Advantages of Non-invasive Imaging Techniques in Monitoring Antigen Induced Arthritis Rat Model

A Gramoun1, LA Crowe1, F Tobaleni1, D Tchemiri1, BMA Delattre1, K Grosemagne1, MI Koenders2, WB Van den Berg3, X. Montel1, J-P Vallette1

1Department of Radiology, Geneva University Hospitals, University of Geneva, Faculty of Medicine, Foundation for Medical Researchers, Geneva, Switzerland;
2Department of Radiology, Geneva University Hospitals, Geneva, Switzerland;
3Department of Rheumatology, Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Center, Netherlands.

OBJECTIVES

- Characterizing the antigen induced arthritis (AIA) rat model using magnetic resonance imaging (MRI) in a longitudinal study
- Validating the efficiency of MRI in assessing synovial and intra-articular oedema as well as bone erosion compared to μCT and conventional histological scoring
- Assessing the effects of an existing anti-rheumatoid arthritis (anti-RA) therapeutic dexamethasone (Dexa) using MRI

RATIONAL

- With many new anti-RA treatments in preclinical development, cost and time effective assessment methods are needed
- RA assessment using MRI in small animal models of rheumatoid arthritis (RA) is not a commonly used method to date
- Infiltration and erosion histological scoring as well as μCT are the gold standard for measuring bone erosion and tissue inflammation and the most conventionally used in studying new animal models and new therapeutics
- These methods are limited in their ability to study several disease parameters simultaneously and can be labor intensive and expensive if a longitudinal study is pursued

A Longitudinal Assessment of Disease Parameters in AIA Rat Model Using MRI

- Figure 1: MRI images of the right arthritic knee and the contralateral control acquired by T2 2D-STIR MR sequence illustrating synovial and intra-articular oedema (white signal) on days 21, 3, 6, 10, 13 and 17
- Figure 2: Assessment of synovial oedema, intra-articular oedema and erosion using MRI scores. While synovial oedema peaks on days 3 and 6 and then significantly declines, intra-articular oedema peaks on day 10 and slowly decreases. Erosion continues to increase over time up to day 16 and plateaus afterwards

METHODS

- AIA was induced in the right knee of 70 female Lewis rats as described previously by Oelzner et al. 2010 while the left served as an internal control
- Knees were scanned using MRI and μCT on days: 0, 3, 6, 10, 13, 17 post-induction using Siemens 3T clinical scanner with 4cm loop coil and Skyscan-1076 scanner respectively
- Four to ten animals were sacrificed at each time point, paraffin embedded and H&E stained; erosion and infiltration were performed as described previously (Koenders et al., 2005)
- T2 2D-STIR MR sequence was used for oedema (TR/TE 3700/20ms, resolution 0.156mm) and 3D-GRE (VIBE) MR sequence was used for bone erosion (TR/TE 14.3/0.9ms, resolution 0.31mm)
- Nine animals of this group were Dexa treated intraperitoneally (dose: 4, 4, 2mg/kg on day 2, 4, 8) scanned on days 3, 6, 10 and sacrificed on day 10
- On MRI images, intra-articular oedema, synovial oedema and erosion were scored based on a blinded clinical scoring (1-3) and μCT images were also clinically scored for erosion in 6 different sites on the joint plate and articular notch (1-3 scoring system) by blinded observer and the mean of those 6 sites was plotted

Evaluating the Effect of Dexamethasone Using MRI Compared to to Histology and μCT

- On day 10 similar trends are seen between infiltration scores obtained by MRI and histology for both intra-articular and control groups (figure 8). * P<0.05
- Erosion scores of the two groups on day 10 measured by MRI, histology and μCT were significantly different (figure 9). * P<0.05

DISCUSSION

- Using MRI multiple disease parameters (synovial oedema, intra-articular oedema and erosion) can be evaluated overtime and repeated measurements can be performed on the same animal
- Two of the disease parameters (synovial oedema and erosion) can only be measured using two different techniques (histology and μCT) while MRI offers one step solution for both parameters in addition to depicting a third parameter (intra-articular oedema) only seen on MRI
- Following the same animal overtime can decrease the number of animals needed to conduct a longitudinal study
- While histology and μCT possess higher resolution to measure erosion, we were able to demonstrate that MRI has sufficient sensitivity to characterize erosion in AIA model in presence and absence of anti-RA treatment
- MRI predicted with very high accuracy synovial inflammation even in absence of a contrast agent using the T2 2D-STIR sequence

ACKNOWLEDGEMENTS

* Work was funded by the EU Commission Research Committee (Grant Agreement number: MIF4-PA-2009-280292) as part of the Nano24RA project.