Imaging Offers Window to Treat RA Earlier

BY MITCHEL L. ZOLER

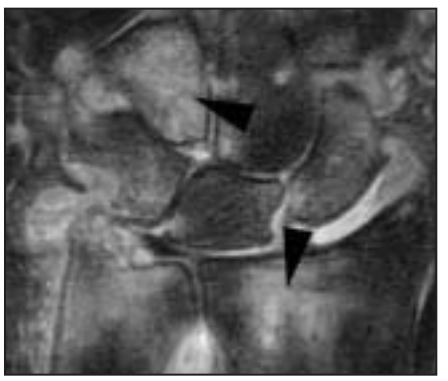
COPENHAGEN — MRI, ultrasound, and digital x-ray radiogrammetry may all have a role in identifying which patients with early, nonerosive rheumatoid arthritis will later develop erosive disease, based on results from a pilot study with 27 patients.

Dr. Pernille Bøyesen reported the findings at the annual European Congress of Rheumatology.

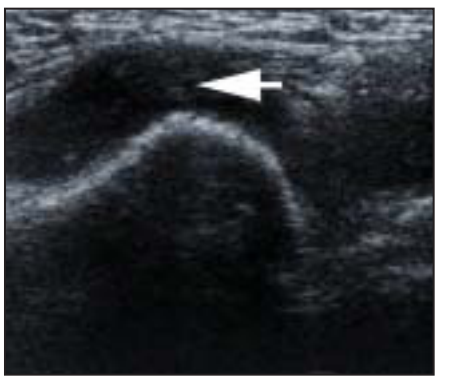
"Our findings support that DXR-BMD [digital x-ray bone mineral density] change, MRI, and US [ultrasound] can all be useful in order to identify early RA patients who will develop radiographic erosions. In addition, 3-month DXR-BMD change might be better based on the significant differences between groups in this limited sample," Dr. Bøyesen, a researcher in the department of rheumatology at Diakonhjemmet Hospital in Oslo, said in an interview. "The findings are in accordance with studies previously published that showed that DXR-BMD change, MRI, and US are associated with subsequent radiographic damage in RA patients."

The study focused on 27 patients who had had RA for less than a year and had no joint destruction evident on a baseline hand x-ray. Their average age was 52 years (range, 41-61 years). Average disease duration was 100 days, their average disease activity 28 score (DAS28) was 3.49 (range, 2.4-4.8), and 79% were women.

Each patient underwent further assessment of their dominant wrist at baseline by MRI (with an RA MRI score calculated), and by gray-scale US (with their synovitis and tenosynovitis scored at 0-3). The researchers also obtained x-ray images of each patient's hands and wrists at baseline and at 3, 6, and 12 months.



MRI shows bone marrow edema (arrows) in a patient with early RA.



This ultrasound image indicates ulnar B-mode synovitis (arrow).

They scored the images by the van der Heijde/Sharp criteria, and applied DXR analysis to calculate the 3-month change in BMD of metacarpal cortical bone.

In all, 10 patients developed x-ray indications of erosive disease during the 1 year of follow-up. The 10 patients had a significantly higher DAS28 (average, 4.5) at baseline, compared with the 17 patients who did not progress (average, 2.7). The 10 patients with progressive disease also had significantly greater bone loss at 3 months as measured by the DXR-BMD assessments. Dr. Bøyesen and her associates also saw a numeric trend toward higher MRI and US scores in these 10 patients at baseline, compared with the 17 nonprogressors, but the differences were not statistically significant.

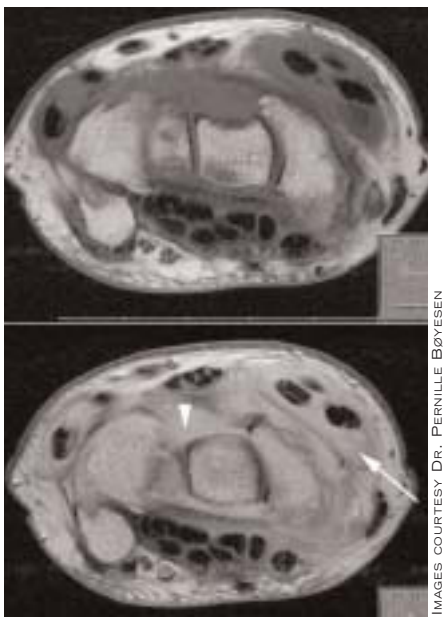
"We found that the 10 RA patients who became erosive had significantly higher DAS28 scores and 3-month DXR-BMD loss. This might point toward the possibility that DXR-BMD change is better at identifying patients at risk of developing x-ray erosions. However, the fact that the DXR-BMD change was larger in the erosive group by a nonparametric comparison does not implicate the superiority of this test in this context. In order to prove the effectiveness of the different methods, further statistical modeling is required, and due to our limited sample size this has not been possible," according to Dr. Bøyesen.

