when compared to an equivalent dose of glucosamine hydrochloride. Whether this difference in synovial levels of glucosamine attained is translated into a therapeutic effect on the joint tissues remains to be elucidated.

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REQUIREMENT FOR TOTAL ARTICULAR REPLACEMENT AFTER DIACEREIN TREATMENT IN HIP OSTEOARTHRITIS: A 5 YEARS FOLLOW-UP OF THE 3 YEARS PLACEBO-CONTROLLED ECHODIAH TRIAL

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Purpose: Evaluation of disease modifying osteoarthritis drug (DMOADs) in hip osteoarthritis (OA) is based on effects on both symptoms and structure. Such a beneficial effect might result in a subsequent hard end-point (e.g. requirement to total hip replacement (THR).
The objective of this study was to evaluate the long term (5 years) effect on requirement for THR of a 3 years intake of diacerein in comparison to placebo in hip OA.
Methods: ***Two periods:*** a) 3 years controlled trial evaluating the effects on the structure and the symptoms of 50 mg diacerein b.i.d. versus placebo (Dougados M, *et al*. Evaluation of the structure modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Arthritis Rheum 2001;44:2539-47); b) 5 years follow-up via an annual phone call contact. ***Collected data:*** *at baseline* demographics and OA characteristics (femoral head migration, radiological joint space width [JSW]). *During the 3 years of the therapeutical trial and the 5 years of follow-up*: requirement to THR. ***Analysis:*** *primary analysis:* percentage of patients requiring THR with regard to the treatment group in patients completing the 3 years placebo controlled trial (clinical trial completers) using life table analysis technique and log-rank test; *secondary analyses:* identical endpoints and statistical analysis but a) in the whole population entering the trial at year 0, b) in the sub-group of patients with supero-lateral and concentric femoral head migration (excluding the patients with a supero-medial femoral head migration) and a baseline (year 0) JSW of at least 1.5 mm as suggested by the Barcelona consensus meeting (Altman RD, *et al*. Measurement of structural progression in osteoarthritis of the hip: the Barcelona consensus group. Osteoarthritis Cartilage 2004;12:515-24.).
Results: Of the 507 included patients (255 and 252 in the diacerein and placebo groups, respectively), 262 completed the 3 years of the therapeutical trial (127 in the diacerein group). For these patients, a THR was required during the subsequent 5 years in 40% after diacerein intake versus 43% after placebo (p=0.60). In the whole group of patients entering the trial, a THR was performed at the end of the 8 years follow-up period in 56% whatever the initial treatment group (p=0.94). In the sub-group of 283 patients fulfilling the criteria proposed by the Barcelona consensus group at entry (149 in the diacerein group), a THR was performed at the end of the 8 years follow-up period in 49% after diacerein intake vs 55% after placebo, (p=0.50). In this subgroup, 157 patients (81 in the diacerein group) completed the 3 years of the therapeutical trial. For these patients, a THR was required during the subsequent 5 years in 32% after diacerein intake vs 44% after placebo (p=0.21).
Conclusions: This study failed to demonstrate a statistical significant difference between the two treatment groups with regard to the requirement to THR after a 3 years intake of diacerein in the a priori defined primary analysis. However, the trend in favor of diacerein in different clinically relevant sub-populations suggests that a 3 years intake of diacerein might have a subsequent long term beneficial effect in a sub-group of hip OA patients. Such findings should be evaluated in further clinical trials.

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PHARMACOKINETICS OF GLUCOSAMINE IN MAN AFTER ORAL ADMINISTRATION OF CRYSTALLINE GLUCOSAMINE SULFATE OR GLUCOSAMINE HYDROCHLORIDE ALONE OR IN COMBINATION WITH CHONDROITIN SULFATE

