Results of the first prospective study to confirm the relationship between rheumatoid arthritis and pregnancy have been presented at the EULAR 2007 conference in Barcelona, Spain

Prospective study shows that rheumatoid arthritis improves during pregnancy

Retrospective studies have demonstrated that rheumatoid arthritis (RA) improves in approximately 75% of pregnant patients, although no prospective data were available to confirm this association. Recently, in a prospective study conducted by Dutch researchers, and supported by the Dutch Arthritis Association, an improvement of RA during pregnancy has been observed. The results of this nationwide cohort study were reported at the European League Against Rheumatism (EULAR) 2007 conference.

The study, conducted by Yaël de Man and colleagues, Erasmus MC University Medical Center, Rotterdam, The Netherlands, aimed to prospectively determine the disease activity in pregnant RA patients using Disease Activity Score (DAS)-28.

'...an improvement of RA during pregnancy has been observed'.

A total of 124 RA patients, with a mean age of 31.6 years and a median disease duration of 48 months, were enrolled in the study. The patients were assessed at the first and third trimester, as well as at 6, 12 and 26-weeks post-partum. In addition to DAS-28, medication use and C-reactive protein levels were also recorded. The patients were categorized as good, moderate or nonresponders according to the EULAR response criteria, using the change in DAS-28 between the first and third trimesters. In order to determine if a severe or moderate flare was present, the change in DAS-28 at 6, 12 and 26-weeks post-partum was calculated.

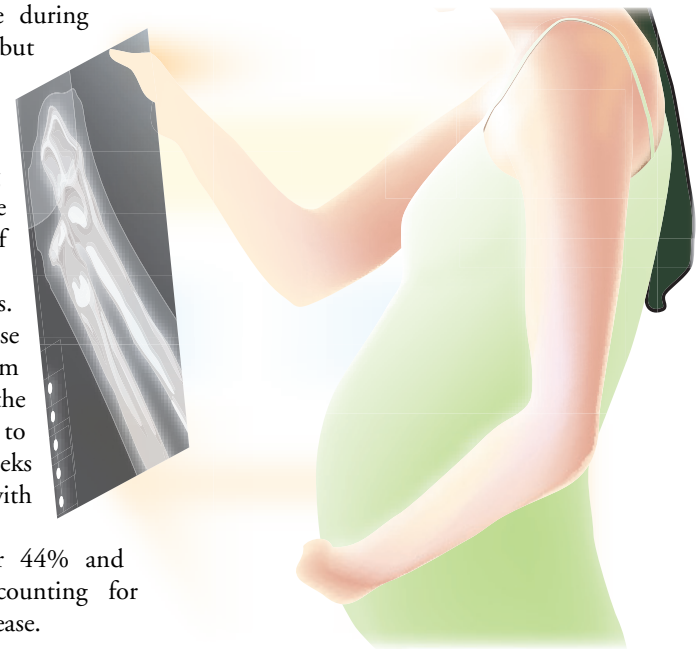
DAS-28 decreased from 3.7 in the first trimester, to 3.4 at the third trimester ($p = 0.003$); a statistically significant decrease. In addition, mean DAS-28 scores of 3.4, 3.7 and 3.6 were recorded at 6, 12 and 26 weeks post-partum, respectively.

"...note the existence of a complex interaction between female hormones during pregnancy and the epidemiology of RA, which may contribute to the development of new prevention and treatment approaches".

According to the EULAR response criteria, during pregnancy 11% of patients were good responders, while 40% were at least moderate responders and 60% were nonresponders. Post-partum DAS-28 scores revealed that 64% of patients remained relatively stable or improved, while severe and at least moderate flare were observed in 5% and 36% of patients, respectively. The study also showed that DMARD use was stable during pregnancy but substantially increased post-partum, mainly owing to to the increased use of methotrexate and biologicals. DMARD use increased from 57% during the third trimester to 82% at 26 weeks post-partum, with methotrexate accounting for 44% and biologicals accounting for 8% of the increase.

Interpreting the results of this study, de Man comments that: "the percentage of patients experiencing flare was much lower than previous studies, which we attribute to adequately used DMARDS and biologicals to suppress disease activity post-partum. It is also interesting to note the existence of a complex interaction between female hormones during pregnancy and the epidemiology of RA, which may contribute to the development of new prevention and treatment approaches".

Source: de Man YA, Dolhain RJEM, van de Geijn FE, Stijnen T, Hazes JMW: Does rheumatoid arthritis improve during pregnancy? Results from a prospective nationwide cohort study (The PARA-study). *Abstracts of EULAR 2007, the Annual European Congress of Rheumatology.* Barcelona, Spain (2007) (Abstract OP0049).



