

Title: A Randomized, Controlled Study of Ibandronate for the Prevention of Bone Loss in Patients Who Have Received Allogeneic Bone Marrow Transplantation for Hematological Malignancies or Hematological Disorders

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1.0 Objectives

This study plans to address the following hypotheses:

- 1.1 The addition of Ibandronate initiated immediately after the transplantation (21 to 60 days) will prevent bone loss in patients undergoing allogeneic bone marrow transplantation (BMT) with underlying hematologic malignancies or hematological disorders.
- 1.2 BMT patients who require prolonged steroid and other immunosuppressive treatment for Graft versus Host Diseases (GVHD) have a higher rate of bone loss, which can be prevented or attenuated by Ibandronate.

Specific objectives to test these hypotheses are:

a. Primary Objective:

1. To prospectively compare the bone mineral density changes of lumbar spine, femoral neck and total hip between patients randomly assigned to Ibandronate and control group over 12 months post bone marrow transplantation at the University of Texas MD Anderson Cancer Center.

b. Secondary Objectives:

1. To measure and compare the accumulated level of steroid used in both treatment and control groups.
2. To collect and compare the level of serum C-terminal telopeptide (CTX) in both treatment and control groups to monitor the bone turnover rate for the duration of the study.
3. To conduct a cost-effectiveness analysis of participating patients for both outcomes on bone mineral density (measured data) and skeletal-related events (modeled data).
4. To record incidence of bone fractures and the graft rate in both treatment and control groups.

2.0 Background

Bone marrow transplantation (BMT) is performed with increasing frequency and for expanding indications, with the majority of patients surviving for many years. In this context, bone loss is a common and serious post-transplant complication. Bone loss, occurs early and most rapidly during the first three to six months after the transplantation, and is often more severe at the femoral neck (1, 2). The degree of bone loss can be severe enough to cause fractures. Lower

bone mineral density in femoral neck in this population has also been associated with avascular osteonecrosis (3).

Osteoporosis developed after BMT has a complex mechanism involving both the direct effect of the transplanted bone marrow on the stromal cell compartment and the effects from immunosuppressive therapies (3). As a result of the decreased osteoblast and increased osteoclast activity, there is both increased bone resorption and decreased bone formation. After the transplantation, over 50% of BMT patients develop some form of Graft Versus Host Disease (GVHD), which requires prolonged use of glucocorticoid as well as other forms of immunosuppression. In addition, BMT recipients may also experience some bone loss before the transplantation (4), that is related to their underlying disease and the modalities used to treat them. Their prior treatment may result in a variety of effects associated with bone loss, including glucocorticoid-induced decreases in bone formation and serum 1,25-dihydroxyvitamin D₃, or chemotherapy-induced hypogonadism. Therefore patients with hematologic malignancies or hematological disorders undergoing bone marrow transplantation are at high risk of bone loss.

In a prospective, randomized 12-month study of Risedronate on bone mass and bone turnover in patients who had undergone allogeneic BMT at least 6 months before the treatment, spine and femoral neck bone mineral density (BMD) did not change significantly in patients on Risedronate and decreased in those taking placebo (5). However, this study did not answer the question of whether bisphosphonates could prevent the rapid bone loss commonly seen during the first three months post-BMT. In another uncontrolled observational study, three monthly intravenous Pamidronate infusions attenuated femoral neck bone loss in the first six months after allogeneic BMT (2). In a recent randomized, controlled study in patients undergoing allogeneic stem cell transplantation, using Pamidronate initiated before the transplantation decreased the bone loss significantly at the lumbar spine, hip, and the femoral neck. However there was still significant bone loss at the hip and femoral neck that was not completely prevented by pamidronate, warranting the use of a more potent bisphosphonate for more durable maintenance of bone mass after transplantation (6).

Ibandronate (Boniva) has been shown to significantly increase bone mineral density in the lumbar spine and the hip bone in postmenopausal patients. Compared to placebo, Ibandronate taken orally at 150 mg once monthly or 3 mg intravenously quarterly significantly increased bone mineral density and decreased the rate of new vertebral fractures (7). Ibandronate is more potent than other bisphosphonates such as Pamidronate, Risedronate and Alendronate.

