MR IMAGING OF ANKLE JOINTS IN MOUSE MODELS OF RHEUMATOID ARTHRITIS

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Target audience: Experimental rheumatologists and other ankle disease researchers

Purpose: Rheumatoid Arthritis (RA) is an inflammatory disease of the joints that causes significant disability and mortality worldwide. Animal models provide insight into the pathogenesis of disease and enable investigators to test novel therapies before proceeding to clinical trials. However, most experimental RA studies rely on subjective clinical scoring of arthritis or on sacrificing animals to examine tissue sections (which can be unreliable due to serious joint deformation secondary to disease). This is a major limitation that introduces uncertainty into results and requires the use of large numbers of animal subjects. µCT has been used to study bone destruction in some models of RA, but this technique does not report on soft tissue swelling, bone marrow edema, or lymph node enlargement. The goal of this project was to develop MRI methods to serially image sites of inflammation and bone destruction within the ankle joints of mice with acute and chronic RA[1], and to validate the MRI data against clinical and optical imaging assessments of inflammatory arthritis. Our findings establish MRI as a highly valuable tool for anatomic localization of articular and soft tissue changes during the development and resolution of inflammatory arthritis in mice.

Methods: Studies of chronic arthritis were performed in the K/BxA^{g7} transgenic model, and bone erosion was measured by MRI in 3 mice at 10 weeks and 1 mouse at 21 weeks of age. MRI was performed on a 9.4T Bruker Biospec using a 4 channel receive-only surface coil and 72 mm diameter transmit-only volume coil. 3D gradient echo FLASH images (TR/TE/α=50 ms/2.4 ms/10°; resolution 0.075 mm isotropic) were obtained to evaluate bony structures. The tibia, fibula, talus, and calcaneus were segmented manually and volume rendered in Amira 5.1. The K/BxN serum transfer-induced arthritis (STIA) model was used for studies of acute inflammatory arthritis. 3 C57BL/6 mice were injected intraperitoneally (IP) with 100 µL of K/BxN serum on day 1 and 3 mice served as controls. Severity of arthritis was measured by clinical scoring, chemiluminescence, and MRI at days 0, 3, 7, 15 and 21 after induction of arthritis. Clinical scores were calculated by rating disease severity in each paw from 0-3 and summing for a total range of 0-12. Optical measurement of inflammation was performed on an IVIS Spectrum after injecting mice IP with 100 µL of XenoLight Rediject Inflammation Probe; total radiant signal over the four paws was quantified using Living Image 5.1. 3D T_2 weighted multi-echo spin echo MSME images (TR/TE=1000ms/10-60ms; resolution 0.075x0.075x0.150mm^3) were used to generate T_2 maps thresholded to include voxels with T_2>40 ms.

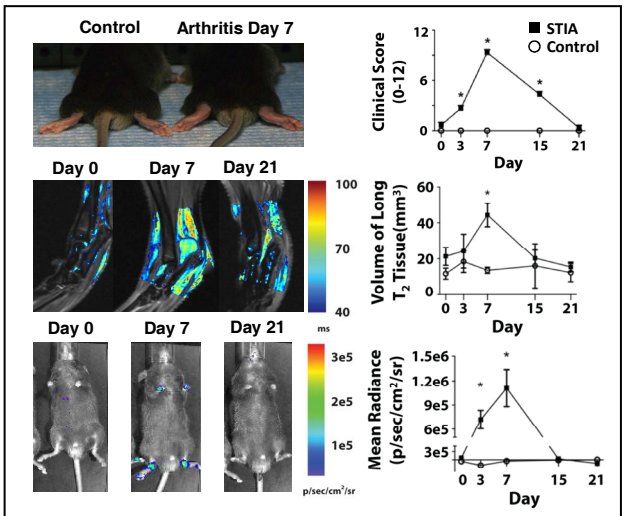

Figure 1: (Top) Photo of control and arthritic mouse showing visibly swollen ankle 7 days after STIA induction, and plot of clinical scores vs. time. (Middle) T_2 weighted MRI of ankles at days 0, 7, and 21 with overlaid T_2 maps, and plot of volume of long-T_2 tissue vs. time. (Bottom) IVIS images showing myeloperoxidase activity in joints, and plot of total radiance vs. time. Note concordance in disease progression by all 3 metrics.

Results: STIA mice exhibited rapid onset of acute arthritis with average clinical scores rising from 0 to 9.3 by day 7, then gradually returning to 0 by day 21. This pattern was mirrored in the MRI and IVIS data, with average volume of tissue with T_2>40 ms doubling between 0 and 7 days, and mean total paw radiance rising from $7x10^4$ to $1x10^6$ over the same time; both metrics returned to baseline by day 21. In the K/BxA^{g7} transgenic model, bone erosion was observed at 10 weeks and had progressed significantly by 21 weeks, with a reduction in talus volume from 1.7mm^3 to 0.4mm^3 in that time.

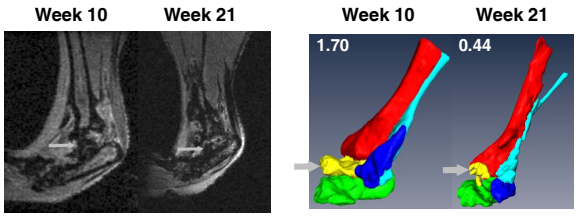

Figure 2: (Left) Representative slices from 3D FLASH images in K/BxA^{g7} chronic arthritis model at 10 and 21 weeks. (Right) 3D bone reconstructions showing severe talar erosion (arrows).

Discussion and Conclusions: In the STIA model of acute arthritis, disease progressed rapidly, peaking at day 7, with inflammation reduced to near baseline levels by day 21. MRI measurements of inflammation were consistent with previously used methods of clinical scoring and chemiluminescent imaging. µCT has previously been used to measure bone erosion; here we demonstrate that MRI has this capability as well. We are pursuing µCT studies to corroborate the MRI measurements. MRI is the only currently available technique that can report, in a single imaging session, on bone erosion, soft tissue inflammation, and the structural details of both (enabling, for example, differentiation of periarticular vs. intra-articular swelling). This represents a major advancement in the field of experimental rheumatology, as development and progression of arthritis in a variety of mouse models can now be followed noninvasively over time, enabling both detailed model characterization and evaluation of novel drug therapies in a way that has not heretofore been possible.

References: [1]Kyburz D, Corr M. The KRN mouse model of inflammatory arthritis. Springer Semin Immunopathol. 2003;25(1):79-90.