of both cytokines is effective early in the process of cartilage damage. In this study it is investigated whether a single intra-articular injection of IL-4 plus IL-10 immediately after a joint bleed limits cartilage damage in an in vivo haemophilia mouse model.

Methods: Factor VIII knockout mice were punctured once with a needle below the patella to induce a joint bleed. Subsequently IL-4 plus IL-10 (n=24) or vehicle (n=24) was injected intra-articularly once. After 35 days, the knee joints were examined for cartilage damage by macroscopic and microscopic evaluation using the OARSI histopathology score specific for mice for cartilage degeneration and the Valensteo score for synovial inflammation. The left knee joint in both groups served as an unaffected control.

Results: Induction of a joint bleed led to a significant increase in macroscopic remains of a joint bleed and to an increase in joint diameter in both groups compared to the unaffected joints (all p<0.05 compared to control). Although not statistically significant, the IL-4 plus IL-10 injected joints tended to present less remains of a joint bleed compared to the vehicle injected joints (46% versus 58%; p=0.386). Moreover, the diameter of the joints injected with IL-4 plus IL-10 tended to be smaller than that of the vehicle injected joints (2.63±0.16mm vs 2.91±0.29mm; p=0.174). After a joint bleed, the OARSI score as well as the Valensteo score increased compared to the unaffected joints. Intra-articular injection of IL-4 and IL-10 ameliorated cartilage degeneration caused by the joint bleed (mean change in OARSI score in experimental joint compared to control joint for vehicle injection 0.9±1.2 (p=0.100) and for IL-4 plus IL-10 injection 0.5±1.8 (p=0.216). No effect on inflammation was observed at 35 days after the joint bleed for IL-4 plus IL-10 compared to vehicle (mean Valensteo score after IL-4 plus IL-10 injection 3.6±1.8 and for vehicle injection 2.9±2.0 (p=0.220)).

Conclusion: A single intra-articular injection of IL-4 plus IL-10 directly after a single joint bleed limits cartilage degeneration, but not synovial inflammation. Improved bioavailability of both cytokines might improve the protective ability of both cytokines in development of cartilage degeneration, and probably also inflammation.

571 DIFFERENT CHANGES IN THE BIOMARKER CTX-II FOLLOWING INTRA-ARTICULAR INJECTION OF HIGH MOLECULAR WEIGHT HYALURONIC ACID AND ORAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS FOR PATIENTS WITH KNEE OSTEARTHRITIS: A MULTI-CENTER RANDOMIZED CONTROLLED STUDY

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Purpose: Intra-articular injections of hyaluronic acid (IA-HA) and oral non-steroidal anti-inflammatory drugs (NSAIDs) are both recommended by OARSI for the management of knee OA. However, their effect on cartilage damage is not well understood. The aim of this study was to investigate the effects of IA-HA and NSAIDs in knee OA patients.

Methods: A total of 200 patients with knee OA (K/L 1 to 3) were registered from 20 hospitals and randomized to IA-HA (High molecular weight 2,700 kDa HA) or NSAID (loxoprofen sodium). For patients treated with NSAID, they used NSAID 3 tablets (180 mg)/day for 5 weeks. For patients treated with IA-HA, IA-HA was conducted 5 times at one week intervals. The fastest second void urine samples collected from all patients were stored at -80°C until analysis. uCTX-II levels were corrected for urine creatinine concentration. The CTX-II data were analyzed by the per protocol set (PPS).

Results: Half (100) of the patients were randomly allocated into the NSAID group, and the other half allocated into the IA-HA group. After the 5 week treatment period, 68 of 100 in the patients in the IA-HA group and 58 of 100 of those in the NSAID group were eligible for CTX-II analysis. At baseline, no significant differences of baseline characteristics were observed between IA-HA and NSAID groups. The Japanese Knee Osteoarthritis Measure (JOM) score of the patients in both the IA-HA (-37.4%) and NSAID (-35.3%) groups were significantly reduced following treatment (p<0.001). The difference in the percent changes of the JOM score between the two intervention arms was -2.1% (90%CI: -10.9 to 6.2%), demonstrating the non-inferiority of IA-HA to the NSAID for the reduction in the clinical symptoms. uCTX-II levels were significantly reduced by the NSAID treatment. In contrast, uCTX-II levels were significantly increased by the IA-HA treatment. The percent changes of uCTX-II by IA-HA treatment (11.6%) were significantly different than those of that by NSAID treatment (9.0%) (p<0.0001). When the patients were analyzed based on the radiographic severity of knee OA, the differences of uCTX-II responses between the NSAID and IA-HA were again observed.

