causing 30% of ulcer incidence and 30% of maximal efficacy, respectively. The plasma concentrations of ketoprofen after oral administration of HCT 2037 (7.1 and 10.7 mg/kg) or equimolar ketoprofen were assessed in separate male Sprague Dawley rats using a HPLC MS/MS technique.
Results: HCT 2037 significantly and dose-dependently decreased paw edema formation. The highest dose tested (35.7 mg/kg) reduced edema formation by 59±6% *vs.* control ($p<0.01$) and the ED30 was estimated to be 7.1 mg/kg, with a UD30 of 3.0 mg/kg. The reference ketoprofen showed a 4-fold lower activity in inhibiting edema formation (ED30>25 mg/kg), and caused marked GI damage, with a UD30 of 1.3 mg/kg. By comparing ED30/UD30 ratios, HCT 2037 emerged as a more favourable compound than ketoprofen (2.4 *vs.* >18.9, respectively). Pharmacokinetic analysis following oral administration to rats of equimolar doses HCT 2037 or ketoprofen revealed that animals were exposed to similar plasma concentrations of ketoprofen.
Conclusions: HCT 2037 showed a tendency towards a better efficacy than ketoprofen in this model of inflammation, accompanied by a three-fold improvement in gastric tolerability. HCT 2037 confirms that CINODs provide improved GI safety while maintaining full anti-inflammatory effects in animals. If confirmed in humans, CINODs may represent a valuable therapeutic option for arthritic pathologies.

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ATTENUATION OF INFLAMMATORY EVENTS IN HUMAN INTERVERTEBRAL DISC CELLS WITH A TUMOR NECROSIS FACTOR ANTAGONIST

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Purpose: Pathologic intervertebral disc (IVD) tissues contain some macrophages and lymphocytes, as well as their proinflammatory cytokine products including TNFα, IL-1β, IL-8 and IFNγ. TNFα is believed to be a key mediator of inflammation in multiple IVD pathologies, with clinical interest in the delivery of TNF antagonists as therapeutic agents for attenuating symptoms of sciatica. Soluble TNF receptors are potent TNF antagonists, capable of high affinity binding to TNFα thereby sequestering the cytokine from cell receptors and downstream effects. Here, we characterize the inflammatory phenotype of primary human IVD cells following TNFα stimulation in vitro, and measure the potential antagonistic activity of soluble TNF receptor II (sTNFRII).
Methods: Human IVD cells were isolated from to-be discarded surgical tissues from patients undergoing surgery for degenerative IVD pathology (n=11, age: 14 - 81yr). Human IVD cells were seeded (50,000 cells/well, 48-well plates) in 300μl culture media supplemented with 25 ng/ml rhTNFα (Abcam) and 10% FBS for 72 hrs; control cells received no TNFα. Four groups received a dose of sTNFRII (12.5-100nM, Abcam) in addition to TNFα for the 72h period. All supernatants were assayed for release of nitric oxide (NO, n=11; Greiss reaction), and a subset of samples were assayed for production of IL-6 and PGE2 (n=4; ELISA, R&D Systems). All values were determined as differences from culture media-only values at 72h, and normalized by control values for cultures in the absence of TNFα to quantify the level of TNFα-induction. Dose-dependent attenuation of TNFα-induction of NO, PGE2 or IL-6 was then quantified by determining a 50% inhibitory concentration (IC50). Statistical significance was evaluated with one-way ANOVA and a post-hoc Tukey's HSD test.
Results: Pathologic IVD cells in the presence of TNFα exhibited an inflammatory phenotype characterized by an average increased production of NO (3-fold over control values of 11.0±2.73 μM), PGE2 (67-fold over control of 188±245 pg/ml) and IL-6 (3-fold over control of 703±421 pg/ml). These cellular responses to TNFα are consistent with values reported previously for human nucleus pulposus cells. Responses to TNFα were characterized by significant patient-to-patient variability, however, with a very large range of values for NO, PGE2, and IL-6 quantified in supernatants. Cells receiving a dose of sTNFRII exhibited some attenuation of TNFα-induced responses, although the patient-variability was significant as for treatment with TNFα alone. sTNFRII attenuation of TNFα effects followed a typical dose-dependent response in IVD cells for measures of NO and PGE2 production, with IC50 values measured to be 29nM and 86nM, respectively.
Conclusions: These data confirm previous reports of statistically significant increases in TNFα-induced release of NO, PGE2, and IL-6 by human IVD cells and demonstrate that targeting TNFα activity can attenuate the TNFα-induced upregulation of inflammatory events of IVD cells These data point to a need for further study of sTNFRII as a therapeutic candidate for treatment of IVD pathologies, and support the current clinical interest in treating sciatica with commercially available receptor analogues.

