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 data 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

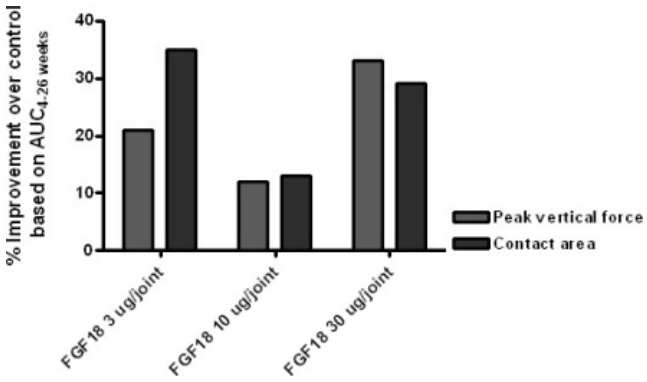
J. Steinmeyer, J. Kordelle. *Orthopaedic Research Laboratories, Dept. of Orthopaedic Surgery, University Hospital Giessen and Marburg, Giessen, GERMANY*

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 systematically 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 rec. human Il-1β (5 ng/ml). PG synthesis was determined by the incorporation of 35SO4 during the final 18 h 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 in media with ELISAs. Results were compared to untreated explants removed from the same joint. Each experimental condition was repeated five times using explants always obtained from 6 different patients (N = 6).
Results: The degree of OA alterations of explants can have a profound modulatory effect on the influence of tetracylines 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 destruction during 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. Ladel[1], R. Capobianco[1], A. Gimona[2], E. vom Baur[2]. [1]*Merck Serono Research – RBM, Colleretto Giacosa, ITALY,* [2]*Merck 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 30 μg/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 30 μg and saline at week 14 (26.2% vs 44.4%, $p = 0.007$). The difference between groups (AS902330 30 μg 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 (CINOD), MODULATES CHONDROCYTES METABOLIC PATHWAYS

F. Kabile[1], D. Miglietta[2], S. Viappiani[1], **M.I. Bolla**[1], J-P. Pujol[3]. [1]*NicOx SA, Sophia-Antipolis cedex, FRANCE,* [2]*NicOx Srl, Bresso, ITALY,* [3]*Laboratoire 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 & Riegger-Krugh, Clin J Pain

2008). Cyclooxygenase-Inhibiting Nitric Oxide Donators (CINODs) are a new class of anti-arthritic drugs, which inhibit in a balanced way both COX-1 and COX-2 while releasing nitric oxide, an important modulator of vascular tone. We present here the effects of HCT 1026, a flurbiprofen-based CINOD, on chondrocytes, focusing on their catabolic and anabolic activities, as well as activation of inflammatory pathways.
Methods: Isolated primary cultures of bovine and human articular chondrocytes (BAC and HAC) were preincubated with 10 μM HCT 1026 or flurbiprofen and stimulated with Il-1β, in hypoxic or normoxic conditions. Levels of mRNA for extracellular matrix proteins (aggrecan and collagen type II) and matrix metalloproteases (MMPs), as well as TGFβ receptor, were determined by quantitative RT-PCR. NO release was assessed on cell supernatants through the Griess reaction, and activities of NF-κB and AP-1 were determined by electrophoretic mobility shift assay. NO donation from HCT 1026 was evaluated by testing its vasorelaxing activity in norepinephrine-precontracted rabbit aortic rings, in presence or absence of 10 μM ODQ (a specific inhibitor of NO-dependent cGMP formation).
Results: In hypoxic human articular chondrocytes stimulated with Il-1β, both HCT 1026 and flurbiprofen decreased expression of MMP-1 and -3 and TGF-β receptor by 20 to 40%. However, only HCT 1026 inhibited Il-1β-dependent NO overproduction while did not affect basal aggrecan or type II collagen mRNAs. Moreover, in BAC cultured in normoxic conditions, HCT 1026 inhibited NF-κB and AP-1 activation, whereas flurbirprofen affected only AP-1 activity. HCT 1026, but not flurbiprofen, induced aorta vasorelaxation, with an EC_{50} of 5.9±1.2 μM. ODQ pretreatment abolished this effect, confirming that vascular relaxation by HCT 1026 was based on its NO donating properties.
Conclusions: The CINOD HCT 1026 modulates chondrocytes catabolic and anabolic metabolism, causing reduction of inflammatory markers such as NO biosynthesis and activation of NF-κB. Moreover, HCT 1026 is able to donate biologically relevant nitric oxide, which can modulate vascular tone. If confirmed in *in vivo* studies, our data may provide evidence that the ability of CINODs to donate NO have a potential beneficial impact on joint cartilage in OA patients.