So far there is no consensus on how to effectively prevent and treat osteoporosis associated with bone marrow transplantation. As for steroid induced osteoporosis, the American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis recommends obtaining a baseline measurement of bone mineral density at the lumbar spine and/or hip when initiating long-term (i.e., in a dose of 5 mg/day or higher for more than 3 months) glucocorticoid therapy with longitudinal follow ups. The committee also recommends bisphosphonates used in such patients in conjunction with calcium and vitamin D supplementation for the prevention of osteoporosis (8). Such consensus has not been tested in cancer patients receiving BMT.

Although there are known risk factors of osteoporosis associated with bone marrow transplantation and the subsequent immunosuppressive treatment, guidelines for the prevention and effective treatment of bone loss in this high risk population are lacking. Data on whether therapy for osteoporosis treatment or prevention initiated around the time of the transplantation reduces fracture risk after transplantation is limited. Bisphosphonates, in particular, suppress

bone resorption for up to 12 months after discontinuation of therapy. Transplantation with immediate addition of bisphosphonates may prevent the accelerated bone resorption that develops immediately after transplantation and could theoretically mitigate post-transplant bone loss. Moreover, anti-resorptive therapy clearly increased bone mineral density and reduces fracture in other populations, including patients undergoing solid organ transplant. Given such, this proposal is designed for the prevention of osteoporosis in this high risk population.

3.0 Patient Eligibility

The study eligibility requirements will include the following inclusion/exclusion criteria:

3.1 Inclusion criteria:

- 1) Age greater than or equal to 18 years.
- 2) Patients with the diagnosis of hematologic malignancies or hematological disorders, who are immediately post- allogeneic bone marrow transplantation.
- 3) Female patients of childbearing potential (i.e. no hysterectomy, no loss of menses for 12 consecutive months), must be willing to use contraception.
- 4) Negative pregnancy test in premenopausal patients.
- 5) Patients with GVHD or infections can be entered only if they respond to treatment and become controlled.
- 6) Dental considerations: patients with negative dental screening for jaw osteonecrosis 0-3 months prior to their transplant and patients that do not have a plan for tooth extraction in the near future.

3.2 Exclusion criteria:

- 1) Patients with documented relapsed malignancy or recurrence of the original hematological disorder after the transplant, uncontrolled acute GVHD, or uncontrolled infection.
- 2) Patients with hypocalcemia of less than 8.4 (corrected to account for the albumin level).
- 3) Patients with hypercalcemia >12.2 , due to a cause not related to their hematological malignancy or hematological disorder (i.e. hyperparathyroidism, multiple myeloma).
- 4) Hypersensitivity to Ibandronate or other bisphosphonates.
- 5) Pre-existing osteoporosis, defined as a bone density T-score of -2.5 S.D. or less.
- 6) Renal insufficiency (calculated creatinine clearance < 30 ml/min).
- 7) Patients already on bisphosphonates (over the past two years), calcitonin, anabolic steroids, or daily oral fluoride supplement.
- 8) Myeloma patients who have previously been on bisphosphonates over the past two years and/or have active bone lesions.
- 9) If corrected calcium is above 10.3 and the iPTH is elevated or normal, the patient will be excluded from the study.
- 10) Patients with a 25-hydroxyvitamin D concentration <20 ng/ml and evidence of osteomalacia (low ionized calcium and elevated intact PTH).
- 11) Patients with recent tooth extraction with signs of incomplete healing or infection will be excluded.

4.0 Treatment/study Plan

Patients who had hematological malignancies or hematological disorders and underwent allogeneic bone marrow transplantation are eligible to participate in the study. Members of the research team

will enroll eligible patients who meet the inclusion criteria in the study after obtaining agreement of their transplant physician. Patients with GVHD or infections can be entered only if they respond to treatment and become controlled.

As part of standard care for pre-BMT work up, all patients will have their 25(OH) Vit D levels checked. Patient with vitamin D deficiency (< 20 ng/ml) will be supplemented to adequate level (≥ 20 ng/ml).

