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SHORT REVIEW

Bisphosphonates in the treatment of thalassemia-associated osteoporosis

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ABSTRACT. Thalassemia major is a common cause of skeletal morbidity, as shown by the increased fracture risk in thalassemic patients. The etiology of this bone disease is multifactorial and culminates in a state of increased bone turnover with excessive bone resorption and remodeling. Despite hormonal replacement therapy, calcium and vitamin D administration, effective iron chelation, and normalization of hemoglobin levels, patients with thalassemia major continue to lose bone mass. The increased bone turnover rate observed in thalassemic patients justifies the use of powerful anti-resorption drugs, such as bisphosphonates. To date, alendronate, pamidronate, and zoledronate seem to be effective in increasing bone mineral density and normalizing bone turnover, but more trials are necessary to evaluate their efficacy in reducing fracture risks in larger thalassemic populations.
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INTRODUCTION

Since treatment with transfusion programs and chelating therapy have significantly prolonged survival in thalassemic patients, osteoporosis represents an important cause of morbidity in adult patients, who display increased fracture risk (1). Recently, according to the North American Thalassemia Clinical Research Network database registry prevalence of fractures among patients with thalassemia major and intermedia is 16.6 and 12.2%, respectively (2).

In the thalassemic population, the lumbar spine and femoral neck bone mineral density (BMD) is below the normal reference control, as shown in previous works by us (3) and other authors (4, 5). The etiology of this bone disease is multifactorial (hormonal deficiency, bone marrow expansion, increased iron stores, desferioxamine toxicity, calcium, and vitamin D deficiency) (3-11) and culminates in a state of increased bone turnover with excessive bone resorption and remodeling (7).

Key-words: Thalassemia, osteoporosis, bisphosphonates.

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However, despite hormonal replacement therapy, calcium and vitamin D administration, effective iron chelation, and normalization of hemoglobin levels, patients with thalassemia major continue to lose bone mass (3, 12).

The increased bone resorption observed in thalassemic patients justifies the use of powerful anti-resorption drugs, such as bisphosphonates, in the treatment of this form of osteoporosis (6).

BISPHOSPHONATES USED FOR THALASSEMIA-ASSOCIATED OSTEOPOROSIS

Bisphosphonates are pyrophosphate analogues, in which the oxygen in P-O-P has been replaced by a carbon, resulting in a P-C-P structure. They are potent inhibitors of osteoclastic bone resorption, by inhibiting osteoclastic recruitment and maturation, preventing the development of monocyte precursors into osteoclasts, inducing osteoclast apoptosis and interrupting their attachment to the bone (13, 14). Because of these pharmacological properties bisphosphonates have been studied and nowadays are extensively used for the treatment of Paget's disease of bone, hypercalcemia of malignancy, bone metastases, and several forms of osteoporosis (15).

Up to now, studies evaluating the effects of bisphosphonates in the treatment of thalassemia-as-

sociated osteoporosis have been few and with small patient samples (Table 1).

Our group performed a randomized, placebo-controlled study to investigate the effects of 2-yr daily oral administration of alendronate or im administration of clodronate every 10 days on bone-remodeling parameters and BMD in a group of osteoporotic thalassemic patients (16). Twenty-five young patients (mean age 26.6±7.1 yr) with β-thalassemia major were randomly divided to receive placebo (8 patients) or 100 mg of clodronate im every 10 days (8 patients) or 10 mg of alendronate per os daily (9 patients). All patients took 500 mg/d of elemental calcium and 400 UI/d cholecalciferol. At the end of the study, the lumbar and femoral BMD decreased significantly in the placebo group. Clodronate was able to reduce pyridinium cross-links levels, but not to increase lumbar or femoral BMD. The daily administration of alendronate normalized bone turnover markers and increased BMD at all studied sites, but statistically only at femoral level. No relevant side effects were recorded during our study.

The ineffectiveness of clodronate was established in another study (17), comparing the effects of long-term cyclical clodronate therapy (300 mg iv infusion every 3 weeks for 2 yr) and of an active placebo (calcium and vitamin D) on bone mass and bone turnover in 30 male patients with thalassemia major. Treatment with clodronate determined a substantial stability of bone mass, which was not significantly changed at the end of the study, whereas in calcium and vitamin D-treated patients a significant decline in spine, femoral, and total bone density was observed.

Pamidronate, a second generation aminobisphosphonate, has been used for the treatment of thalassemia-associated osteoporosis by Voskaridou et al. (18), who used this drug in 26 patients at doses of 30 or 60 mg iv once a month over 12 months. The effects were monitored by measuring BMD in association with markers of bone turnover. Thirty healthy individuals were also studied as controls. Administration of pamidronate was followed by a clear decrease of bone turnover markers and by a significant increase in the BMD of the lumbar spine, which was similar in patients of both treatment groups.

