*osteoporosis is of considerable public health importance. In the United States alone, this preventable disease is common and often devastating: women reaching age 50 look forward to a 1 in 3 chance of a vertebral fracture and a 1 in 6 chance of hip fracture; once hip fracture occurs, up to a quarter lose their independence and 20% die within one year.*

*The success of several orally administered bisphosphonates and growing concerns regarding HRT have increased focus on bisphosphonate therapy as a first-line option to treat or prevent osteoporosis. Limitations to their use include occasional side effects (primarily gastrointestinal) requiring discontinuation and inconvenient early morning oral dosing regimens. Formulations requiring only weekly administration have improved the situation.*

*Reid* et al. *(1) evaluated zoledronic acid, a potent parenteral bisphosphonate, in a study that employed a high quality design: it consisted of a double blind, placebo-controlled trial of several doses infused over 5 minutes at variable intervals. The only questionable aspect of the study design was its requirement that a subset of these postmenopausal subjects with markedly low bone mineral density (BMD) (mean T score of –2.9) receive placebo for one year; it could be argued that all such patients should receive active treatment (even though that would have weakened the study's conclusions).*

*These researchers found increased bone mineral density (BMD) at one year (4.3-5.1% at the lumbar spine; lesser increases at the femoral neck) for all doses and at all intervals of therapy, including a single 4 mg infusion. In addition, all treatment regimens were associated with diminished bone turnover based on an analysis of bone resorption and formation indices as well as bone biopsy. Toxicity was minor and the number of withdrawals was similar to that in the placebo group. Of note, however, the treatment-related adverse events were more common in the zoledronic acid-treated patients, consisting of musculoskeletal pain, nausea and fever. Although most reactions were rated as mild, 5 women withdrew from the study because of these reactions.*

*Although all treatments resulted in increased BMD, the studies did not define an optimal dosing schedule. All treatment regimens produced suppression of bone remodeling that was sustained at one year, even among patients receiving a single infusion. In animal models sustained suppression of bone remodeling is associated with an accumulation of microdamage and the alteration of several parameters of bone material properties that might predispose to fracture risk (2,3). Long-term studies with zoledronic acid are needed to establish the optimal interval between treatments and the optimal treatment dose; efficacy might be maintained with infusions even more than one year apart. In addition, although the increase in BMD observed with zoledronic acid was comparable to other bisphosphonates, fracture data will be needed to establish the clinical efficacy of this treatment approach. In addition, it is not clear whether occasional infusions of zoledronic acid would be more acceptable to patients than oral bisphosphonates, especially the once weekly regimens.*

*Although more data are needed regarding the long-term effects on fracture risk,toxicity and cost when compared with current options, this drug is a promising new addition to the arsenal in the war against osteoporosis.*

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## Long-term treatment with diacerein has a structure/disease modifying effect on hip osteoarthritis

**Authors:** M. Dougados *et al.*
**Title:** Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Evaluation of the chondro-modulating effect of diacerein in OA of the hip.
**Source:** *Arthritis Rheum* 2001; 44: 2539-47

**Aim**

Osteoarthritis (OA) is a very common, often painful and disabling condition. For this reason, drugs that can slow and modify the course of the disease are of great interest in daily clinical practice. Diacerein is a senna family compound with IL-1 inhibitory properties (1) and offers symptom relief in patients with osteoarthritis (OA) (2). A study was conducted to elucidate whether diacerein can slow the progressive decrease in joint space width and act as a structure/disease modifying in patients with hip OA.

**Methods**

In this randomized, multi-center, double-blind, placebo-controlled 3-year study, 507 patients with primary OA of the hip (by the American College of Rheumatology criteria) (3) received diacerein (50 mg twice a day) or placebo. Inclusion criteria were the presence of symptomatic disease, a Lequesne algofunctional index of at least 3 points, and a 1-3 mm hip joint space width. The patients were allowed analgesics and/or non-steroidal antinflammatory drugs (NSAIDs), but a 3- or 7-day wash-out period, respectively, was required before each visit. Systemic and/or intra-articular corticosteroids and potential disease-modifying drugs for OA were not allowed.

Patients were monitored by means of pelvic radiographs exe-

cuted once a year and at the end of the study, using a 0.1 mm graduated magnifying glass to assess the hip joint space. The minimal hip joint space width was measured by a single reader. Every 3 months functional impairment (Lequesne index), pain (visual analogue scale), consumption of analgesics or NSAIDs, requirement for hip replacement, and safety parameters were assessed. Moreover, at the time of entry into the study, at month 6, and at years 1, 2 and 3 biologic parameters, liver and kidney function were evaluated.

