INFLIXIMAB (IFX) MIGHT BE PROTECTIVE AGAINST INTERPHALANGEAL OSTEARTHRITIS (OA)

M. Güler-Yüksel1, M. Kloppenburg1, C.F. Allaart1, I. Watt1, B.A. Dijkmans2, T.W. Huizinga1, W.F. Lems2.

1LUMC, Leiden, NETHERLANDS, 2VUMC, Amsterdam, NETHERLANDS

Purpose: To investigate the association between inflammation and the incidence and progression of interphalangeal OA and the effect of IFX on interphalangeal OA.

Methods: Data from patients from the BeSt study with X-rays available were utilized. In the BeSt study 508 recent-onset rheumatoid arthritis (RA) patients were randomized into 4 treatment strategies: 1. sequential monotherapy, 2. step-up combination therapy, 3. combination therapy with prednisone and 4. IFX and methotrexate (MTX). In groups 1–3, patients proceeded to treatment with IFX and MTX after failing on at least 3 previous DMARDs. The IFX dose varied between 3 and 10 mg/kg/8 weeks. X-rays of the hands were scored random in time for osteophytes (grade 0–3 for each joint) using the Osteoarthritis Research Society International atlas in 10 DIP joints (DIPJs) and 8PIP joints (PIPJs) at baseline and after 3 years. The incidence and progression of OA was defined as a change from baseline in the osteophyte score greater than SDC (1.7 units) in patients without and with one or more osteophytes at baseline. Erosions were measured according to the Sharp-van der Heijde score. In multivariate analyses, adjusted for age, gender, postmenopausal status and BMI, associations between the components of the DAS and erosion scores and the incidence and progression of interphalangeal OA was determined.

Results: 416 patients (67% women, mean age 54 years) were included. At baseline, osteophytes were present in 37% of the patients in one or more DIPJs and in 13% of the patients in one or more PIPJs. After 3 years, 6 and 4% of the patients had incident OA in the DIPJs and PIPJs. Radiographic progression was present in 18 and 15% of the patients in the DIPJs and PIPJs. Number of swollen joints at baseline, erosion score at baseline, change in erosion score after 3 years and postmenopausal status were associated with incidence of interphalangeal OA. Change in erosion scores after 3 years was associated with progression of interphalangeal OA.

178 (43%) patients were treated with IFX during some period of the study and these patients had less incident OA (4% in patients who received IFX versus 7% in patients who did not receive IFX, p=0.211) and less progressive OA (10 versus 38%, p=0.020) in the PIPJs. Combination therapy with IFX did not affect the incidence of OA (7 versus 7%, p=0.974), nor the progression (29 versus 24%, p=0.516) in the DIPJs.

Conclusions: The incidence and progression of interphalangeal OA was associated with more inflammatory activity in RA patients, suggesting that inflammation might play a role in the pathogenesis of interphalangeal OA. Combination therapy with infliximab reduced the progression of OA in the PIPJs in the period of three years after baseline, suggesting that anti-TNF might be an effective treatment against hand OA.
still present for the patients that were under therapy after 42 months. All scores obtained at followup visits showed statistical significance (p < 0.001) when compared with scores obtained at baseline.  

Conclusions: Our findings suggest that hip viscosupplementation may be an effective and cost-saving treatment for both patients and Healthcare system, not only because the spending for NSAID is lowered (direct costs), but also because gastrointestinal and cardiovascular side effects commonly associated with NSAID may be reduced (indirect costs).

539 THE EFFECT OF TETRACYCLINES ON HUMAN ARTICULAR CARTILAGE METABOLISM ARE DEPENDENT ON THE DEGREE OF OSTEOARTHRITIC ALTERATIONS

J. Steinmeyer, J. Kordelle, Orthopaedic Research Laboratories, Dept. of Orthopaedic Surgery, University Hospital Giessen and Marburg, Giessen, GERMANY

Purpose: In search for potential new therapies in the treatment of osteoarthritis (OA), attention has focused also on tetracyclines and their ability to slow down the progression of OA. Several possible mechanisms have been proposed, including inhibition of the activity and expression of inducible nitric oxide synthase (iNOS) and matrix metalloproteinases (MMPs). Using normal bovine articular cartilage, minocycline were found to have a stronger inhibitory effect on e.g. the expression of iNOS and MMP-1 than doxycycline. 

In this line, the purpose of this in vitro study was to determine systemically whether tetracyclines (1) influences the synthesis and release of PGs, MMPs and PGE2 also from human OA cartilage, (2) are affected by the degree of OA alterations, (3) are different with respect to their individual ability to modulate cartilage metabolism, and (4) affect chondrocyte viability within human OA cartilage explants.

Methods: Full-thickness cartilage explants of the lateral compartment of the femoral condyles were taken from OA patients undergoing knee replacement surgery. 4-mm-diameter articular cartilage discs were obtained using a biopsy punch. The degree of OA changes of the femoral condyles was determined according to Collins. Explants from mild (Collins grade 0–1.5) or moderately (Collins grade >1.5–3) affected human OA condyles were cultured separately in supplemented Ham’s F12 media with media changes every 3–4 days. Explants were treated with 1, 10, 50 or 100 μM minocycline, doxycycline or tetracycline in the presence or absence of recombinant human II-1β (5 ng/ml). PG synthesis was determined by the incorporation of 35SO4 during the final 18h of the 11 days experiments whereas the content of PGs were quantitated with the DMMB-assay. The viability of chondrocytes was assessed microscopically using fluorescein diacetate and propidium iodide. Nitrite levels in media were measured by using the Griess reaction. MMP-1, -8, and -13 as well as PGE2 were determined and propidium iodide. Nitrite levels in media were measured by using the Griess reaction. MMP-1, -8, and -13 as well as PGE2 were determined by the incorporation of 35SO4 during the final 18h of the 11 days experiments whereas the content of PGs were quantitated with the DMMB-assay. The viability of chondrocytes was assessed microscopically using fluorescein diacetate and propidium iodide. 