Table 1 - *Bisphosphonates used for thalassemia-associated osteoporosis.*

Bisphosphonate	Dose	Population	Results	References
Clodronate	100 mg im every 10 days for 24 months	8 patients with β-thalassemia major	No significant changes in BMD either at lumbar or femoral levels with respect to baseline values	Morabito et al. (16)
	300 mg iv every 3 weeks for 24 months	15 patients with β-thalassemia major	No significant changes in BMD either at lumbar or femoral levels with respect to baseline values	Pennisi et al. (17)
Alendronate	10 mg po every day for 24 months	9 patients with β-thalassemia major	Significant increase in BMD only at femoral level with respect to baseline values	Morabito et al. (16)
Pamidronate	30 or 60 mg iv every month for 12 months	18 patients with β-thalassemia major and 8 patients with thalassemia intermedia	Significant increase in BMD at lumbar level with respect only to baseline values for both doses	Voskaridou et al. (18)
Zoledronate	1 mg iv every 3 months for 12 months	26 patients with β-thalassemia major and 3 patients with thalassemia intermedia	Significant increase in BMD at lumbar level with respect to baseline values	Perifanis et al. (19)
	4 mg iv every 6 or 3 months for 12 months	66 patients with β-thalassemia major	Significant increase in BMD at lumbar level compared to baseline values only in patients treated every 3 months	Voskaridou et al. (20)
	4 mg iv every 6 months for 12 months	18 patients with β-thalassemia major	Significant increase in BMD at lumbar and femoral level compared to baseline values	Otrock et al. (21)
	4 mg iv every 3 months for 24 months	23 patients with β-thalassemia major	Significant increase in BMD at lumbar and femoral level compared to baseline values	Gilfillan et al. (22)

BMD: bone mineral density.

Recently, various trials were conducted in thalassemic patients using zoledronic acid, a novel biphosphonate compound. In particular, Perifanis et al. (19) enrolled 29 patients with transfusion-dependent β-thalassemia (3 with thalassemia intermedia). Thirteen patients were male and 16 were female, with a mean age of 27.2±7.3 yr. All patients had severe osteoporosis and were receiving calcium and vitamin D supplement prior to and during the study. They were given zoledronic acid iv at a dose of 1 mg every 3 months over 12 months. The effects were monitored by measuring the BMD of the lumbar spine. Twenty age- and sex-matched healthy blood donors were also studied as controls. Administration of zoledronic acid was followed by a significant increase in the BMD of the lumbar spine. No treatment-related side-effects were observed.
In a recent paper Voskaridou et al. (20) randomized to receive 4 mg of zoledronic acid iv, every 6 months (23 thalassemic patients) or every 3 months (21 patients), or to receive placebo every 3 months (22 patients). Only patients treated more frequently had a significant increase in their lumbar spine BMD, which was accompanied by dramatic reductions in bone pain and markers of bone turnover. These data were confirmed by Otrock et al. (21) in 18 thalassemic patients who also had an increase of BMD at femoral level.
Only Gilfillan et al. (22) conducted a longer trial, 24 months, treating 23 patients with thalassemia-associated osteopenia with 4 mg of zoledronic acid iv every 4 months. At the end of the study average lumbar spine BMD was 8.9% greater and average femoral neck BMD was 9.1% greater in the treated group compared to placebo. Moreover, the Authors observed that age, gender, height, weight, and BMI did not interact with the effect of treatment.

DISCUSSION AND CONCLUSION

Adequate transfusion programs, hormonal replacement, and chelating therapy are necessary, but often insufficient in preventing osteoporosis in thalassemic patients. It is important to enrich diet with calcium and vitamin D supplements, to discourage smoking and to encourage physical activity. In patients with increase of bone turnover markers and a low BMD evaluated by dual-energy x-ray absorptiometry (DEXA) at lumbar or femoral level (Z-score <–2 SD) the use of bisphosphonates is correct. To date, bisphosphonates such as alendronate, pamidronate, and zoledronate seem to be effective in normalizing bone turnover rate and in increasing BMD. In particular, zoledronic acid at a dosage of 4 mg iv every 4 months appears, from various recent studies, to be very efficacious in increasing BMD both at lumbar and femoral level. Moreover, this treatment seems well-tolerated and also to be able to reduce pain. The normalization of bone turnover and the increase of BMD are probably a good surrogate of anti-fracture efficacy, but up to now no data about reduction of fracture risk have been available in the literature. Apart from the open question of the treatment duration, the administration of iv bisphosphonates for several years in thalassemic patients could raise the problem of side effects. Indeed, pamidronate and zoledronate have recently been associated with cases of jaw osteonecrosis (23), even if no case is to date reported in thalassemic patients.
It is important to observe that all studies reported in this review use areal BMD, which it is not a measure of true bone density (24, 25). True bone density is volumetric BMD, that can be assessed only by quantitative computed tomography, but this technique involves high radiation exposure. Up to now, it has been possible through mathematical models to adjust the values of the areal BMD measured by DEXA for bone size and thus to calculate the apparent volumetric BMD (26, 27). This parameter should be used to compare growing people in a single study or people of different ages among different studies. It would therefore be worth adopting in future trials with thalassemic patients.
In conclusion, even if bisphosphonates seem from various studies to normalize bone turnover and increase BMD in thalassemics, more trials with larger populations are necessary to define the exact role of each bisphosphonate, the long-term benefits and side-effects, and above all the efficacy in reducing fracture risk.

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