Priority Paper Alerts

Altered coronary vasomotor function in young patients with systemic lupus erythematosus.

Hirata K, Kadirvelu A, Kinjo M *et al.*: *Arthritis Rheum.* 56(6), 1904–1909 (2007).

This study aimed to compare coronary flow reserve (CFR) in premenopausal women with systemic lupus erythematosus (SLE) with healthy controls, since a major cause of morbidity and mortality in SLE patients is accelerated atherosclerosis. It is suggested that alterations in coronary microvascular function act as a marker of changes that predispose to coronary vascular disease. The study included 18 premenopausal women with SLE and 19 healthy controls (matched for age, sex and race). Transthoracic Doppler echocardiography was utilized to assess coronary flow velocity and CFR was calculated. The mean duration of SLE was 8.2 years (range = 0.25–25 years) and SLE Disease Activity Index Scores ranged from 4.0 to 21.0 (mean = 11.0). Adequate readings of flow velocity were obtained for all 37 participants, allowing a CFR value to be calculated. The study found CFR to be significantly decreased in SLE patients compared with the healthy control subjects ($p < 0.0001$). This suggests that many SLE patients have impaired coronary vasomotor function and subclinical coronary artery disease.

Radiographic progression in patients with ankylosing spondylitis after 4 yrs of treatment with the anti-TNF-α antibody infliximab.

Baraliakos X, Listing J, Brandt J *et al.*: *Rheumatology (Oxford)* DOI:10.1093/rheumatology/kem166 (2007) (Epub ahead of print).

Describes a study investigating the effect of infliximab on structural changes in ankylosing spondylitis (AS) over 4 years. Infliximab, a monoclonal antibody that neutralizes TNF-α, has proven effective in improving the signs and symptoms of AS. The modified Stokes AS spinal score (mSASSS) was used to score radiographs of the cervical and lumbar spine of 33 AS patients at baseline (BL) and 2 (FU1) and 4 (FU2) years after beginning infliximab therapy. Radiographic progression was lower than previously reported data. Definite radiographic progression from BL to FU2 was observed in 30.3% of patients and patients with definite damage at BL showed more chronic changes at FU2 compared with patients without damage at BL. There was a significant ($p = 0.007$) change in mSASSS at FU1 compared with BL, but there was no significant change at FU2. The study concluded that after 2 and 4 years of infliximab therapy there is some radiographic progression. Although historical comparison suggests that infliximab may decelerate that progression of structural damage, larger studies are required to confirm this.

Pregabalin (Lyrica®) has been approved by the US FDA for use in reducing the pain associated with fibromyalgia

First drug for the treatment of fibromyalgia approved by US FDA

Fibromyalgia is a chronic condition affecting muscles and ligments. Patient suffering from fibromyalgia experience long-lasting fatigue and pain, in addition to muscle stiffness and tenderness. Between three and six million people are affected by fibromyalgia in the USA each year, the majority of whom are women between 30 and 60 years of age.

There is no specific test for the diagnosis of fibromyalgia and symptoms can vary between individuals. Diagnosis is based on physical examination and evaluation of symptoms, as well as using blood tests, x-rays and scans to rule out other conditions with similar symptoms, for example, lupus and RA.

The US FDA has recently approved the use of pregabalin for the treatment of fibromyalgia, the first drug to treat this condition. Pregabalin has proved to reduce pain and improve daily function in some patients with fibromyalgia and is already approved for the treatment of partial seizures, pain following the rash of shingles and pain associated with diabetic neuropathy. Speaking on the day of approval, Steven Galson, director of the FDA's Center for Drug Evaluation and Research, MD, USA, said that the "…approval marks an important advance, and provides a reason for optimisim for the many patients who will receive pain relief with Lyrica". However, he also warns that "…consumers should understand that some patients did not experience benefit in clinical trials. We still have more progress to make for treatment of this disorder".

Approval for the treatment of fibromyalgia with pregabalin 300 or 450 mg/day was supported by two double-blind, controlled clinical trials that involved approximately 1800 patients. The mechanism of action is as yet unknown, and dose-related side effects have been observed. Mild-to-moderate dizziness and sleepiness are amongst the most common side effects, with weight gain, blurred vision, dry mouth and swelling of the hands and feet also being reported. Pregabalin can also impair motor function and affect concentration and attention.

Don Goldenberg, cochair of the American Pain Society's fibromyalgia guideline panel and professor of medicine at Tufts University, MA, USA, believes "this is an important day for people with fibromyalgia and a real opportunity to help physicians effectively manage this disorder". Adding, "having a medication approved for use in fibromyalgia, along with research advances, will go a long way to improving our understanding and treatment of this common disorder".

The manufacturer of Lyrica, Pfizer, Inc., NY, USA, has agreed to perform studies of the drug in breastfeeding women and children with fibromyalgia.

