MRI REMAINS THE METHOD OF CHOICE IN TESTING DISEASE MODIFYING OSTEOARTHRITIS DRUGS.

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Introduction.
The guinea pig is a useful model to test Disease Modifying Osteoarthritic Drugs (DMOADs)because osteoarthritis (OA) develops spontaneously on the medial tibial plateau (MTP) cartilage (1). Metalloproteinase inhibitors (Mpi) have been shown to inhibit cartilage degeneration in the guinea pig model (2). The ability to use urinary biomarkers and understand how it correlates with cartilage volume changes identified by MRI would have many applications. The aim of the study was to compare MRI medial tibial plateau (MTP) cartilage volumes with two urinary biomarker of type II collagen degeneration with and without MPi treatment to evaluate its use as a surrogate outcome measure of drug efficacy.
Collagen type II cleavage (C2C) and collagen crosslinks (CTXII) were chosen as they measure changes specifically occuring in articular cartilage collagen and both are being investigated in the clinic for the measurement of human OA disease progression.

Methods.
Nine-month-old male Dunkin Hartley guinea pigs were dosed for 66 days with 0.3mg/kg/day Mpi (2) (n=10) & vehicle (n=16) via osmotic mini-pump.
At both time points, images were acquired for 105 minutes using a double balanced matched 3 cm diameter solenoid (π=50µs at 50W), and a spoiled fat-suppressed 3D gradient echo (TR=75ms, TE=2.7ms) at 4.7T (Varian 'Inova'). The images covered the entire left knee joint with a resolution of 59×117×234µm. Segmentation was performed blinded using code written in-house in IDL. Three observers measured cartilage volume on the MTP independently. This technique has previously demonstrated sufficient statistical power to detect loss of cartilage volume in this model over 3 months (3). Urine collected early morning pre and post-dosing was tested for biomarkers.
C2C cleavage assay (IBEX) was used to measure Type II collagen cleavage product and CTXII (collagen crosslink levels) were assessed using the Cartilps assay (Osteometer Biotech, Denmark). Data from both assays were normalised to creatine.

Results
MRI: Mpi dosed animal increased MTP cartilage volume by 16.8 ± 3.0% (mean±sem) while the vehicle group lost 20.1%±3.0% (P<0.001,two-sided t-test).
C2C assay: In the MPi dosed animals the biomarker decreased by 42.4 ± 38.7 µg/mmol creatinine (mean ± sem) while in the vehicle group it increased by 38.2 ± 46.2 µg/mmol creatinine (P<0.36, two-sided t-test).
CTXII assay: In the Mpi dosed animals the biomarker decreased by 7.2 ± 13.2 µg/mmol creatinine (mean ± sem) while in the vehicle group it decreased by 0.6 ± 5.81 µg/mmol creatinine (P<0.08, two-sided t-test).
CTXII and C2C assay results showed no correlation between MTP volume change versus biomarker for MPi treated and vehicle group animals. As opposed to MRI, these urinary biomarkers could not differenciate treated from controls (Figures 1 and 2).

Conclusion
MRI allows accurate quantification of MTP cartilage volume change in the guinea pig model of osteoarthritis. The technique is sensitive enough to achieve significance with only 16 animals.
The analysis of collagen degradation with two biomarker assays, C2C and CTXII, currently being investigated in the clinic, demonstrated high inter-animal variability with a non-significant trend towards reduced collagen fragment release with MPi treatment. The confidence intervals for both C2C and CTXII are far too wide for them to be used as predictive markers of MRI changes associated with osteoarthritis.
As opposed to MRI, the use of these urinary biomarkers in this animal model as a tool for the evaluation of DMOADs is not feasible without the use of unacceptably large numbers of animals or the collection of more data points.
These findings may have implications in the design of clinical trials to assess Disease Modifying Osteoarthritic Drugs (DMOADs).

References:
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