SCIENCE TO PRACTICE

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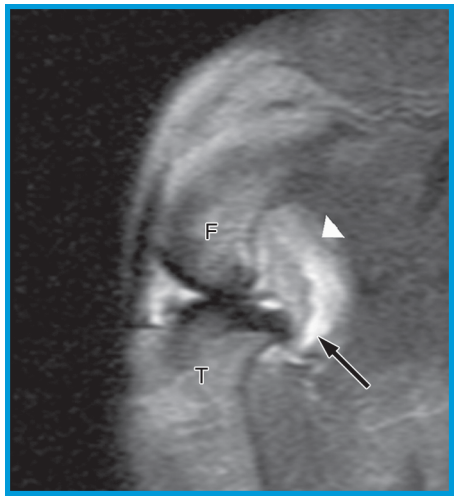
Science to Practice
Imaging of Rheumatoid Arthritis: Can MR Imaging be Used to Monitor Cellular Response of Disease?[1]

The Setting

Current application of magnetic resonance (MR) imaging in rheumatoid arthritis (RA) trials has been focused on detection of bony erosions and assessment of synovial volume and joint effusion as measures of synovial inflammation—that is, detection and monitoring of tissue response to disease (1). As therapy moves from minimizing synovial inflammation to targeting specific disease pathways, the next step is to use MR imaging to detect and monitor cellular response of the disease. In this issue of *Radiology*, Lutz et al (2) report promising results using ultrasmall superparamagnetic iron oxide (USPIO) particles to evaluate phagocytic macrophage activity in an experimental rabbit model of antigen-induced arthritis.



The Science

The trend in the treatment of patients with RA is early and aggressive use of disease-modifying antirheumatic drugs (DMARDs) that are targeted at critical elements within the inflammatory cascade (3,4). Because MR imaging can provide information on soft-tissue inflammation of the joint, it provides a sensitive measure of early disease activity and has been recommended as an outcomes measure in clinical trials on RA (5). The aim of using DMARDs in the treatment of RA is to block the effects of inflammatory cytokines that lead to synovial proliferation and joint destruction through activation of synovial fibroblasts and matrix metalloproteinases. Two key cytokines, tumor necrosis factor-α and interleukin-1β, are produced by activated macrophages that reside within the inflamed synovium. There is growing evidence that synovial macrophages play a central role in RA. Results of recent studies demonstrate a marked reduction in macrophage content of the synovial membrane in patients with RA who achieve clinical remission induced with use of DMARD therapy (6). These reports provide a theoretical basis for using synovial macrophage content as a relevant marker of disease activity.

Because of their small size, USPIO particles are able to extravasate through capillary pores and are well suited for targeting synovial macrophages. Results from the study of Lutz et al (2) demonstrate the feasibility of using clinical MR imaging both to detect changes in synovial contrast following intravenous USPIO administration in an accepted model of RA and to localize uptake of the iron oxide particles in macrophages. While no change in synovial contrast enhancement was identified in control joints, a statistically significant decrease in signal intensity ($P < .05$) was observed in the inflamed joint on both T2- and T2*-weighted MR images. Results of histologic evaluation demonstrated uptake of iron particles within synovial macrophages of the inflamed joint but not within the contralateral control joint or within the joints of control animals.

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The Practice

Clinical use.—USPIO agents are currently undergoing clinical trials for evaluation as targeted lymph node contrast agents, primarily for the detection of regional lymphadenopathy in patients with cancer. As the results of Lutz et al demonstrate, these agents have potential clinical application in the evaluation of inflammatory arthropathies. Phagocytosis of the paramagnetic iron oxide within cells distorts the local magnetic field, which produces signal loss on T2*-weighted images. Because the field distortion extends beyond the confines of the cell, the T2* changes are detectable with relatively low spatial resolution that is achievable on current clinical MR imagers, thereby making USPIOs useful in targeted contrast agents.

Future opportunities and challenges.—Application of macrophage-targeted contrast agents may provide valuable information on the underlying pathogenesis of RA and may provide a sensitive and specific image marker to monitor disease activity. Prior to the application of these

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techniques to human clinical trials, it will be necessary to validate USPIO uptake in macrophages of patients with RA, determine the responsiveness of the technique to changes in disease activity, and demonstrate reproducibility within a more heterogeneous human population. Because of the strong field dependence of T2* contrast enhancement, future application of USPIO agents with 3.0-T clinical MR imaging is likely to further increase sensitivity and provide opportunity for greater spatial resolution. Results of the study of Lutz et al (2) support development of human clinical trials to evaluate the role of USPIO particles in RA.

Summary

By using methods achievable with routine clinical MR imagers, Lutz et al (2) have shown that intravenous administration of USPIO particles provides a valuable image marker of macrophage content within inflamed synovium. With the continuing development of new DMARDs directed toward suppressing synovial macrophage activity, the ability to noninvasively detect and monitor synovial macrophage content has high clinical and research importance.

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