Source: US FDA News www.fda.gov/bbs/topics/NEWS/2007/NEW01656.html

Dietary calcium superior to supplements in protecting against osteoporosis

Researchers at Washington University School of Medicine, MO, USA, have studied the protective effects of calcium on bone and discovered that women who obtain most of their calcium from their diet have healthier bones than women whose main calcium intake comes mainly from supplements. Calcium is vital for bone health; adequate calcium intake is important in preventing osteoporosis.

A total of 183 postmenopausal women detailed their diet and calcium supplement intake for 1 week, which was assumed to be representative of their typical diet. Bone mineral density (BMD) and urinary concentrations of estrogen metabolites were also determined.

It was found that the women could be divided into three groups: the 'supplement group', who obtained at least 70% of their daily calcium from tablets; the 'diet group', who obtained at least 70% of their calcium from dairy product and other food; and the 'diet plus supplement group', which consisted of women whose calcium-source percentages fell between these two groups.

Although the intake of calcium was lowest (830 mg/day) in the diet group, this group had higher bone density than the supplement group (who on average consumed 1030 mg calcium/day). Calcium intake was highest in the diet plus supplement group (1620 mg/day) and women in this group also had the highest bone density. Furthermore, women in the diet and diet plus supplement groups had higher ratios of active to inactive urinary estrogen metabolites compared with women in the supplement group. This is significant because estrogen maintains bone mineral density.

"This suggests that dietary calcium is associated with a shift in estrogen metabolism that favors production of active forms of estrogen", explains Reina Armamento-Villareal. "It's also known that dairy products, which are a major source of calcium, can contain active estrogenic compounds, and these can influence bone density and the amount of estrogenic metabolites in the urine". Armamento-Villareal also points out that differences in the absorbtion of calcium from supplements and food may have been responsible for the study's findings: "only about 35% of the calcium in most supplements ends up being absorbed by the body. Calcium from the diet is generally better absorbed, and this could be another reason that women who got a high percentage of calcium in their food had higher bone densities".

Source: Napoli N, Thompson J, Civitelli R, Armamento-Villareal RC: Effects of dietary calcium compared with calcium supplements on estrogen metabolites and bone mineral density. *Am. J. Clin. Nutr.* 85, 1428–1433 (2007).

Study investigates efficacy of belimumab in lupus patients

In a presentation at EULAR 2007, the Annual European Congress of Rheumatology, researchers reported on the efficacy of belimumab in treating SLE, as assessed using a novel combined responder index.

As the authors of the study explain, measuring the therapeutic response to treatments for SLE is complicated by the diversity of disease manifestations. Thus, the researchers developed a new index, which combined three commonly used measures of disease progression: Safety of Estrogens in Lupus Erythematosus: National Assessment, SLE Disease Activity Index (SELENA SLEDAI), Physicians Global Assessment (PGA) and presence of British Isles Lupus Assessment Group (BILAG)-classified new 1A or 2B flares.

The combined responder index was utilized in assessment of the response of 449 SLE patients to the human monoclonal antibody belimumab. Belimumab inhibits B-lymphocyte stimulator (BLyS), which is required for maturation of B-lymphocytes into plasma B cells capable of producing antibodies. It has been suggested that high levels of BLyS activity are partly responsible for the production of autoantibodies in SLE. Thus, belimumab acts to reduce levels of these autoantibodies.

The randomized, double-blind, placebo-controlled study observed a combined response (i.e, SELENA SLEDAI improvement of at least 4 points, no new 1A or 2B BILAG flares and no PGA worsening) in 46% of serologically active SLE patients receiving belimumab at 52 weeks. Further improvement was observed at week 76, with 56% showing a combined response.

"While the results demonstrated that treatment with belimumab resulted in a sustained improvement in SLE symptoms in patients with serologically active disease, we also confirmed that combining multiple disease activity measures is a successful method of assessing overall disease activity, and appears to be associated with the presence of biomarkers and quality of life improvements in responders," says Ellen Ginzler, SUNY-Downstate Medical Center, NY, USA, lead author of the study.

Source: Ginzler E, Furie R, Wallace D *et al.*: Novel combined response endpoint shows that Belimumab (fully human monoclonal antibody to B-lymphocyte stimulator [BLyS]) improves or stabilizes SLE disease activity in a Phase 2 trial. *Abstracts of EULAR 2007, the Annual European Congress of Rheumatology.* Barcelona, Spain (2007) (Abstract OP0018).

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology. The editorial team welcomes suggestions for timely, relevant items. If you have newsworthy information, please contact: Sarah Jones, Commissioning Editor, *Future Rheumatology,* s.jones@futuremedicine.com