Injectable bisphosphonates in the treatment of postmenopausal osteoporosis

Leonardo Sartori¹,², Silvano Adami³, Paolo Filipponi⁴, and Gaetano Crepaldi¹,²
¹Department of Medical and Surgical Sciences, University of Padova, Padova, ²Center for the Study of Aging, National Research Council, Padova, ³Rheumatological Rehabilitation, University of Verona, Verona, ⁴Metabolic Section, Department of Internal Medicine, Pathology and Pharmacology, Perugia University, Perugia, Italy

ABSTRACT. Osteoporosis is a “silent” disease and the patient has usually no clue of it until the occurrence of a fragility fracture. Prevention requires a continuous daily treatment that could be uncomfortable to the patient. Besides the recently introduced weekly oral schedules, injectable bisphosphonates have often been used as an off-label option to ameliorate compliance. In general, although with different efficiency, almost all injectable bisphosphonates can improve bone mineral density and suppress bone resorption markers. The effect of intravenous infusions of bisphosphonates are, to a large extent, similar to equivalent intramuscular administrations, but doses and dosing intervals represent the critical issues. Pain at the injection site and acute phase reactions are relatively common to intramuscular clodronate and intravenous infusions of nitrogen-containing bisphosphonates, respectively. Under certain circumstances, intermittent treatment with injectable bisphosphonates might represent a feasible alternative when compliance is at risk. (Aging Clin Exp Res 2003; 15: 271-283)

©2003, Editrice Kurtis

INTRODUCTION

Bisphosphonates nowadays are the most widely used drugs for the treatment of osteoporosis. Osteoporosis is characterized by an imbalance between bone resorption and formation that induces progressive bone loss, trabecular thinning, and increased risk of fracture. Bone loss in osteoporosis also depends on the degree of bone turnover since more bone is lost per unit of time when turnover is increased (1).

The skeletal effects of bisphosphonates are mediated by a direct action on osteoclasts with decreased recruitment, differentiation, resorptive activity, and lifetime as well as through an indirect effect on osteoblast-mediated stimulation of osteoclasts. The reduction in bone turnover induced by bisphosphonates, together with a much longer life span of osteoblasts in comparison with osteoclasts, results in an early inhibition of osteoclast activity and a later effect on osteoblast deposition (2-4). The consequent filling of the remodeling space allows, under most circumstances, a substantial increase in bone mineral density (BMD) (5).

The increase in BMD is matched by a parallel decrease in biochemical markers of bone turnover, confirming the temporary uncoupling between resorption and formation that leads to a positive calcium balance (6). Bone turnover will subsequently be adjusted to a lower level, thus lengthening the bone-sparing effect of the drug. The suppression of bone resorption depends on several factors such as potency of the compound, dose, route of administration, degree of bone remodeling, and skeletal site. Besides the increase in BMD, improved skeletal mineralization might also contribute to reducing fracture incidence (7).

In the treatment of osteoporosis, bisphosphonates are usually administered by oral route. The absorption of bisphosphonates in the upper intestine, ranging from 0.6 to 3.5%, is extremely low and is further reduced by concomitant food intake (8). This leads to substantial differences in inter- and intra-individual bioavailability, which can be partially offset by taking the drug in a fasting state with a large amount of water, while remaining in
a sitting or upright position. Nevertheless, in clinical practice, daily doses of oral bisphosphonates, particularly those containing amino-groups, are associated with a variable incidence of gastrointestinal side effects such as discomfort, pain, diarrhea, and erosive esophagitis (9). Poor and variable absorption, gastrointestinal intolerance, and enforced tight schedules are likely to hamper long-term therapeutic programs, making compliance to oral treatments rather questionable.

Alternatives to daily oral administration have then been sought and a substantial improvement has been achieved by modifying doses and dosing intervals with weekly administration of alendronate and risedronate (10, 11). In addition to discontinuous oral cycles, intermittent parenteral administration of bisphosphonates has been seen as an alternative way to deal with the low compliance associated with daily oral administration. For most bisphosphonates, intravenous or intramuscular formulas have been available for years and, under certain circumstances, used as an off-label option in the treatment of osteoporosis.