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PHARMACEUTICAL COST IN PATIENTS WITH KNEE OSTEOARTHRITIS

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Purpose: Knee osteoarthritis is a frequent cause of joint pain and is estimated to be the most common cause of painful knee in adults.It is very frequent in the Spanish population. According to the EPISER study, performed by the Spanish Society of Rheumatology, 29% of the Spanish population over age 60 showed symptomatic knee osteoarthritis (KOA). The goals of management of patients with knee osteoarthritis are to control pain, minimize disability, improve the quality of life, and educate the patient about his or her role in the management team. The aim of this study was to assess the pharmacological cost generated by a group of patients diagnosed with knee osteoarthritis.
Methods: This is a transversal descriptive study performed in 2008. The study included 188 patients both male and female over age 40, diagnosed with knee arthrosis (KOA) according to ACR diagnostic criteria. Patients were collected from the OMI-AP program database. This study analyzed the total number of drug packs consumed per year per patient with KOA. The average cost of each medication and the annual cost were then calculated. The cost per patient per year was obtained as the total cost and total number of patients ratio.
Results: Seventy-eight percent (78%) of patients included in the study were female and 26% were male (3,5:1). The average age was 69,22 years (DE ±9,29) and 56% of patients were older than 70 years and. Sixty-seven percent (67%) of the patients showed bilateral KOA, 18% showed right knee involvement and 15% left knee involvement.
NSAID were the most frequent prescribed drug to treat KOA (36%) followed by SYSADOAs (17%), Paracetamol 1g. (14%), topical treatments (13%), other painkillers such as metamizol, opioids and tramadol (10%), and gastric protectors (10%). From all NSAIDS, Diclofenac was the most frequent prescribed drug (72 %) and Glucosamine Sulfate was the most frequent prescribed SYSADOAs (65%). Chondrotin Sulfate and Diacerheine represented 21% and 14% respectively.
From all prescribed drugs the highest spending was due to NSAIDs administration (35%), followed by SYSADOAs (27%), painkillers other than Paracetamol (18%), Paracetamol 1g. (8%) and topical and IBP 6% each. Interestedly, although COXIB drugs repre-

sented only 18% of total NSAIDs, its cost represented the 64% of all NSAIDs. Glucosamine Sulfate represented the 60% of the spending on SYSADOAs. Total pharmacological cost per patient per year was 151,60€.
Conclusions: Knee osteoarthritis is a major cause of utilisation of health care resources and sick leave. The total pharmacological cost per patient per year was 151,60€. This amount is less than needed to treat most chronic rheumatic diseases, and represents a small fraction of the cost for the management of KOA.

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THE EFFECTS OF RUANGULI IN THE TREATMENT OF EXPERIMENTAL OSTEOARTHRITIS OF THE KNEE IN RABBITS

