifestations of the disease responded much better than those with renal manifestations.

A total of six patients who had originally been ascribed to the 'traditional regimen' group were allowed to switch to the high-dose group as they were not achieving complete responsiveness. Three of these patients went on to achieve complete responsiveness with high-dose treatment. Of the remaining three that were allowed to switch groups, two patients showed no observable change in response and, rather worryingly, the condition of one of the patients worsened.

The investigators, led by Michelle Petri, concluded that "high-dose cyclophosphamide appeared to be equivalent to the traditional regimen in complete response rate, duration of remission and toxicity." However, they did go on to add that "nonresponders to monthly intravenous cyclophosphamide can sometimes be rescued by high-dose cyclophosphamide."

Source: Petri M, Brodsky RA, Jones RJ, Gladstone D, Fillius M, Magder LS: High dose cyclophosphamide versus monthly intravenous cyclophosphamide for systemic lupus erythematosus. *Arthritis Rheum.* (2010) (Epub ahead of print).

Arthritis and arthritis-attributable activity limitations are more prevalent in the USA than in Canada, particularly in women

In the first ever cross-border comparison, researchers have found that arthritis and arthritis-attributable activity limitations (AAL) are more prevalent in the USA than in Canada. The greater prevalence in the USA has been attributed to higher rates of obesity and physical activity, particularly in women. The researchers stress the importance of these findings and their inclusion in future public health messages.

Researchers at Toronto Western Research Institute, Ontario, Canada, conducted analysis of the 2002–2003 Joint Canada/US Health Survey, which documented cases of health professional-diagnosed arthritis and arthritis stated as the cause of disability in the two countries.

Results show that on average, the estimated crude prevalence of arthritis and AAL were 18.7 and 9%, respectively, in the USA, and 16.9 and 7.4%, respectively, in Canada. The overall occurrence of arthritis and AAL in men was similar in both countries. Interestingly, the researchers found that the disparity between countries was mainly attributable to differences in women. When considering women alone, prevalence of arthritis and AAL in the USA were 23.3 and 13%, respectively, whilst in Canada, the respective prevalences were only 19.6 and 9.2%.

Elizabeth Badley, who led the research, remarked: "Our study results suggest that the higher prevalence of arthritis and AAL in the USA may be a consequence of greater obesity and physical inactivity in that country, particularly in women." Badley went on to conclude: "Public health initiatives that promote healthy weight and physical activity may benefit from including arthritis concerns to its message, and could potentially reduce the incidence of arthritis and AAL."

> "...higher prevalence of arthritis and arthritis-attributable activity limitations in the USA may be a consequence of greater obesity and physical inactivity..."

Source: Badley EM, Ansari H: Arthritis and arthritis-attributable activity limitations in the United States and Canada: a cross-border comparison. *Arthritis Care Res.* 62, 8–15 (2010).