The primary end-point of the study was the radiographic progression of OA, assessed by evaluating the change in the minimal joint space width. Statistical analysis was performed both in the intention-to-treat population, comprising all patients entering the study and with at least 1 pelvic radiograph obtained during treatment, and in the completer population, comprising all patients who had received the study drug for at least 34 months.

**Results**

The baseline characteristics of the 507 OA patients were comparable between the 2 treatment groups (255 patients receiving diacerein, 252 receiving placebo); 238 out of 507 patients (47%) discontinued the study, mainly because of adverse events (such as diarrhea) in the diacerein group (25% versus 12% with placebo) and because of inefficacy in the placebo group (14% versus 7% in the diacerein group). The completers comprised 138 in the placebo group and 131 in the diacerein group.

The percentage of patients with radiographic progression, defined by a joint space loss of at least 0.5 mm, was significantly lower in patients receiving diacerein than in patients receiving placebo, both in the intent-to-treat analysis and in the completer analysis [50.7% versus 60.4% (P = 0.036) and 47.3% versus 62.3% (P = 0.007), respectively].

In patients who completed 3 years of treatment, the rate of joint space narrowing (expressed in mean ± SD) was significantly lower in the diacerein group (0.18 ± 0.25 mm/year) versus the placebo group (0.23 ± 0.23 mm/year), P = 0.042.

By intent-to-treat analysis, a smaller proportion of OA patients on diacerein had significant joint space loss (defined as the loss of ≥ 0.5 mm of joint space) during the study (50.7% versus 60.4%).

Diacerein had no symptom-relieving effect on the OA in this study. However, by a *post hoc* covariate analysis considering the use of analgesics and NSAIDs, a significant effect of diacerein on the Lequesne functional index was shown (P < 0.05).

Hip replacement was performed in 87 patients during the study or in the 3 months after study discontinuation:37 in the diacerein group and 50 in the placebo group (14.5 and 19.8 %, respectively; P = 0.286).

Diacerein produced a significantly higher number of side effects than placebo (P = 0.001), but overall it was well tolerated during the 3-year study. The most frequent adverse events due to diacerein was transient diarrhea (46% versus 12% in the placebo group; P= 0.001).

**Conclusion**

This study demonstrates for the first time that long-term therapy with diacerein has a structure-modifying effect in hip OA as compared with placebo, coupled with a good safety profile. However, before diacerein can be formally added to the other accepted OA therapies, further investigations are needed.

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**Comment**

*Dougados* et al. *have recently published a report of their study examining the potential of diacerein, a drug used for the treatment of osteoarthritis (OA) that has inhibitory activity against IL-1, as a structure/disease-modifying agent for the treatment of hip OA patients. The study protocol of this randomized, multi-center, double-blind placebo controlled 3-year study had as a primary aim to evaluate the effect of diacerein on the progression of OA. The effect was assessed by evaluating the change in minimal joint space, which was measured on pelvic x-rays using a magnifying glass. The results of this study demonstrated that diacerein could effectively reduce the progression of the structural changes (joint space narrowing) in these hip OA patients over three years' time.*

*This study is interesting from many perspectives. Firstly, it provides a large body of novel information about the natural evolution of the progression of structural changes in hip OA patients (1,2). These findings will be most useful in providing clinicians with information that will help to predict the evolution of the disease in the patient population. Secondly, this study is one of the masterpieces in the pioneering work realised in the last decade that has made it possible to validate the concept of disease-modifying drugs (DMOAD). Moreover, this study was one of the first to demonstrate that the evaluation of the effect of drugs on the major pathophysiological pathways of OA using pre-clinical studies could help to predict the effect of the drug on the natural course of the disease. In a number of* in vitro *and* in vivo *pre-clinical studies, diacerein has previously been demonstrated to reduce the synthesis of major catabolic factors involved in OA cartilage degradation. It has also been demonstrated to reduce the progression of experimental OA. These findings make us realise just how much progress has been made in OA research in the last few decades.*

*Much remains to be done in the development of DMOAD therapeutics and treatment strategies. The development of new drugs that are specific, effective and safe should hopefully become a reality in the next decade. In order that the effects of these drugs can be assessed accurately, new investigative imaging technologies that are more sensitive and*