542 EFFECTIVENESS OF MELOXICAM FOR TREATMENT OF PAIN SYNDROME UNDER KNEE OSTEOARTHRITIS, LOW BACK PAIN AND NECK PAIN IN ELDERLY PEOPLE

V.V. Povoroznyuk, M.A. Bystrytska, T.V. Orlyk. *Institute of Gerontology AMS Ukraine, Kiev, UKRAINE*

Purpose: The research was aimed at evaluating of the effectiveness of meloxicam (revmoxicam) for treatment of pain syndrome under knee osteoarthritis, low back pain and neck pain in elderly people.
Methods: The patients were devided into three groups. The first group included 11 patients (aged 61.1±5.54 years) with neck pain, the second group included 10 patients (aged 59.4±4.65 years) with low back pain and the third group included 10 patients (aged 57.9±7.5 years) with knee osteoarthritis. All patients took meloxicam 15 mg once per day during 5 days. The following methods of study were used: Mc-Gill questionnaire, VAS, WOMAC, determination of life quality by Roland-Morris questionnaire, Neck disability index, EuroQol 5D scale.

Table 1. Dynamics of pain syndrome intensive after meloxicam treatment in patient of different groups.

Index	Group	Before treatment	After 5 days of treatment	P	Two weeks without treatment	P
Index of pain, cm	I	444±0.71	4.11±0.78	0.35	3.22±3.00	0.01
	II	5.13±0.59	4.13±0.79	0.03	3.63±0.52	0.003
	III	5.98±2.22	3.56±1.74	0.001	3.66±1.86	0.043
Descriptors, ball	I	9.56±2.23	7.56±2.40	0.09	7.56±1.71	0.12
	II	11.0±2.29	8.63±2.79	0.016	9.63±3.65	0.49
	III	10.60±4.70	7.40±4.80	0.008	8.70±6.00	0.043
Ranks, ball	I	18.78±5.17	13.22±5.28	0.07	12.00±3.52	0.03
	II	23.50±6.71	16.88±6.61	0.006	18.88±8.06	0.36
	III	23.30±16.10	16.50±11.70	0.01	18.50±15.0	0.57

Results: After 5 days of treatment patients, who was taking meloxicam, noticed a significant decrease of pain syndrome and it became low after two weeks without treatment [Table].
Significant decrease of all parameters of pain syndrome in second and third groups was observed after 5 days. Intensity of pain syndrome was also certainly decreased after two weeks without treatment in all groups by some parameters. The difference of effectiveness of meloxicam in patient with different diseases was observed by VAS: decrease of pain syndrome in the first group was – 7%, in the second groups – 17%, and in the third group – 39%, F = 2.76, p = 0.08. During the period of research no patients who undergone treatment had registered any side effects. There was no significant difference between groups dealing with the improvement of patient's everyday activity.
Conclusions: It can be concluded that the meloxicam is effective and safe in the treatment of low back pain syndrome, neck pain syndrome and pain syndrome under knee osteoarthritis in elderly people. However, the best effect of meloxicam was observed in patients with pain syndrome under knee osteoarthritis that can be explained by the inflammatory component of osteoarthritis pathogenesis.