Conclusions: We observed in this RCT that IA-HA treatment increased uCTX-II levels, while oral NSAID reduced uCTX-II levels, while both treatments improved symptoms of pts. with knee OA. The differences in biomarker response suggest different modes of action, each with a beneficial effect on symptom: one being stimulatory of cartilage/bone interface extracellular matrix type II collagen turnover (IA-HA) and the other reducing such turnover.

572 PHARMACOKINETICS OF A THERMALLY RESPONSIVE CURCUMIN CONJUGATE FOR LOCAL ANTAGONISM OF NEUROINFLAMMATION IN DISC HernIATION


Purpose: Tumor necrosis factor alpha (TNFα) is believed to be a key mediator of inflammatory events associated with herniated intervertebral disc (IVD). Local delivery of TNFα antagonists via epidural injections to treat pain or dysfunction associated with herniated IVD has been studied in the clinic with some success. We hypothesize that sustained release of injectable depots containing cytokine antagonists can be a safer, cost-effective treatment for relieving pain associated with IVD herniation. We have designed novel drug conjugates comprised of elastin-like polypeptides (ELP) and a small anti-inflammatory compound, curcumin, which has an excellent safety profile in clinical trials. ELPs are biocompatible, biodegradable polymers that are soluble below a transition temperature (Tt) and form micron-sized depots above Tt. Here, we report on the pharmacokinetics and clearance rates of injectable, ELP-curcumin conjugate ‘depos’ delivered to the perineural space in mice.

Methods: A novel derivative of curcumin, monofunctional curcumin carbamate (MCC, Fig 1), was chemically coupled to glutamate-containing ELPs (Fig 2). Drug-carrier ratio, conjugate purity, Tt and hydrodynamic radius (Rh) were quantified with UV-Vis, RP-HPLC, and dynamic light scattering. In vitro bioactivity of conjugates against TNFα-induced proliferation was quantified with 1929 cells as previously described. For in vivo studies, the right sciatic nerve of C57BL/6 female mice (n=3 per group, 12 weeks old) was surgically exposed, and curcumin or ELP-MCC (25μl, 150nmol) was delivered to the perineural space. Blood was collected at times from 0.5 to 168 hours and tissues were harvested at sacrifice times from 2 to 168 hours. Plasma and solubilized tissue was analyzed for curcumin presence via fluorescence.

Results: ELP-MCC conjugates were synthesized and characterized to have mean drug-carrier ratios of 5.7 to 1 (MW=37.8kDa), >90% purity, and stability.
T<37°C, and mean Rh<20nm before aggregation into micron-sized depots. ELP-MCC retained bioactivity against TNF in vitro with an IC50 2-fold higher than curcumin (24.1uM and 13.5uM, respectively, n=4). Following perineural delivery to the sciatic nerve, ELP-MCC displayed decreased plasma exposure levels compared to curcumin and evidence of sustained drug release over 96 hrs (Fig 3). Curcumin was completely cleared from the delivery site after 48 hrs, while low levels of ELP-MCC remained at the delivery site 96 hrs after delivery.

Conclusions: ELP-MCC conjugates retain activity against TNF and provided for sustained release of drug in vivo. These findings suggest that ELP may be a suitable carrier for local antagonism of inflammation in back pain. The development of sustained-release drug delivery systems, such as ELP-MCC, has substantial translational potential for treating chronic pain and inflammation for localized pathologies.

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ASSOCIATIONS BETWEEN STATIN USE AND CHANGES IN PAIN, FUNCTION AND STRUCTURAL PROGRESSION: A LONGITUDINAL STUDY OF PERSONS WITH KNEE OSTEOARTHRITIS
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Purpose: Recently published research suggests that statins may have beneficial structural effects in persons with knee osteoarthritis. The potential effects of statins on patient-reported knee pain and function have not been examined. We studied a large prospective community-based cohort of persons with knee osteoarthritis to determine if statin usage was associated with changes in knee structure, pain and function trajectories over a 4-year period.

