Safety of Oral Bisphosphonates: Controlled Studies on Alveolar Bone

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Purpose: *Osteoporosis and osteopenia are characterized by reductions in bone mass and may lead to skeletal fragility and fracture. The latest generation of oral bisphosphonate drugs, including alendronate and risendronate, has been approved for the prevention and treatment of osteoporosis. These medications are chemically absorbed into bone, decreasing osteoclast number and activity and thereby decreasing bone resorption. The purpose of this report is to present safety data from 2 controlled studies in patients receiving oral bisphosphonates.* ***Materials and Methods:*** *Study 1 tested the effect of alendronate, an inhibitor of bone resorption, on alveolar bone. A total of 335 patients (162 men and 173 women, aged 30 to 79 years) with moderate or severe periodontal disease were randomized to either placebo or 70 mg alendronate once weekly. Alveolar bone height and safety were assessed over a 2-year period. Study 2 was a longitudinal single-blind controlled design comparing implant success in 50 consecutive patients (210 implants), 25 patients who received bisphosphonate therapy and 25 age-matched control subjects. Implant success and safety, including incidence of osteonecrosis of the jaws (ONJ), was blindly assessed for at least 3 years.* ***Results:*** *In study 1, no cases of ONJ were observed in either treatment group. Furthermore, a trend toward lower incidences of infection and tooth loss was observed in the alendronate group. In study 2, no cases of ONJ were observed in either group, and implant success was greater than 99% in both groups.* ***Conclusion:*** *On the basis of 2 controlled clinical studies, oral bisphosphonate usage was not associated with occurrence of ONJ.* (Controlled Clinical Study) Int J Oral Maxillofac Implants 2006;21:349–353

Key words: *alveolar bone, bisphosphonates, clinical trials, implants, periodontal disease, treatment*

Osteoporosis and osteopenia are characterized by reductions in bone mass and may lead to skeletal fragility and fracture. In 1994 the World Health Organization defined osteoporosis as a bone mineral density (BMD) level more than 2.5 standard deviations below the mean of normal young women.[1]

Risk factors for osteoporosis can be categorized as nonmodifiable or modifiable.[1,2] The nonmodifiable risk factors for osteoporosis include sex, age, early menopause, thin or small body frame, race, and heredity. Lack of calcium intake, lack of exercise, smoking, and alcohol are modifiable risk factors. Low bone mass, certain medications, and systemic diseases such as hyperparathyroidism are modifiable to some extent. Many of the risk factors for osteoporosis are similar to risk factors for dental implant osseointegration failure.

Bone loss in women occurs most rapidly in the years immediately following menopause, when natural levels of estrogen are greatly reduced. In most women, bone mass reaches its peak in the third decade of life (around 25 to 35 years of age) and declines thereafter. This decline in bone mass accelerates with the onset of menopause.[3,4] While estimates of the rate of postmenopausal bone loss may differ by population and measurement technology, a rate of about 0.5% to 1.0% per year has been reported.

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Osteoporosis is not a substantial health risk, but treatment of osteoporosis is important to the health of patients. Nearly 50% of women develop osteoporosis. Furthermore, almost 24% of women who suffer a hip fracture die within a year due to sequellae of the fracture. Therefore, prevention and treatment of osteoporosis is an important part of the chemotherapeutic regimen for patients who may be candidates for dental implants. Recent case reports have included observations of osteonecrosis of the jaws (ONJ) in patients receiving bisphosphonates.[5–12] However, in the vast majority of these cases, bisphosphonate drugs were administered intravenously rather than taken orally for the prevention and treatment of osteoporosis.

The purpose of this report is to present safety data from 2 controlled studies of oral bisphosphonates.

STUDY 1

Materials and Methods

The first study was a double-blind placebo-controlled study of the safety of oral alendronate taken on a once-weekly basis. The study was designed to explore the effects of alendronate, a potent inhibitor of bone resorption, on alveolar bone loss in patients with moderate or severe periodontal disease.[13] The rationale for the study was based on the fact that periodontal bone loss is mediated by osteoclasts, whose function is selectively inhibited by alendronate.[6] Alendronate had previously been shown to decrease periodontal bone loss in 2 animal models of periodontal disease[14,15] and to decrease loss of alveolar bone height and density in a small number of subjects with moderate periodontal disease.[9] The dose studied was 70 mg once weekly.

A total of 335 patients (age range, 30 to 79 years) with moderate or severe periodontal disease were enrolled in the study. Moderate to severe periodontal disease was defined by the presence of pocketing, loss in clinical attachment, and loss of at least 3 mm of alveolar bone height (ABH). A diagnosis of osteoporosis was not an inclusion criterion for the study. Patients were randomized at 12 US sites to either 70 mg alendronate or a placebo once weekly; they received nonsurgical periodontal treatment at the time of randomization. Patients were examined at 2 clinic visits (screening and baseline) prior to randomization and once every 3 months thereafter for 2 years. Maintenance treatment was performed every 3 months.