Table 1 summarizes the majority of the data published on intravenous or intramuscular use of bisphosphonates in the treatment of osteoporosis with the notable exception of etidronate and alendronate. The somehow narrow margin between therapeutic and toxic threshold as well as the mineralization concern associated with etidronate makes in fact a further development of this compound for parenteral use unlikely (12), while the leading position of alendronate as oral treatment of osteoporosis does not suggest, at least in the near future, any development of an injectable preparation. We also chose to summarize in the Table, whenever possible, only randomized, placebo-controlled studies dealing with postmenopausal osteoporosis.

INJECTABLE BISPHOSPHONATES

Clodronate

Clodronate [(dichloromethylene) bisphosphonate] is a first generation bisphosphonate characterized by Cl-C-Cl bond in substitution for the P-O-P structure of pyrophosphate. In vivo, clodronate has been estimated to be 10 times more potent than etidronate (13). For almost two decades clodronate has been in use for the treatment of high turnover bone diseases such as Paget’s disease, hypercalcemia of malignancy, and osteolytic bone metastases (14-18). Clodronate, given by oral route (400 and 800 mg daily), has been found effective in the prevention of postmenopausal osteoporosis (19, 20). With the 800 mg dose, a trend consistent with antifracture efficacy was also reported (20).

In early postmenopausal women with spine BMD values below the mean of normal premenopausal subjects, cyclical administration of clodronate (200 mg by monthly i.v. infusion for 2 years) held up menopause-associated bone loss while there was a progressive decrease in lumbar spine BMD values in controls, the difference being significant both at 12- and 24-month time-points. Bone resorption markers (urinary hydroxyproline and cross-linked carboxy-terminal telopeptide of type I collagen) were significantly reduced (36 to 57%) from the sixth month onward while osteocalcin reduction, although present, never reached statistical significance. In this study, the effects obtained by clodronate were comparable with those obtained with transdermal estradiol (21).

The long-term protective effect of short courses of clodronate (150, 300 and 600 mg i.v. per week, for 3 consecutive weeks) was also sought in early postmenopausal women. These data are somehow contradictory since only the intermediate 300 mg clodronate group yielded a small but significant reduction in BMD loss at the lumbar spine and at the femoral neck after 12 months. In an open follow-up, the effect at the femoral neck was still detectable at 24 months. The etidronate group (300 mg i.v. per week, for 3 consecutive weeks) showed a significant decrease in BMD at the lumbar spine at 12 and 24 months, while the only significant effect at the femoral neck was seen at 6 months. When compared to placebo, no significant decrease in bone turnover markers (carboxy-terminal cross-linked telopeptide of type I collagen and osteocalcin) was seen at any time-point in clodronate-treated patients, although serum procollagen 1 carboxy-terminal propeptide was significantly reduced at 1 and 3-month time-points. Etidronate significantly reduced osteocalcin levels as well as serum procollagen 1 carboxy-terminal propeptide at 3 months. The histomorphometric evaluation of iliac crest specimens performed in a subset of patients showed no difference between treated and control subjects (22).

The first paper to directly address the use of intramuscular clodronate in the treatment of postmenopausal osteoporosis was published in 1999 (23). Late postmenopausal women were treated with 100 mg clodronate i.m. every 1 or 2 weeks. Weekly clodronate injections were associated with an early (6 months) and marked increase in lumbar spine BMD that subsequently tended to level off albeit remaining significantly different from controls at 12 and 24 months. In the group treated with clodronate 100 mg i.m./2 weeks, lumbar spine BMD increased more slowly, becoming significant only at the 24-month time-point. Femoral neck BMD was not increased in either group of treatment, whereas a significant decrease was seen in controls at 24 months. Both lumbar spine and femoral neck BMD remained stable at the 36-month open follow-up. Compared to baseline, biochemical markers of bone turnover (serum bone alkaline phosphatase, urinary N-telopeptide and urinary hydroxyproline) were significantly decreased at any time-point in either clodronate group. The effect of clodronate on both BMD and biochemical markers was clearly dose-de-