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Purpose: The objective of the present study was to investigate the mRNA expression level of α-actin, MHC (myosin heavy chain) isoforms (MHCI, IIa, IId/x, IIb), ADAMTS5 and Aggrecan in rabbit osteoarthritis model. To explore the effects of Ruanguli (A kind of Chinese herbal medicine compound recipe) in the treatment of knee osteoarthritis.
Methods: 36 adult, female New Zealand white rabbits were randomized in three groups, including sham control group, model control group, treatment group (RuanGuLi 2mg/day, 4 weeks). Osteoarthritis of the knee was induced surgically in 28 rabbits (model control group, treatment group). The other animals wee sham operated. One week after operation, interfering measures were taken into practice and lasted for 4 weeks. Animals were euthanized at 5 weeks postoperatively. RT-PCR was used to assess the mRNA expression level of α-actin, MHC isoforms in quadriceps femoris, Aggrecan and ADAMTS5 in knee cartilage. Mankin score was used to assess cartilage degeneration in the knee.
Results: The result of Mankin score suggested that there was significant difference between model control group and treatment group, Ruanguli treatment led to a significant reduction in articular cartilage degeneration. The results of RT-PCR suggested that the expression level of MHCIIa mRNA,MHCIId/x mRNA and α-actin mRNA in model group was significantly lower than that in sham control group. Ruanguli treatment significantly increased the level of MHCIIa,MHCIIb and α-actin mRNA when compared to model control group. Ruanguli treatment led to a significant increase in the expression level of Aggrecan mRNA expression and reduction in ADAMTS5 mRNA expression in articular cartilage.
Conclusions: In OA animals, the level of α-actin and MHC isforms mRNA was lower compared with normal animals. Ruanguli significantly increased α-actin, some MHC and Aggrecan expression as well as inhibited the expression of ADAMTS5 and reduced cartilage degeneration in knee.
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EFFECT OF BOVINE CHONDROITIN SULFATE ON IL-1BETA-STIMULATED HUMAN CHONDROCYTE C-20/A4 CELL LINE

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Purpose: The pathogenesis of primary osteoarthritis involves an imbalance between anabolic and catabolic pathways by chondrocytes. Expression of pro-inflammatory cytokines and matrix metalloproteinases, chondrocyte hypertrophy and apoptosis participate in the pathogenesis of osteoarthritis. Chondroitin sulfate (CS) is an important structural component of cartilage and is approved as a symptomatic slow-acting drug for osteoarthritis (SYSADOA) in Europe and other countries. Indeed, numerous studies showed the good tolerance and its clinical benefits to decrease pain, to improve functional disability and to reduce non-steroidal anti-inflammatory drug (NSAID) or acetaminophen consumption. However, mechanisms of action in vivo and in vitro are unknown.The goal of the study was to explore the effects of bovine CS on two main features of osteoarthritis: proteolysis and chondrocyte apoptosis.
Methods: To address these questions, we submitted immortalized human chondrocyte cell line C-20/A4 to bovine CS. Chondrocytes were treated or not with 2 ng/ml human interleukin 1 beta (IL-1 beta) alone or with 500 μg/ml of bovine CS for 20 hours in DMEM culture medium free from foetal bovine serum. Expression of collagenases MMP-1, MMP-13 and their specific inhibitor TIMP-1 was checked by ELISA assay in the culture medium. ADAMTS-5 expression (a disintegrin and metalloproteinase with thrombospondin motifs) was analyzed by western blot. Cell viability was performed by trypan blue, cell cycle analysis and apoptosis level were investigated by flow cytometry.
Results: Treatment of chondrocytes by 500 μg/ml CS protected the cells from death induced by 6 days incubation with 2 ng/ml IL-1β: upon CS and IL-1, 75% cells were alive compare to 50% without CS. Cell cycle analysis by FACS showed a significant decrease by CS of apoptosis in IL1-treated cells: 2% apoptotic cells with versus 15% without). Moreover, CS decreased the IL-1 mediated expression of ADAMTS-5 contrary to that of MMP-1, MMP-13 and TIMP-1.
Conclusions: The proinflammatory cytokine interleukin-1 beta participates in the pathogenesis of cartilage damage in osteoarthritis. In this study we provided experimental evidence that bovine CS decreases ADAMTS-5 expression and protects from apoptosis of human chondrocyte cell line stimulated by IL-1β. These results emphasize the potential beneficial effect of bovine CS in osteoarthritis.

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RECOVERY OF PHYSICAL FUNCTIONING AFTER TOTAL HIP ARTHROPLASTY: A SYSTEMATIC REVIEW OF THE LITERATURE

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Purpose: Today's total hip arthroplasty (THA) patients, who are