Evaluation of clinical analgesics in a nonhuman primate model of knee osteoarthritis

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Goals
- Behavioral characterization of a nonhuman primate model of knee osteoarthritis.
- Pharmacological validation of a nonhuman primate model of OA pain with clinically used analgesics.
- In vivo imaging of the knee joint.

Methods

Animals
Young adult cynomolgus macaques (SNBL, Japan).

Behavioral assessments
Weight bearing: Macaques were restrained in a monkey walker and weight bearing of the left and right legs were measured using scales. Normal weight bearing is 50%.

Knee pressure threshold: Pressure threshold was measured using a hand-held field pressure meter. The amount of force needed to evoke a withdrawal response was recorded. The maximum threshold was 3 kg. Ipsilateral knee pressure threshold was reported as a % of the contralateral, uninjured knee. Normal knee pressure is 100% of the contralateral knee.

In vivo imaging over time
Knee joints were imaged 6, 8, and 18 weeks following MMx using a 3.0 T-MRI (Signa EXCITE HDxt, GE Healthcare). N = 4, data expressed as mean ± S.E.

T2 maps were created from multi-echo data using Osiris (Pimeko, Bernex, Switzerland). A coronal section of the center of the knee joint was selected and T2 values (msec) were recorded in four regions of interest (ROI).

3D-SPGR images were registered from T2 maps and cartilage thickness (mm) was measured at three areas within each of the four ROIs. Cartilage thickness at each ROI was the average of three measurements.

Pain Assessment

Imaging Results

T2 mapping
- T2 femur, lateral
- T2 femur, medial
- T2 tibia, lateral
- T2 tibia, medial

Cartilage thickness
- cartilage femur, lateral
- cartilage femur, medial
- cartilage tibia, lateral
- cartilage tibia, medial

Representative photomicrograph of knee joint pathology 4 months after MMx. Note the loss of cartilage (arrows) and exposure of subchondral bone.

Conclusions
- Potential species-based difference in responsiveness to clinical OA analgesics.
- Need for disease-modifying drugs in addition to drugs that relieve pain.
- Nonhuman primate model as a surrogate model of clinical OA.

Preclinical success = clinical efficacy?

Summary

Risk: Disease-modifying drugs in addition to drugs that relieve pain.

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