Ibandronate and periprosthetic bone mass: new therapeutic approach in periprosthetic loosening prevention

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Summary

A prosthetic implant modifies the physiological transmission of loads to the bone, initiating a remodeling process. Studies of the mechanisms responsible for periprosthetic bone loss contributed to the definition of new pharmacological strategies that may prevent aseptic implant loosening. Bisphosphonates are a class of drugs useful to this purpose, and have been shown to be effective in reducing periprosthetic resorption during the first year after the implant. We aimed to assess the inhibitory effect on periprosthetic osteolysis of ibandronate, a highly potent aminobisphosphonate, administered orally and IV with an extended interval between doses and optimal treatment adherence. In view of the fact that periprosthetic remodeling takes place during the first 6-12 months after surgery and is ultimately responsible for prosthesis longevity, we may conclude that the administration of high dosage ibandronate post-surgery by IV bolus and subsequently as cyclic oral treatment reduced cortical osteopenia in the metaphyseal region, and in the calcar region of the proximal femur. This therapy might therefore be used as preventive measure against post-surgical osteopenia and probably also against aseptic loosening.

KEY WORDS: periprosthetic bone loss, ibandronate, bisphosphonates.

Introduction

A prosthetic implant modifies the physiological transmission of loads to the bone, initiating a remodeling process.
The studies conducted to date allowed to identify the events that take place around the periprosthetic bone and lead to prosthesis loosening. The first effect seems to be intraoperative damage, which is immediate and "acute", and includes mechanical, thermal and chemical damage (1). All of these events cause necrosis in a bone region of varying size, which takes approximately three months to heal (2).
Therefore, periprosthetic remodeling takes place following stress redistribution, especially in the proximal-medial region of the femur, where a resorption process known as "stress shielding" occurs (3), while in the distal diaphyseal area, and particularly near the stem apex, neo-apposition phenomena take place.
Studies conducted show that, one year after the implant, periprosthetic bone loss tends to stabilize, and subsequently shows only minor changes associated with bone ageing rather than the remodeling process itself (4). Five years after surgery, there are phenomena related to debris-induced osteolysis, which lead to prosthesis loosening. The debris produced by prosthetic component wearing seems to contribute to the activation of an immune-inflammatory response, with a recall of monocytes/macrophages, the continuous phagocytosis of wear debris and the production of cytokines and phlogosis mediators, including IL-1 and TNF-alpha, that can stimulate bone resorption by activating the RANKL-RANK axis.
All of these phenomena initiate a bone remodeling process, expressed as changes in periprosthetic bone density (5). All densitometry study published to date show bone resorption in the femur metaphyseal region, including in high proportions.
The kinetic of bone mass loss was reconstructed by serial densitometric assessments of different periprosthetic bone areas: three months after the implant, a significant decrease in BMD in all regions assessed was observed, followed by a slower progression, except for the calcar region, where bone loss due to stress shielding continues to progress, until it eventually stabilizes after one year (6).
Additionally, the BMD changes reported after six months seem to have a statistically significant relationship with those reported five years after surgery (2), leading to assume that early periprosthetic remodeling taking place in the first six to twelve months after surgery may also be responsible for the tendency shown in the following years.
Studies of the mechanisms responsible for periprosthetic bone loss contributed to the definition of new pharmacological strategies that may prevent aseptic implant loosening. Bisphosphonates are a class of drugs useful to this purpose and have been shown to be effective in reducing periprosthetic resorption during the first year after the implant (7).
Based on data resulting from these studies, we aimed to assess the inhibitory effect on periprosthetic osteolysis of ibandronate, a highly potent aminobisphosphonate, administered orally and IV with an extended interval between doses and optimal treatment adherence.
We therefore conducted a two-year study aimed to examine the effect of early treatment with ibandronate on periprosthetic bone resorption assessed by densitometry in patients undergoing cementless hip joint replacement, in terms of magnitude of periprosthetic resorption as the difference between BMD measured shortly after surgery and during the follow-up period.
Studies conducted to date show how bisphosphonates can reduce periprosthetic resorption in the first year after the implant, both of hip and knee, with cemented and cementless prostheses, with bet-

