MRI Bone Edema Predicts Rheumatoid Arthritis

BY BRUCE JANCIN

FROM ARTHRITIS & RHEUMATISM

Magnetic resonance imaging evidence of bone edema in the wrist and metatarsophalangeal joints was an independent predictor of future development of rheumatoid arthritis in a prospective Danish study of patients with early undifferentiated arthritis.

Incorporating MRI bone edema findings, together with clinical and biochemical parameters, yielded a prediction model that showed unprecedented accuracy in identifying which patients would or would not develop rheumatoid arthritis, Dr. Anne Duer-Jensen of Copenhagen University Hospital at Hvidovre and Copenhagen University Hospital at Glostrup, and her associates reported in Arthritis & Rheumatism (2011;63:2192-202).

The study involved 116 patients with early undifferentiated arthritis, 23% of whom went on to meet American College of Rheumatology 1987 criteria for RA during a median 17 months of follow-up. They were matched with 24 healthy controls. The predictive model had a sensitivity of 81% and a specificity of 82% for progression to RA. Thus, it classified 82% of patients correctly.

That's a markedly better predictive accuracy than achieved when the investigators applied the published and validated van der Helm-van Mil prediction model to the same study population. The van der Helm-van Mil model (Arthritis Rheum. 2007;56:433-40) had a 60% predictive accuracy.

Participants in the Danish study had two or more tender joints and/or two or more swollen joints among the wrist, metatarsophalangeal (MTP), proximal interphalangeal, or metacarpophalangeal joints for more than 6 weeks but less than 2 years. None of the 116 subjects had a specific rheumatologic diagnosis at baseline. Thus, they were typical of the patients often referred to rheumatologists for early undifferentiated arthritis, a condition that can morph into osteoarthritis, RA, persistent arthralgias, or nonprogressive disease.

The investigators developed their predictive model based on the findings of a multivariate logistic regression analysis that encompassed numerous variables. The final prediction model included four independent predictors of RA: serum positivity for rheumatoid factor, the presence of hand arthritis, morning stiffness lasting longer than 1 hour, and the MRI summary score for bone edema in the wrist and MTP joints that grew out of the Outcome Measures in Rheumatology Clinical Trials, or OMERACT (J. Rheumatol. 2003;30:1385-6).

Of note, in the Danish study the presence of rheumatoid factor was an independent predictor of subsequent RA, whereas a positive anti–cyclic citrullinated peptide test was not, unlike in several recent studies.

MRI summary scores for bone edema proved to be a significantly more potent predictor of RA than MRI scores for synovitis or erosion.

VITALS

Major Finding: Incorporating MRI bone edema findings, together with clinical and biochemical parameters, yielded a prediction model that had a sensitivity of 81% and a specificity of 82% for progression to RA.

Data Source: The study involved 24 healthy controls and 116 patients with early undifferentiated arthritis, 23% of whom went on to meet American College of Rheumatology 1987 criteria for RA during a median 17 months of follow-up.

Disclosures: This study was funded by the Danish Rheumatism Foundation and other foundation grants. While Dr. Duer-Jensen reported having no financial conflicts of interest, several of her associates did. Those can be found on the full text of the journal article.

The formula for the current iteration of the prediction model is cumbersome. A simpler version would be welcome.

Toward that end, the investigators tried using MRI bone edema scores for the wrist or MTP joints alone, but they found that it unacceptably weakened the model's predictive power.

The next step in this project will be to see how the prediction model performs in other cohorts of patients with early undifferentiated arthritis.

The goal is to develop a tool that enables physicians to extend the current, highly successful early and aggressive treatment strategy for RA into the pre-RA setting. ■

Panel Urges Revamping of Rheumatology Clinical Trials

BY BRUCE JANCIN

FROM ARTHRITIS & RHEUMATISM

Clinical trials in rheumatoid arthritis that have been done for drug approval fail to address numerous issues critically important to clinical care, according to an American College of Rheumatology task force report.

The group was critical of current clinical trial design and offered half a dozen recommendations for reforms aimed at boosting clinical relevance. The task force also drew up a ranked priority list for the next generation of RA clinical trials, i.e., studies needed to address current major knowledge gaps. Topping this must-have list are trials of induction therapy in early disease.