Methods: Data were obtained from a subset of 2,207 persons in the Osteoarthritis Initiative with radiographically suspected or confirmed knee osteoarthritis. The changes in WOMAC Pain and Physical Function scores, pain intensity and Kellgren-Lawrence radiographic grade over four years were examined. Data from persons were coded based on whether they were incident users of statins over the 4-year period. Statin use duration data also were collected. Outcome trajectories and probability of statin use were examined over the 4-year study period using parallel processing growth curve modeling. The analysis adjusted for potential confounders and determined if statin use predicted outcome trajectories.

Results: Statin users accounted for 6.7% of the sample in year 1 and 16.4% in year 4. Extent of statin use was not associated with improvements in knee pain, function or structural progression trajectories. The only significant finding indicated that increased duration of statin use was associated with worsening in WOMAC Physical Function scores over the study period (beta = 0.161, p = 0.005). The Figure illustrates the full structural equation model for WOMAC Physical Function scores and statin use over the study period.

Conclusions: Statin use was not associated with improvements in knee pain, function, or structural progression over the 4-year study period.

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IMPROVEMENT OF SYMPTOMS IN THE GENERALIZED OSTEOARTHRITIS USE OF ZOLEDRONIC ACID ZOLA STUDY

Purpose: In the past it was thought that osteoarthritis (OA) was a disease of wear, current evidence indicates that the OA is an inflammatory disease signs given by the presence of synovial hyperplasia, increased angiogenesis, increased expression of IL-1, TNF, COX-2 and matrix metalloproteinases (MMP). The activation of chondrocytes by mechanical stress, inflammatory cytokines, fragments of collagen and fibronectin, leading to the production of IL-1, TNF-alpha and PGE2 nitric oxide, which in turn determine the reduction of proteoglycan synthesis, activation of MMP, peroxynitrite, JNK activation and apoptosis of chondrocytes which ultimately leads to cartilage destruction. The cartilage damage leads to increased transmission of forces to the underlying bone due to the decreased elasticity of cartilage, bone microfractures and this produces increased bone turnover. All these changes occur in the subchondral bone, we know the holding capacity of bisphosphonates on bone turnover in 2005 presented the results of the BRISK study (Risedronate in OA), however the dose used was 15mg / d with increased adverse effects and poor adherence to medication.

Methods: The type of study was a prospective, uncontrolled with quarterly assessments following the application of zoledronic acid 5mg/100cc semester. The selection of patients was conducted during October 2009 to December 2011, including 85 patients (n = 85), with over 50 years and diagnosed with osteoarthritis in three or more joint groups (distal and proximal interphalangeal, first carpometacarpal, axial skeleton, hips, knees and metatarsophalangeal). We excluded patients who were receiving bisphosphonates for 6 months before recruitment as well as patients with a history of fractures, severe osteoporosis and joint replacement. We used the WOMAC index that measures 3

ITEM: Pain, stiffness and physical function, in addition we applied the visual analog scale (VAS) and asked about the use of NSAIDs and / or pain in the last days of applying 5-3-2 the questionnaire. We measured serum CTX-II every 3 months. The analysis adjusted for potential confounders and determined if statin use predicted outcome trajectories.

Results: Of all patients who entered the study (n = 85): 73.3% (n = 49) were female and 26.6% (n = 9) male, with a mean (M ± SD) of 61.88 ± 7.33 years, BMI 29.2 ± 5.85 baseline WOMAC Kg/m² 2.3, 59.1 ± 2.0 3m WOMAC, WOMAC 6m 47 ± 16; measurement baseline VAS 7.5 ± 0.2; VAS3m 4.2 ± 0.5; VAS6m 2.5 ± 1.2; baseline Ctx-II 0.735 ± 0.036 ng / mol; Ctx-II 3m 0.548 ± 0.014 ng / mol; Ctx-II 6m 0.233 ± 0.002 ng / mol.

Conclusions: In this study we observed a substantial improvement with the use of bisphosphonates in cross section at 6 months was achieved in addition to reducing the taking of NSAIDs and / or pain after implementation, the sustained reduction in Ctx-Biomarker II remained even last 3 months of the first application. Because the court date is not radiological control measures were shown to be effective from a structural standpoint