"Our findings support that DXR-BMD change, MRI, and US can all be useful to identify early RA patients who will develop radiographic erosions. [The 3-month] DXR-BMD change might be the better test, based on the significant differences between groups in this limited sample," she said.

By combining the various modalities, the investigators hope to "achieve higher accuracy in identifying RA patients who will develop erosive disease at a later time point. In order to appropriately address the roles of DXR, MRI, and US in clinical practice, we estimate that the sample would need [to comprise] approximately 100-150 RA patients."

In response to a question from the audience after her presentation, Dr. Bøyesen acknowledged that cortical bone is known for being less susceptible to erosion. Why DXR-BMD detected early density loss in metacarpal cortical bone remains to be answered, she said.

Dr. Bøyesen also noted that both US and x-ray studies are relatively quick and inexpensive, and use equipment that is widely available. US has a slight advantage because it doesn't even expose patients to radiation. MRI examinations take longer, use equipment that is more expensive and less widely available, and require treatment with a contrast agent. However, MRI provides information on multiple structures affected by RA, such as bone marrow edema, synovitis, tenosynovitis, and erosions, she said.



IMAGES COURTESY DR. PERNILLE BØYESEN

Digital x-rays show synovitis and tenosynovitis in early RA (arrows).

Further analysis showed that findings from DXR-BMD change, MRI, and US were as accurate at predicting erosion as established biomarkers of disease intensity, including erythrocyte sedimentation rate, rheumatoid factor positivity, and anti-citrullinated protein antibody, she said.

Dr. Bøyesen reported no conflicts of interest. ■

Well-Timed Prednisone Eased Morning Stiffness in RA

BY MICHELE G. SULLIVAN

A modified-release formulation of prednisone reduced morning stiffness duration in patients with rheumatoid arthritis, according to data presented at the annual European Congress of Rheumatology.

The new formulation is designed to be taken at bedtime. The medication is released about 4 hours after ingestion, with the goal of adapting glucocorticoid drug release to the circadian rhythms of endogenous cortisol and symptoms of the disease, both of which have their peaks during the early morning hours. It has been theorized that morning glucocorticoid dosing only inadequately controls the circadian rhythm of RA symptoms in these patients, Prof. Frank Buttgereit of Charité Medical University of Berlin, said in an interview.

"It's well known that symptoms of rheumatoid arthritis follow circadian rhythms and are typically most prominent in the early morning hours," he said. "Therefore, the timing of systemic glucocorticoid therapy may be important with respect to the natural secretion of endogenous glucocorticoids as well as the control of symptoms."

Findings from research conducted by Prof. Buttgereit and his associates involved a 3-month randomized, controlled trial of 288 patients with long-standing active rheumatoid arthritis that was published last year in The Lancet (2008;371: 205-14).

The data he presented at EULAR concerned 219 patients who completed a new 9-month follow-on open-label trial of the same group, during which all patients took the modified-release formulation.

At baseline, patients' mean age was 55 years; their mean duration of disease was 10 years. Patients who were randomized to the active group took a placebo tablet in the morning and the study drug in the evening. The comparator group took immediate-release prednisone in the morning and placebo in the evening. The prednisone dose was individually titrated (range, 3-10 mg/day).

The mean relative reduction of morning stiffness duration was significantly higher in the modified-release group than in the immediate-release group (23% vs. 0.4%). Patients taking the modified-release drug experienced a significantly greater decrease in the duration of morning joint stiffness than did those taking the immediate-release tablet (44 fewer minutes vs. 23 fewer minutes of morning stiffness). Median levels of interleukin-6 were also reduced in the modified-release group compared with the immediate-release group (29% vs. 0%).

Adverse events led to premature discontinuation of the drugs in 8% of the modified-release group and 7% of those in the immediate-release group. The frequency of serious adverse events was low and similar in both groups (3% vs. 2%).

Prof. Buttgereit reported that the combined results of the randomized and open-label trials. In both groups, morning stiffness duration remained similarly low over the entire study duration. At 12 months, the reduction was somewhat greater in the group that had taken the modified-release formulation during both trials (55%) than among those who took the immediate release during the first trial and the modified-release during the follow-on study (45%). The incidence of adverse events remained low throughout the open-label study, he said.

Among his expected conclusions is that "bedtime administration of prednisone via the new modified-release tablet provides significantly greater efficacy for at least 12 months over conventional immediate-release prednisone, due to prednisone release which occurs prior to the circadian flare-up of IL-6 synthesis and inflammatory activity."

The study was sponsored by Merck Pharma GmbH and Nitec Pharma AG. Prof. Buttgereit and some of the coauthors said they had received consulting and grant funding from the companies. ■