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Purpose: Crystalline glucosamine sulfate and glucosamine hydrochloride alone or in combination with chondroitin sulfate have been evaluated as a treatment for knee pain from osteoarthritis (OA) in two recent studies of 6-month duration. The NIH-sponsored GAIT study did not show any effect of treatment with 500 mg glucosamine hydrochloride three times daily (t.i.d.) alone or in combination with 400 mg of chondroitin sulfate t.i.d. Conversely, the GUIDE trial indicated that, at the dose of 1500 mg once-a-day, crystalline glucosamine sulfate soluble powder provided a significant symptomatic effect, thus confirming previous long-term study observations. The pharmacokinetics of crystalline glucosamine sulfate 1500 mg once-a-day were recently investigated and showed glucosamine peak plasma levels in the 10 μM range. These levels were effective in vitro in inhibiting IL-1-induced gene expression, currently regarded as the putative mechanism of action of glucosamine in OA. Conversely, preliminary studies of the pharmacokinetics of glucosamine after administration of the glucosamine hydrochloride capsule formulation used in GAIT, suggested that the peak levels might be much lower. The aim of the present study was therefore to investigate in a direct comparative study, the relative bioavailability of glucosamine following repeated oral administration of the two glucosamine salt formulations and dose regimens, or of the glucosamine hydrochloride/chondroitin sulfate combination, to assess if differences in exposure to the active ingredient and especially in peak plasma levels, might provide a possible explanation for the contrasting clinical results.
Methods: Twelve healthy volunteers (5 males and 7 females) received three consecutive once-daily oral administrations of crystalline glucosamine sulfate soluble powder at the dose of 1500 mg, or glucosamine hydrochloride capsules at the dose of 500 mg t.i.d. for thee consecutive days either alone or in combination with chondroitin sulfate 400 mg t.i.d. in an open, randomised, cross-over fashion. Glucosamine was determined at steady state in plasma collected up to 48 h after the last dose by a validated LC-MS/MS method.
Results: Glucosamine was bioavailable after administration of the three products. After crystalline glucosamine sulfate 1500 mg once-daily, peak concentrations ($C_{ss,max}$) and extent of exposure (AUC_{ss}) averaged 9.1$\pm$6.3 μM and 76.5$\pm$23.0 μM.h, respectively. Significantly ($p \leq 0.005$) lower plasma concentrations were determined after the administration of 500 mg glucosamine hydrochloride alone ($C_{ss,max}$ and AUC_{ss} averaged 4.5$\pm$1.8 μM and 21.4$\pm$7.6 μM.h, respectively) or in combination with 400 mg of chondroitin sulfate ($C_{ss,max}$ and AUC_{ss} averaged 3.3$\pm$1.0 μM and 13.8$\pm$5.4 μM.h, respectively).
Conclusions: Administration of glucosamine hydrochloride at the dose of 500 mg t.i.d might produce a similar extent of systemic exposure to glucosamine throughout the day, but at significantly lower (less than a half) peak plasma concentrations compared to 1500 mg of crystalline glucosamine sulfate

once-a-day. Such lower peak plasma concentrations might not reach the pharmacologically effective threshold and could explain the lack of efficacy of glucosamine hydrochloride observed in GAIT compared to the GUIDE and previous long-term trials of crystalline glucosamine sulfate. Combination of glucosamine hydrochloride with chondroitin sulfate further reduces glucosamine bioavailability.

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INTRA-ARTICULAR DELIVERY OF INTERLEUKIN-1 RECEPTOR ANTAGONIST FUSED TO A THERMALLY RESPONSIVE PEPTIDE IS EFFECTIVE IN MODULATING THE PATHOLOGIC RESPONSE TO INTERLEUKIN-1 INDUCED KNEE JOINT DESTRUCTION

