DOXYCYCLINE SLOWS MRI-ASSESSED CARTILAGE VOLUME LOSS IN THE GUINEA PIG MODEL OF OSTEOARTHRITIS

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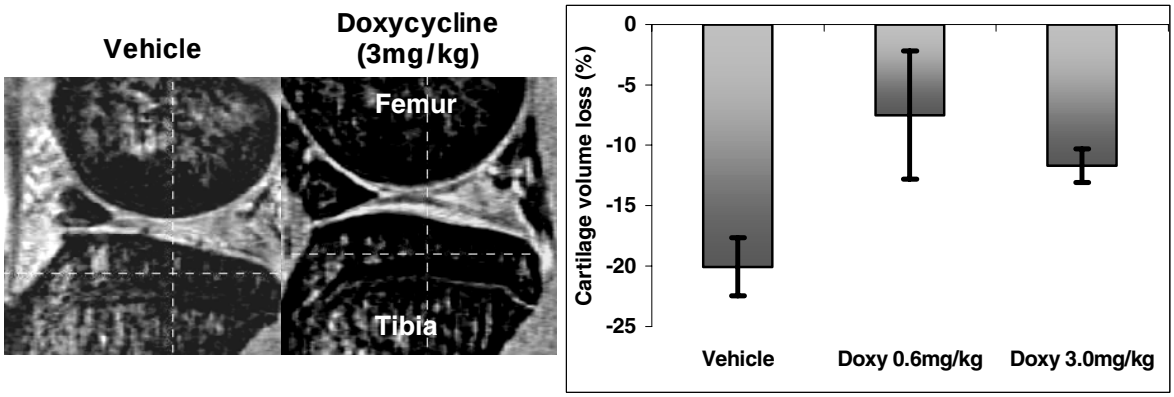
Introduction: The guinea pig is a useful model to investigate osteoarthritis (OA) because in this species it develops spontaneously initiating on the medial tibial plateau (MTP)(1). Doxycycline is an antibiotic that at sub-microbrial exposure reduces the degenerative changes that occurred in OA joints of both animal models and humans (2). The aim of this study was to assess the effect of doxycycline on the MTP cartilage loss by 3D MRI and correlate the findings with activity levels of MMP13, MMP8, MMP9 and MMP1.

Methods: Male Dunkin Hartley guinea pigs (9 months old) were dosed for 66 days with vehicle, (n=13) or 0.6mg/kg/day, (n=8), 3.0mg/kg/day (n=9) doxycycline via osmotic mini-pump. MR images were acquired for 105 min using a double balanced matched 3 cm diameter solenoid 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(3). A blinded segmenter used in-house software to determine medial tibial plateau (MTP) cartilage volume change. At study termination, tibial cartilage was scraped from both hind knees of each animals and frozen @-80°C. MMP activity was determined using fluorescent peptide substrate kits (R&D Systems).

Results: The vehicle group lost 20.8±2.4% (mean±sem) of its MTP cartilage volume by MRI. The doxycycline (0.6mg/kg/day) group lost 7.5±5.3% ($P<0.05$, two-sided t-test) whilst the 3.0mg/kg/day group lost 11.7±1.4%, ($P<0.02$). Doxycycline treatment ablated MMP13 levels and MMP8 levels, reduced MMP9 levels by 65%, but had minimal effect on MMP1 (17% reduction).



Conclusions: 3D MRI allowed accurate quantification of cartilage volume change associated with disease progression. Doxycycline treatment at 0.6 and 3.0mg/kg/day reduced cartilage volume loss and was associated with a complete reduction in total MMP13 and MMP8 protein levels in the cartilage and a partial reduction in MMP9 activity. These data suggest that doxycycline exerts its effect through selective suppression of MMP13 and 8 levels compared to MMP1. The protective effect of doxycycline on cartilage volume observed by MRI correlates with the clinical data on reduction of joint space narrowing in the knee (2) as assessed by x-radiology and strengthens the hypothesis that cartilage volume measured by MRI would be a useful tool to evaluate OA therapies in the clinic.

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