The primary safety endpoint, or measure of safety, was ONJ. Infection and progressive alveolar bone loss were also considered. All radiographs were coded for blind assessment of alveolar evidence, and presence of ONJ and radiolucency. Thus, assessment of the radiographs was completed by a single investigator with no knowledge of the treatment group or the patient's clinical adherence to the study regimen. Other tooth-related safety data, such as caries and gingival index (GI) data, have been reported elsewhere.[16] No adverse pattern of events was observed.

The primary efficacy endpoint was the change in ABH. ABH is defined as the distance between the cementoenamel junction (CEJ) and the alveolar bone crest. In normal conditions, the level of the crest is 1 to 2 mm apical to the CEJ.

Statistical Evaluation. Safety data was tabulated but not amenable to statistical analysis due to the low level of adverse events in both the placebo and alendronate groups.

Changes in ABH from baseline were analyzed by the analysis-of-variance method (ANOVA), including treatment group and study center as factors. Treatment-by-center interaction was not found to be significant at the .05 level. Analyses were performed on per-patient summaries of the measurements at qualified tooth sites for each individual patient.

Results

Baseline Characteristics. A total of 162 men and 173 women were enrolled in the study. The patients ranged in age from 30 to 79 years (mean, 50 years). Approximately 75% of the patients enrolled were Caucasian, while 17% were African Americans. Sixty-two percent were smokers, and 71% of the patients had severe periodontal disease. Only 3% were diabetic. There were no differences between groups in terms of baseline characteristics.

Efficacy. Figure 1 shows the ABH at baseline and after 2 years in subjects with low and normal mandibular BMD. A significant gain in ABH was seen in the alendronate-treated group (periodontal bone loss 4.16 ± .11 mm baseline, 3.75 ± .18 mm 2 years) relative to the placebo group (periodontal bone loss 4.22 ± .13 mm baseline, 4.61 ± .23 mm 2 years) ($P <$ .001) in patients with low mandibular BMD at baseline. This significant difference was not observed in alendronate-treated patients with normal BMD at baseline (4.33 ± 0.13 mm baseline, 4.49 ± 0.21 mm 2 years) compared with placebo-treated subjects (4.32 ± 0.11 mm baseline, 4.31 ± 0.18 mm 2 years).

Safety. Table 1 shows the alveolar bone and periodontal safety profile. No cases of ONJ were observed over the 2-year study period. In fact, fewer teeth were lost in the bisphosphonate group, in spite of the existence of periodontal disease at baseline, than in the placebo-treated group.

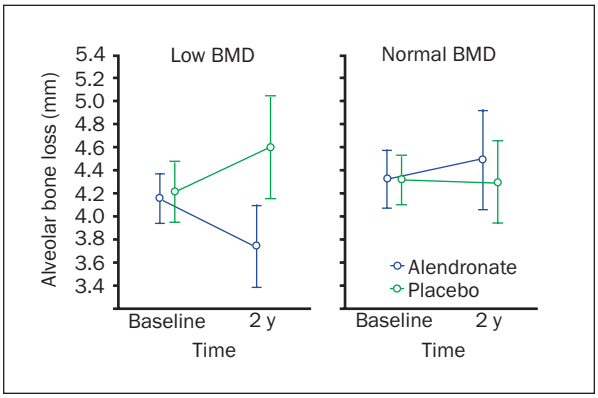

Fig 1 Effect of alendronate on alveolar bone. Bone loss from the CEJ (mean ± SD) is shown for patients with low BMD at baseline versus those with normal BMD at baseline. Note a significant decrease in bone loss[16] in the alendronate-treated group in subjects with low BMD at baseline.

Table 1 Number and Percentage of Patients with Adverse Experiences

Adverse experience	Alendronate (n = 167)		Placebo (n = 168)	
	n	%	n	%
Dental pain	33	19.8	32	19.0
Gingival/periodontal disorder	44	26.3	38	22.6
Gingivitis	12	7.2	11	6.5
Periodontal disease	5	3.0	11	6.5
Tooth loss*	30	—	52	—
ONJ	0	0	0	0

*Number of teeth lost shown rather than number of patients who lost teeth.

STUDY 2

The second study was a parallel-arm controlled study of dental implant patients receiving oral bisphosphonates versus control dental implant patients.

Materials and Methods

Design. This single-blind controlled study involved the consecutive analysis of 3-year results from 25 patients (102 implants) receiving oral bisphosphonates (alendronate or risendronate) versus 25 age-matched patients (108 implants) who did not receive bisphosphonates. All patients were postmenopausal women with BMD scores indicative of osteoporosis. Only 1 patient per study arm smoked. Patients in the bisphosphonate arm had taken the drug for 1 to 4 years (mean 3 ± 0.1 years) prior to inclusion in the study.