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Purpose: While systemic administration of interleukin-1 (IL-1) receptor antagonist (IL1Ra) is approved for treating RA, a high incidence of side effects and need for frequent dosing does not suggest utility for treating OA. Local delivery of an IL1Ra-containing drug depot could provide for sustained drug presence, decreased dosing requirements, and reduce systemic toxicity for OA. Elastin-like polypeptides (ELPs) have been developed as injectable, and thermally-responsive intra-articular drug depots. ELPs had a joint space half-life 25-fold greater than that of comparable non-responsive proteins. Here we evaluate the activity of an intra-articular injection of IL1Ra conjugated to ELP in attenuating IL-1β induced pathology in a rat knee joint model.
Methods: A fusion protein of human IL1Ra and ELP (ELP-IL1Ra) was synthesized as described previously. Right knee joints of 18 rats were injected with 12,500 rat dermal fibroblasts modified to over-express human IL-1β. After 24h, 6 rats each received one of the following injections: ELP-IL1Ra fusion protein (120μg), commercial IL1Ra (0.24μg), or no treatment. Protein doses insured that IC_{50} values were equal for fusion and commercial IL1Ra. Daily weights, coronal and sagittal knee joint diameters were recorded. After 7 days, rats were sacrificed and right knees evaluated for grade of gross pathology (0-2, 0 = non-degenerate). Joints were placed in explant culture for 24h and human and rat IL-1β expression was measured in supernatants via ELISA. Joint sections were evaluated for histological evidence of OA (OARSI Histopathology Assessment; 0-6, 0 = non-degenerate). All data are reported relative to contralateral controls. Chi-square analysis was performed on gross and OARSI grades; one-way ANOVA was performed on body weights, knee joint diameters, and ELISA data. Bonferroni post-hoc analyses were used.
Results: There was no difference in body weight gain, or coronal or sagittal knee joint diameters amongst groups. Gross pathology was different amongst groups ($p<0.04$, Chi-square, Table). The ELP-IL1Ra group had less pathology than no treatment animals ($p<0.01$, Figure 1). OARSI grades were significantly lower for the ELP-IL1Ra group at patellofemoral ($p<0.006$) and condylar sites ($p<0.015$), but not tibial plateau, compared to no treatment animals (Table 1). There was no statistical difference between commercial IL1Ra and either no treatment or ELP-IL1Ra groups in gross pathology or OARSI grades. There was no difference in amount of human or rat IL-1β in explant cultures indicating that all groups had the same potential to develop pathological changes.
Conclusions: These data show efficacy for the ELP-IL1Ra fusion protein in mediating effects of IL-1β induced knee pathology. Single intra-articular administration of the fusion protein ELP-IL1Ra has the potential for release of an active IL1Ra domain for up to 4 weeks in the rat model, and may have potential to provide therapeutic effects when delivered locally in patients with OA.

Table 1. Grades relative to contralateral control

	Gross grades	OARSI grades		
		Femoral groove	Femoral condyle	Tibial plateau
ELP-IL1Ra	0.17±0.93*	2.8±2.2*	-0.17±1.6*	-0.83±1.8
Commercial rhIL1Ra	1.1±0.74	4.6±2.6	2.2±2.4	4.0±2.0
No treatment	1.7±0.3	4.3±3.1	5.5±0.84	1.5±2.5

*Significant difference from no treatment group, Bonferroni post-hoc test.

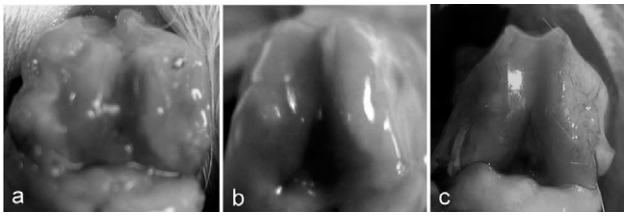

Figure 1. Images of fibroblast injected knee joints receiving no treatment (a), commercial IL-1Ra (b), or the ELP-IL1Ra fusion protein (c).

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ORAL GLYCINE IN TREATMENT OF CANINE EXPERIMENTAL OSTEOARTHRITIS

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Purpose: In osteoarthritis (OA) pain, and not the structural changes in the joint, are the main reason for a patient to seek medical attention. The exact origin of joint pain in OA is hardly known, but undoubtedly pain is related to the secondary inflammatory responses in OA. This inflammation contributes to joint damage and therefore, by diminishing inflammation pain will be diminished and development of OA will be slowed down. NSAIDs and COXIBs might be useful in this respect, although with restrictions. Therefore, the need remains for alternatives, of which many presently under investigation. Glycine might be a novel candidate in this respect. Glycine as a single molecule has anti-inflammatory capacities; amongst others, dietary glycine showed an inhibitory effect on the development of arthritis (Li X, e al. Infect Immun 2001; 69: 5883-). In the present study glycine was evaluated as a dietary supplement on the development of OA. For this purpose we choose an experimental canine OA model with moderate but clearly evident synovial inflammatory activity; the ACLT model combined with medial meniscectomy (Mx).
Methods: Knee osteoarthritis (OA) was induced in dogs by ACLT-Mx (n=12). Double blind, either glycine (10g/dog) or placebo was given orally daily, every morning at the same time before the meal was given. Longitudinal as well as endpoint parameters of cartilage damage, synovial inflammation and pain were evaluated.
Results: Twelve weeks post-surgery OA characteristics were clearly present; radiographs revealed progressive osteophyte formation in the experimental joints ($p<0.05$). Gait analysis re-