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# Evidence-Based Rheumatology

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## Intermittent infusions of zoledronic acid are as effective as daily bisphosphonates in increasing bone mineral density in post-menopausal women

**Authors:** I.R. Reid *et al.*

**Title:** Intravenous zoledronic acid in postmenopausal women with low bone mineral density.

**Source:** *N Engl J Med* 2002; 346: 653-61

### Aim

Zoledronic acid (ZA) is a potent bisphosphonate, its infusions having been shown to be effective in the treatment of cancer-related hypercalcemia. In order to investigate the effect of ZA on bone mineral density (BMD) in postmenopausal women with low BMD, a one-year multicentre, randomized, double-blind, placebo controlled trial was conducted. Lumbar BMD was the primary end point of the study.

### Methods

351 post-menopausal women with spine BMD at least 2.0 SD below the T score and no more than one vertebral fracture at screening, who had entered menopause at least 5 years before the beginning of the study, were enrolled at 24 centers in 10 countries. A total of 316 women completed the study, 35 having withdrawn for personal reasons or adverse events. All women received a calcium supplement of 1 g per day. At the beginning of the study the women were assigned to receive one of six treatments regimens in a double-blinded fashion. Three groups received ZA by intravenous (IV) infusions every 3 months in doses of 0.25 mg (60 women), 0.5 mg (58 women) or 1 mg (53 women). One group received a total annual dose of 4 mg as a single dose at the beginning of the trial (60 women) and another group received a total annual dose of 2 mg each, one at baseline and the other after 6 months (60 women). The sixth group received only placebo (saline) (59 women). To maintain the blinding, all women received an IV infusion of either zoledronic acid or placebo every 3 months.

Lumbar spine (L1-L4), non-dominant proximal femur and forearm, and total body BMD were measured by dual-energy x-ray absorptiometry (DEXA) at baseline, and at 6, 9, and 12 months. Biochemical markers of bone formation (serum bone alkaline phosphatase and osteocalcin) and resorption (urinary N-telopeptide and serum C-telopeptide) were also measured at baseline and at 6, 9, and 12 months.

### Results

Throughout the study all groups receiving ZA showed a progressive increase in lumbar BMD which was significantly higher than in the placebo group ( $P < 0.001$ ). No difference was found among the ZA groups. At 12 months the mean lumbar BMD in the groups receiving ZA was 4.3-5.1% higher than in the placebo group. Accordingly, mean BMD values

for the femoral neck were 3.1-3.5 times higher than those in the placebo group ( $P < 0.001$ ). In addition, mean values for the distal radius and total body BMD were significantly higher in the ZA than in the placebo groups. Biochemical markers of bone resorption decreased significantly in all ZA groups with respect to the placebo group ( $P < 0.01$  for all comparisons). No difference was found among the ZA groups. Biochemical markers of bone formation showed similar response. The suppression persisted at 12 months with all the doses ( $P < 0.001$ ).

The rates of adverse effects were similar for all ZA groups and higher in the treated than in the placebo groups (rates of 45-67% vs 27%). In the ZA groups the most common adverse events were myalgia, fever and nausea, generally mild and occurring after the first ZA infusion. Five women withdrew from the study due to drug-related side events, all experienced after the first infusion of ZA. These withdrawals were not dose-related. Symptoms at the infusion site were rare in all the groups.

### Conclusions

Oral bisphosphonates are effective in managing osteoporosis, but they must be administered on an empty stomach, often inducing gastrointestinal side effects and reducing the compliance of the patients. Such problems should be completely solved with the use of IV ZA. Intermittent IV administration of the potent bisphosphonate ZA produce an increase in lumbar, femoral and total body BMD and effects on bone biochemical markers comparable to those seen with daily oral bisphosphonates, which have been proven to be effective in reducing osteoporotic fractures. This suggests that semi-annual or annual infusion of ZA might be an effective therapy both for treating and preventing post-menopausal osteoporosis, with a significant reduction in the direct and indirect costs of osteoprotective therapies.

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### Comment

*The importance of developing safe and effective therapies for*

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 antiinflammatory 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 ex-