Results: The degree of OA alterations of explants can have a profound modulatory effect on the influence of tetracyclines on cartilage metabolism. Furthermore, doxycycline partly displayed a weaker pharmacological effect than minocycline, whereas tetracycline was found to have the lowest potential to change cartilage metabolism. The viability of explants was not affected by any of the drugs tested.

Conclusions: Our study indicate that the pharmacological efficacy of tetracyclines can be dependent on the clinical stage of OA. In addition, our findings indicate that minocycline possess a stronger potential than doxycycline to slow down cartilage degradation in OA.

540 FUNCTIONAL AND STRUCTURAL IMPROVEMENTS IN A DOG ANTERIOR CRUCIATE LIGAMENT MODEL: RECOMBINANT HUMAN FIBROBLAST GROWTH FACTOR 18 AS THERAPY FOR OSTEOARTHRITIS

C.H. Ladel1, R. Capobianco1, A. Gigina2, E. vom Baur1. 1Merck Serono Research – RBM, Colliere Gigosa, ITALY, 2Merck Serono S.A., Geneva, SWITZERLAND

Purpose: To investigate the efficacy of the anabolic agent fibroblast growth factor 18 (rhFGF18; AS902330) in counteracting structural damage and functional impairment in a dog anterior cruciate ligament (ACL) model of osteoarthritis (OA) over 26 weeks.

Methods: From week 4 after surgical section of the right ACL in mongrel dogs, intra-articular injections of AS902330 3 μg, 10 μg or 30 μg per joint (n = 8/dose group) or placebo (saline; n = 8) were given into the OA knee once a week for 3 consecutive weeks. The animals were followed up through week 26. Peak vertical force (PVF) was recorded at baseline and at weeks 4, 8, 14, 20 and 26. MRI of the stifle joint was performed at weeks 4, 8 and 26. Semi-quantitative scores were determined for osteophytosis, bone marrow lesions and cartilage defects, and cartilage volume was measured. Macroscopic measurements of cartilage lesions (condyles and plateaus) were performed at weeks 8 (3 dogs/group) and 26 (5 dogs/group). Exposure was determined using high performance ELISA. All injections were undertaken and evaluations performed by investigators blinded to the assigned treatment.

Results: Following section of the ACL, all dogs developed functional impairment, but there was less loss of PVF in dogs treated with any of the tested doses of AS902330 than in controls. In placebo-treated dogs, the evolution of structural damage over time (weeks 4–26) correlated with worsening limb function as expressed by PVF. As early as week 8 (i.e. at the end of intra-articular therapy), differences in joint functionality could be detected between AS902330-treated dogs and placebo-treated dogs. At week 8, mean PVF loss in the AS902330-treated group given 30μg/joint was 36.3% of baseline values, versus 47.8% in controls (p = 0.082; Mann-Whitney U test). A significant difference in PVF loss was also seen between AS902330 30μg and saline at week 14 (26.2% vs 44.4%, p = 0.007). The difference between groups (AS902330 30μg vs saline) was less pronounced at weeks 20 and 26 (35.2% vs 38.5%; 23.9% vs 33.5%, respectively). Measures of contact area followed a similar pattern to PVF. Macroscopic gross pathology and microscopic evaluation of cartilage using the International Cartilage Repair Society scoring system revealed a clear reduction in the severity of cartilage lesions in AS902330-treated dogs compared with controls at the end of therapy (8 weeks) and after longer term follow-up (26 weeks). In addition, immunostaining for catabolic factors (e.g. matrix metalloproteinases, inducible nitric oxide synthase) revealed a reduction in staining in the cartilage of AS902330-treated dogs, which was maintained up to the end of the study period (26 weeks). Systemic exposure after intra-articular administration of AS902330 was below the lower limit of quantification (50 pg/ml).

Conclusions: Intra-articular injection with the anabolic agent AS902330 was shown to reduce progression of structural damage and alleviate limb impairment in an ACL model of OA in dogs. The reduction in catabolic parameters in the OA joint of treated animals, improved histopathology scoring, and the improved functionality compared with saline-treated controls support the hypothesis that treatment with rhFGF18 may influence the course of OA and reduce functional impairment.

541 HCT 1026, A CYCLOOXYGENASE-INHIBITING NITRIC OXIDE DONATOR (CINO D), MODULATES CHONDROCYTES METABOLIC PATHWAYS

F. Kabile1, D. Miglietta2, S. Viappiani1, M.I. Bolla1, J-P. Pujol3, 1NicOx SA, Sophia-Antipolis cedex, FRANCE, 2NicOx Srl, Bresso, ITALY, 3Laboratoire de Biochimie du Tissu Conjonctif, Caen, FRANCE

Purpose: Osteoarthritis (OA) and rheumatoid arthritis are characterized by a reduction of extracellular matrix and increased catabolism of collagen fibers and glycosaminoglycans in joints. Conventional therapy with traditional non steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors may increase progression of cartilage degradation, especially in long-term treatments (Mastbergen, Arthritis Res Ther 2006). The role of nitric oxide (NO) in OA is still controversial, since it has been recognized as a marker of inflammation and a possible cause of chondrocyte loss, but also as a potent immuno-modulating factor improving joint vascular perfusion (Hancock & Rieger-Krugh, Clin J Pain