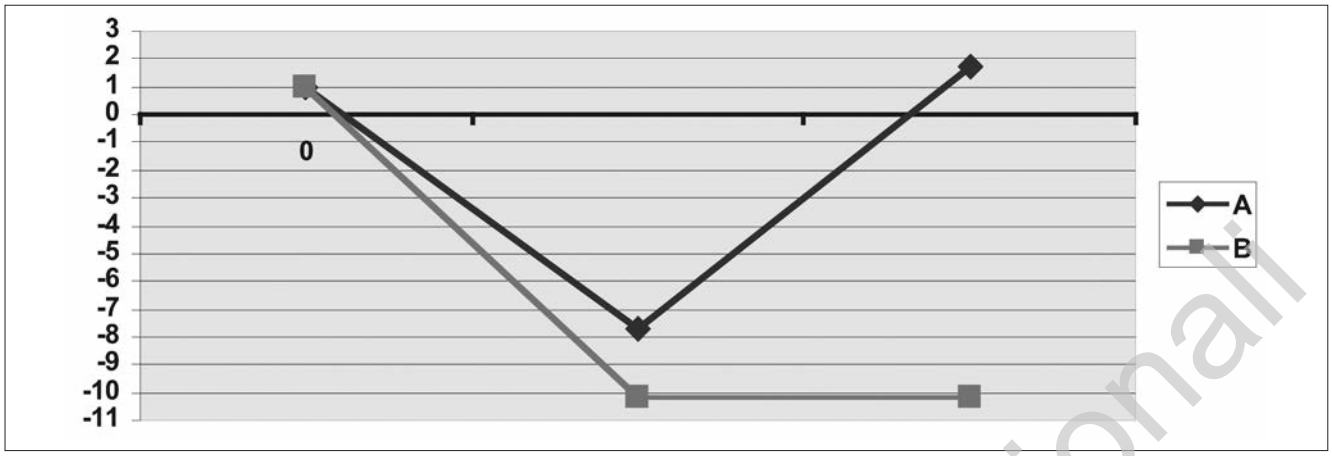

Figure 1 - Percentage differences between average values at T0, T1, and T2 of TOTAL BMD in groups A and B.

ter and longer lasting outcomes when treatment is started shortly after surgery and continued for over six months (7). The rationale is the blockage of osteoclastic resorption activation and the induction of osteoblastic activity (8) and, therefore, of prosthesis osseointegration thanks to direct and indirect effects.

This study included 40 women (> 60 years of age), not necessarily osteoporotic, assigned to two groups: **group A** included 22 patients who received, within five days after the hip replacement surgery with an hydroxyapatite-coated prosthesis, a single administration of 3 mg ibandronate IV and subsequently 150 mg orally once monthly, with calcium carbonate (1 g) e cholecalciferol (880 UI) integration; **group B** (control) included 18 patients treated with calcium carbonate (1 g) and cholecalciferol (880 UI) integration. Patients were assessed by DEXA with Hologic Discovery on Day 15 after surgery (T0), and then at 6 (T1) and 12 months (T2), measuring the total BMD of the periprosthetic femur (TOT) and 7 Gruen's subregions of prosthetic femur, contralateral femur and rachis. Statistical analysis was carried out by using a Mann-Whitney Test.

Despite the lack of literature data from studies of ibandronate in the prevention of periprosthetic remodeling in humans, the decision to administer this molecule to our patients was supported by studies that, by means of histomorphometric measures, documented the effect of this bisphosphonates, at a dosage matching the one used in humans against osteoporosis, on osteoblastic activity and therefore on prosthesis osseointegration, and its stimulating effect on bone formation in rats with cementless femoral implant (9).

In line with these studies, we detected a BMD decrease during the first 6 months after the implant in patients of both groups, the control group treated with Ca and Vit. D only (-10.2%) and the one treated with an IV bolus of ibandronate and then with oral ibandronate plus Ca and Vit. D, even if the latter showed a lower decrease (-7.7%) compared to the global BMD control group. At 12 months, however, the trend reversed, with a statistically significant ($p<0.01$) BMD percentage recovery compared to the baseline value at T0, T1, and T2 of about 1.74% in global BMD, more obvious in the R1 region (+3.81%) and the lateral metaphyseal region (R2) (+4.12%) in group A, while virtually no recovery of global BMD was observed in group B, which had stabilized to the values measured at 6 months (T1) (Figure 1).

Therefore, the comparison at 12 months shows a significant difference between groups, both in terms of total BMD and subregion values, in favor of the group treated with ibandronate (Figure 1). In view of the fact that periprosthetic remodeling takes place during the first 6-12 months after surgery and is ultimately responsible for prosthesis longevity, we may conclude that the administration of high dosage ibandronate post-surgery by IV bolus and subsequently as cyclic oral treatment reduced cortical osteopenia in the metaphyseal region, and in the calcar region of the proximal femur in particular; this therapy might therefore be used as preventive measure against post-surgical osteopenia and probably also against aseptic loosening, in the hope to increase the stability of the prosthetic implant. By taking advantage of its analgesic action, it may also improve pain and quality of life in the post-surgical period and even more at 12 months.

We are aware that the follow-up period of this study is too short to draw a definitive conclusion on the potentially higher longevity of the prosthesis, but in our opinion this study supports the anabolic effect of bisphosphonates and therefore of ibandronate on osteoblasts, an action that can increase growth inside implant porosities, and therefore prevent bone resorption under predisposing conditions and probably extend long-term duration of joint prostheses.

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