► **Induction therapy.** The group recommended as an initial practical step a three-armed trial comparing current standard conventional methotrexate monotherapy to methotrexate plus a tumor necrosis factor (TNF) inhibitor versus methotrexate plus a non-TNF inhibitor biologic agent. This trial should be double-blind and consist of three phases: induction, maintenance therapy, and treatment withdrawal in patients whose disease goes into remission. It was the strong consensus of the task force that such a trial holds the greatest potential for advancing clinical care.

Biologic specimens should routinely be collected during this and all the other next-generation clinical trials in an intensive effort to identify biomarkers that will allow rational selection of medications and the tapering of treatment without triggering relapse. The urgent need for such biomarkers was "a recurrent theme that prominently permeated and at times dominated our discussions," according to the report of the task force chaired by Dr. James R. O'Dell, professor of medicine and chief of the section of rheumatology and immunology at the University of Nebraska, Omaha, who is also incoming president of the American College of Rheumatology.

In descending order of importance and urgency, the other topics on the task force's clinical trials priority list are:

► **Treatment of disease that remains active despite methotrexate and a first anti-TNF biologic.** The group believed that in an ideal world, a clinical trial addressing this scenario would continue background methotrexate while randomizing patients to a different TNF inhibitor, the T-cell mediator abatacept, the CD20-directed cytolytic antibody rituximab, or the interleukin-6 receptor blocker tocilizumab. That may be too big an undertaking to be practical. At the very least, the next generation of studies in this patient population ought to compare two biologics having different mechanisms, according to the task force report (Arthritis Rheum. 2011;63:2151-6 [doi:10.1002/art.30402]).

► **Patients in remission while on treatment.** At present there are essentially no data to guide medication tapering and discontinuation decisions. The panel proposed piggybacking tapering trials – with liberal collection of biologic specimens – on the back of current trials and next-generation induction trials.

The need for such biomarkers was 'a recurrent theme that prominently permeated and at times dominated our discussions.'

DR. O'DELL

► **Active disease despite methotrexate therapy.** Roughly 70% of patients with early RA fail to achieve low disease activity on methotrexate monotherapy. There is a need for clinical trials aimed at defining optimal methotrexate dosing strategies, the panel agreed. Beyond that, however, the task force was split on the best way forward. Some argued that active comparator trials of various add-on therapies in suboptimal responders to methotrexate are badly needed now, while others said it makes more sense to hold off until biomarkers can be identified that will help in making individualized treatment decisions based on an agent's mechanism of action.

The task force didn't address the issue of how the proposed research agenda will be funded. Of note, however, of 25 experts invited to an ACR conference on clinical trial priorities and design that was held last year, most were from academia, four came from the National Institutes of Health, three were Food and Drug Administration officials, and none were from the pharmaceutical industry.

The task force proposed numerous changes in clinical trial design aimed at yielding results that are more meaningful to clinical rheumatology practice. For example, the group declared that in the current era of proven highly effective RA therapies, placebo-controlled clinical trials have become ethically questionable and should be greatly de-emphasized in favor of active comparator studies. The task force also raised ethical concerns about the current rule that an assigned therapy must be continued for a prolonged period of follow-up, often 1-2 years, even though modern therapies are expected to bring maximum clinical benefit in 3-6 months.

The panel expressed reservations about the generalizability of clinical trials in RA that are increasingly being conducted in developing countries. The group recommended that when these trials are reported, the investigators should fully describe the study population and assess the generalizability of the findings.

In addition to Dr. O'Dell, the members of the ACR Rheumatoid Arthritis Clinical Trial Investigators Ad Hoc Task Force were co-chair Dr. Michael E. Weinblatt of Brigham and Women's Hospital, Boston; Dr. Ted R. Mikuls of the University of Nebraska, Omaha; and Dr. Robert A. Colbert of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Md. Dr. Weinblatt has received consulting fees from Abbott, Amgen, Astellas, AstraZeneca, Biogen Idec, Bristol-Myers Squibb, Centocor, Crescendo, Lilly, Pfizer, and Roche. ■