Optimizing the Management of Postmenopausal Osteoporosis with Bisphosphonates: The Emerging Role of Intermittent Therapy

Paul D. Miller, MD

Colorado Center for Bone Research, Lakewood, Colorado

ABSTRACT

Background: The utility of bisphosphonates in the treatment of postmenopausal osteoporosis is compromised by the requirement of frequent oral administration or complex cyclic regimens. Recognition that simplified dosing regimens and reduced frequency of administration are important factors for improving adherence to therapy has led to the development of bisphosphonates with less frequent dosing regimens that aim to offer greater convenience.

Objective: This paper reviews the available data concerning the efficacy and tolerability of intermittent (less frequent than weekly) bisphosphonate dosing regimens for the treatment of postmenopausal osteoporosis, with particular focus on the potential implications for clinical management.

Methods: Papers on intermittent or cyclic bisphosphonate dosing regimens were identified by searching MEDLINE using the following terms: *dose, dosing, dosage*, or *drug therapy*; *intermittent, cyclic, cyclical, weekly, monthly, month, week, administration, regimen*, or *schedule*; and *etidronate, alendronate, risedronate, zoledronate, neridronate, pamidronate, clodronate, ibandronate*, or *tiludronate*.

Results: Because the currently available bisphosphonates differ in chemical structure, potency, and other physicochemical and biologic characteristics, comparable dose-free intervals may not be appropriate for all drugs. Several bisphosphonates have demonstrated efficacy in terms of an increase in bone mineral density (BMD) and a decrease in markers of bone turnover when administered intermittently. However, evidence of fracture benefit from a less frequent bisphosphonate dosing regimen was demonstrated recently. The nitrogen-containing bisphosphonate ibandronate was associated with a significant decrease in vertebral fracture risk when administered as an intermittent dosing regimen ($P < 0.001$ vs placebo). This study supports the concept that bisphosphonates such as ibandronate can be effectively administered less frequently than daily or weekly.

Conclusions: Bisphosphonate therapy using intermittent schedules with between-dose intervals longer than 1 week is capable of reducing the risk of fracture, improving BMD, and suppressing biochemical markers of bone turnover. Planned and ongoing trials will determine the place of intermittent bisphosphonates in the treatment algorithm for postmenopausal osteoporosis. (*Clin Ther.* 2005;27:361–376) Copyright © 2005 Excerpta Medica, Inc.

Key words: intermittent/less frequent, administration, osteoporosis, bisphosphonates, oral, intravenous, ibandronate, etidronate, alendronate, clodronate, neridronate, pamidronate, risedronate, zoledronate.

INTRODUCTION

The past 15 years have seen rapid development of oral bisphosphonates for the treatment of postmenopausal osteoporosis. Alendronate, risedronate, etidronate, and ibandronate are currently licensed in several countries for the treatment and prevention of postmenopausal osteoporosis (**Table I**). In randomized, placebo-controlled trials in patients with osteoporosis, these agents have increased bone mineral density (BMD) at the spine and hip in a dose-dependent manner and reduced the risk of vertebral fractures by ~30% to ~50%.[1]

Although the currently available bisphosphonates are effective,[1] their utility is somewhat compromised by daily administration or by complex cyclic regimens. In particular, dosing guidelines include stringent

Accepted for publication February 8, 2005.
doi:10.1016/j.clinthera.2005.04.005
0149-2918/05/$19.00

Table I. Bisphosphonates currently licensed for the treatment and prevention of postmenopausal osteoporosis.

Bisphosphonate	Approved Dosage*
Alendronate	For treatment: 70-mg oral tablet once weekly, 70-mg oral solution once weekly, or 10-mg oral tablet QD. For prevention: 35-mg oral tablet once weekly or 5-mg oral tablet QD.
Etidronate	For treatment and prevention: 400-mg tablet QD for 14 days followed by 76 days of calcium carbonate 500 mg QD.†
Ibandronate	For treatment and prevention: 2.5-mg oral tablet QD.
Risedronate	For treatment and prevention: 5-mg oral tablet QD or 35-mg oral tablet once weekly.

*As approved by the US Food and Drug Administration unless otherwise noted.
†As approved in the United Kingdom.

requirements for pre- and postadministration fasting and posture. Patients should take bisphosphonates following an overnight fast, with plain water only, and remain upright and fasting for at least 30 minutes after administration. These factors may cause inconvenience for some patients and lead to decreased long-term adherence to treatment, which may reduce antifracture efficacy.[2] As in other asymptomatic chronic conditions,[3] nonadherence to treatment is increasingly recognized as an important determinant of long-term clinical outcome with bisphosphonate therapy.[2] Results of a recent study using paid claims from a large health insurance company highlighted the need for better adherence to osteoporosis therapy. Of 3720 postmenopausal women prescribed bisphosphonates, only 24% (~900 patients) continued with therapy for >360 days.[4]

Simplified dosing regimens[5] and reduced frequency of administration[6–10] are important considerations for improving adherence to therapy. These factors formed the major impetus for investigations of intermittent administration of bisphosphonates. Further justification comes from a prospective study showing that >85% of 272 patients preferred once-weekly bisphosphonate administration and found weekly administration to be more convenient than a daily regimen.[11] A study of treatment preferences among women with postmenopausal osteoporosis supports these findings[12] and suggests that physicians should consider patients' preferences regarding dosing regimens when prescribing drug therapy. Therefore, future therapeutic decisions in osteoporosis may depend not only on efficacy and tolerability but also on ease of administration.

Less frequent than weekly dosing intervals may further enhance the acceptability of bisphosphonates among women with postmenopausal osteoporosis. Studies have evaluated the efficacy and tolerability of a range of intermittent bisphosphonate dosing regimens, including monthly oral regimens, IV injections every 3 months, and an annual IV infusion. This paper reviews the available data concerning the efficacy and tolerability of intermittent (less frequent than weekly) bisphosphonate dosing regimens for the treatment of postmenopausal osteoporosis, with particular focus on the potential implications for clinical management.

METHODS

The aim of the literature search was to provide an overview of research on intermittent or cyclic bisphosphonate dosing regimens. The search strategy included English-language publications collated using key search terms. MEDLINE was searched using the following terms: *dose, dosing, dosage*, or *drug therapy*; *intermittent, cyclic, cyclical, weekly, monthly, month, week, administration, regimen*, or *schedule*; and *etidronate, alendronate, risedronate, zoledronate, neridronate, pamidronate, clodronate, ibandronate*, or *tiludronate*. Medical subject headings were incorporated as alternatives where available. Results from each fragment of the search were then combined to gather references containing terms from each stage of the search. Publications were then assessed for inclusion. References were rejected if they were not related to the use of bisphosphonates in osteoporosis or were determined to be beyond the scope of the review.