543 EFFECTIVENESS OF TWO REGIMES OF GLUCOSAMINE AND CHONDROITIN FOR TREATMENT OF PAIN SYNDROME IN PATIENT WITH KNEE OSTEOARTHRITIS

V.V. Povoroznyuk, N.V. Grygoryeva, N.I. Dzerovych, T.A. Karasevskaya. *Institute of Gerontology AMS Ukraine, Kiev, UKRAINE*

Purpose: The research was aimed at evaluating the effectiveness of two regimes (continuous and interrupted) of Theraflex (500 mg glucosamine hydrochloride, 400 mg chondroitin sulphate) in patients with knee osteoarthritis. Outcomes evaluated were pain, measures of performance (function, activity of daily living, disability), employment status, range of motion, and patient satisfaction/patient global perceived effects.
Methods: The first group included 50 patients (aged 64.5±1.1 years) with knee osteoarthritis (II stage, Kellgren-Lawrence's classification), who took the drug in continuous regime during 9 months. The second group included 50 patients with the same diagnosis (aged 64.6±1.0 years), who took Theraflex twice during 3 months with 3 months interruption. We examined the patients before the treatment and after 1, 3, 6, 9 and 12 months. Methods of study: Mc-Gill questionnaire, visual-analogical scale (VAS), Lequen's index, WOMAC, EuroQol-5D, 15-m. test, 6-min. test.
Results: After three months of Theraflex's treatment it was observed a reliable decrease of pain syndrome in both groups by WOMAC, decrease of constraint in movements, improvement of index of everyday activity, VAS, 15-m.test. Examination of patients during 6, 9 and 12 months show the effectiveness of both regimes of the therapy. Intensity of pain syndrome and functional activity didn't differ between the groups.
Conclusions: During 1-year period two regimes of Theraflex it was established effective decrease of intensity of the pain syndrome and improvement of everyday activity in patients with knee osteoarthritis. The analgesic effect after taking Theraflex becomes noticeable after three months and quality of life significantly improved in patients of both groups.

544 THE FLEXX TRIAL OF OSTEOARTHRITIS OF THE KNEE: INTRA-ARTICULAR HYALURONAN (EUFLEXXA™)

R.D. Altman[1], J.E. Rosen[2]. [1]*David Geffen School of Medicine at UCLA, Los Angeles, CA, USA,* [2]*New York University School of Medicine, New York, NY, USA*

Purpose: The FLEXX trial studied the 6 month efficacy and safety of a non-avian form of IA hyaluronan for OA of the knee.
Methods: This was a randomized, saline-controlled, double-blind study of 586 patients with primary OA of the knee were evaluated prior to and following 3 weekly IA injections of hyaluronan or buffered saline. The primary efficacy measurement was pain recorded for the signal knee after a 50-foot walk. Secondary variables included the 3 subscales of the WOMAC, OARSI responder criteria, patient global assessment, use of rescue medication, quality of life (SF-36), and safety.
Results: The ITT population included Hyaluronan n = 291 and Saline n = 295. There were 12% dropouts (Hyaluronan n = 34; Saline n = 34). Hyaluronan demographics: Age 62.5±10.6 (SD), women 63%, BMI 32±7, Kellgren-Lawrence grade 2−41%, grade 3−59%, initial pain 56±22 with minimal differences from the saline group. After 26 weeks, there was a significant improvement in pain recorded after a 50-foot walk (ANCOVA; p = 0.028). Secondary variables were generally supportive of the primary measurement. Serious adverse events occurred in Hyaluronan (n = 10) and Saline (n = 9) groups. Arthralgia occurred in Hyaluronan (n = 27) and Saline (n = 35) groups. Local injection site reactions occurred in Hyaluronan (n = 2) and Saline (n = 1) groups.
Conclusions: IA hyaluronan was significantly superior to saline for OA of the knee over a 6-month period despite a large beneficial effect of IA saline.