Following implant placement, patients were followed for at least 3 years with oral examinations, radiographs, and routine maintenance. Two-stage osseointegrated implants were used in all patients. Fixed screw-retained prostheses were placed and removed to assess implant mobility, which was assessed at least once a year.

Outcomes. Coded digital radiographs were used to provide yearly measurements of bone loss and were examined for evidence of ONJ. Calibrated clinicians also measured mobility and assessed clinical evidence of pain, infection, and ONJ.

Statistical Analysis. A Kaplan-Meier analysis was used to compare the success rate of implants in patients receiving oral bisphosphonates to implants in patients not receiving oral bisphosphonates. Success was defined as less than 2 mm of alveolar bone loss over the 3-year study period, lack of mobility, lack of infection, and absence of pain and ONJ.

Results

Analysis revealed that 100.0% of the implants placed in patients receiving bisphosphonates were successful, compared with 99.2% in the group not receiving bisphosphonates (Fig 2). There was no significant difference between the 2 study groups ($P > .95$).

DISCUSSION

A number of cases of ONJ following treatment with high-dose bisphosphonates, especially in cancer patients treated parenterally and in the presence of additional risk factors such as chemotherapy, glucocorticoids, and poor oral hygiene, have been reported to regulatory agencies.[5–12] Patients receiving intravenous bisphosphonate therapy were not studied as part of the present study. This smaller population with especially complex medical problems is deserving of controlled studies.

The present study is, thus far, the largest randomized, placebo-controlled study of an antiresorptive agent in patients with oral disease that was designed to assess oral side effects and outcomes in a blinded controlled manner. After 2 years of treatment, a significant positive effect of alendronate was observed relative to placebo in the subgroup of patients with low mandibular BMD at baseline.

Other investigators have reported positive results with alendronate therapy, primarily on ABH and alveolar bone density, with daily doses equivalent to the weekly dose used in the current study.[16–22] However, the duration of follow-up in these studies was only 6 months.

Study 1 also provided additional data on the safety of once-weekly alendronate. As previously observed in a study of postmenopausal women,[20,23]

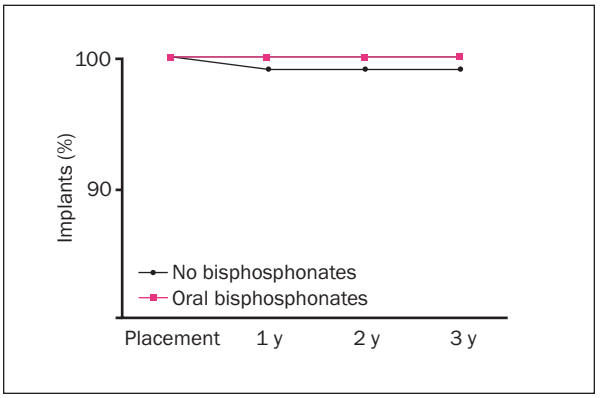

Fig 2 Implant success in bisphosphonate-treated and control patients. One hundred percent of implants in patients receiving oral bisphosphonate met the success criteria, and 99.2% of implants in patients not receiving the drug were successful.

70 mg oral alendronate once weekly was generally safe and well tolerated. This favorable safety profile included maxillary gingival index and dental adverse experiences. This study supports prior research[17–19,21,22] and shows both reduced rates of bone loss and reduced bone loss with absence of ONJ in a multicenter study population. However, it is acknowledged that, given the relatively long half-life of bisphosphonates, the long-term effects of alendronate therapy cannot be determined from the 2- to 3-year follow-up presented here.

In study 2, oral bisphosphonate therapy was not associated with any implant failures or adverse events. The patients were followed for at least 3 years, and no implant had evidence of aloveolar bone loss exceeding 2 mm around the implant. No evidence of ONJ was observed.

The implications of this data are profound, since they directly address an area of considerable debate in the medical and scientific communities. Although a large majority of bisphosphonate-associated cases of ONJ have concerned patients receiving intravenous bisphosphonate therapy, some instances of ONJ in patients on oral therapy have been reported as case reports.[5–12]

The findings of the present study suggest that there is benefit to oral bisphosphonate therapy in that it protects individuals against periodontal bone loss and osteoporosis. This correlates well with previous studies suggesting that osteoporotic individuals are at higher risk for alveolar bone loss and that postmenopausal women with osteoporosis are likely to be missing a greater number of teeth than postmenopausal women with normal BMD.[23] Therefore, given the large number of women routinely taking oral bisphosphonates and the relatively few cases of osteonecrosis seen in the present sample, it appears that the small risk of developing osteonecrosis should be considered with due regard for the potential benefits (retardation of alveolar bone loss).

CONCLUSION

The decision to proceed with any medical or dental procedure, be it prescription of oral bisphosphonates or placement of a dental implant, involves balancing the risks against the benefits and making choices. Osteoporosis is a serious bone disease requiring treatment in the absence of major risks. In the 2 controlled studies presented, oral bisphosphonates were not found to pose a risk to alveolar bone compared to placebo.

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