Patients will then be randomized into the following two groups: 1) treatment: Ibandronate 3 mg intravenously over 15-30 seconds for 4 doses at 0-1.5, 3, 6, and 9 months free of charge; or 2) control: Patients will only receive daily oral calcium and vitamin D supplements. Patient's prior vitamin D supplement status will be considered as one of the randomization factor. After entering the trial, all patients will receive 500 mg of elemental calcium carbonate and Vitamin D Analog 400 IU orally twice daily for 12 months to be taken at home during the trial. Patients who do not tolerate the calcium pills provided by the trial are allowed to take another brand of calcium/vitamin D at home as tolerated with equivalent dosing. Patients who are still on weekly Ergocalciferol have the option of holding their daily vitamin D 400 IU twice daily and must resume the daily vitamin D when they are off the weekly Ergocalciferol.

BMD at lumbar spine, femoral neck and total hip will be determined at baseline (up to 3 months prior to the transplant or prior to the enrollment), 6, 12 months (± 4 weeks) post transplants for all patients in both groups by DEXA at MDACC. The change of BMD between baseline and 12 months in both Ibandronate treatment and control groups will be summarized and analyzed for statistical significance.

The members of the research team will collect data and/or blood for the following:

1. Bone turnover marker, the serum CTX will be measured at baseline, 3, 6, and 12 months (± 4 weeks)
2. Routine laboratory monitoring includes calcium, magnesium, alkaline phosphatase, albumin, and creatinine at baseline and at 3, 6, 9, and 12 months (± 4 weeks) post-transplant.
3. Other factors affecting bone metabolism will be measured which include 25(OH) Vit D and intact PTH levels at baseline (as part of pre-transplant workup, or prior to the enrollment) and at the end of the trial. If a patient was found to have vitamin D deficiency 3 months prior to the transplant and if a patient had been on weekly Ergocalciferol supplement, the patient will be eligible for this study and their vitamin D supplementation status will be considered as one of the randomization factor. Patient had prior Ergocalciferol supplement are randomized to either treatment or control group following the stratum 1 of the Randomization Scheme, Appendix F. Patients with no prior Ergocalciferol supplement are randomized according to the stratum 2 of the Randomization Scheme, Appendix F.

Sex hormones will be measured at the baseline (± 8 weeks) and the 12 months (± 8 weeks) (Testosterone or Estradiol, FSH and LH). Female patients who have documented laboratory values indicating postmenopausal state prior to the study entry will not be required to have new levels drawn. Female patients whose sex hormone levels showing menopausal state at baseline will not have repeat sex hormone study at the end of the trial. Serum for future research will also

be collected and banked at baseline and at 3, 6, 9, 12 months post transplant for measurements of cytokines and antibodies involved in the metabolism of the bone and the development of GVHD after the trial. Examples of future cytokine measurements may include: Osteoprotegrin (OPG), TNFa, Interleukin-6, GM-CSF, and IGF-1.

4. Incidence of fractures will be radiologically confirmed and compared between the two groups. Graft rate will be collected at 12 months for both groups and analyzed for statistical difference.

5. Data collection for the pharmaco-economic benefit model includes drug and administration costs via patient medical record databases and MDA Cost Accounting System.

Table 1: Summary of Treatment/study Plan

Assessments	1 month (21-45 days)	3 months	6 months	9 months	12 months
Medicine (IV)	x	x	x	x	
DEXA (bone mineral density)	x		x		x
Serum CTX	x	x	x		x
Routine lab : Ca, Mg, albumin, Cr, Alk phos	x	x	x	x	x
25 (OH)VitD, intact PTH, x					x
Sex Hormones Testosterone or Estradiol, FSH and LH (blinded and banked)	x				x
Serum collection for future x testing may include the following examples: Osteoprotegrin (OPG), TNFa, Interleukin-6, GM- CSF, IGF-1 (Banked)		x	x	x	x
Graft rate and Fracture rate					x

5.0 Statistical Consideration

This is a randomized phase III trial to determine whether the use of Ibandronate significantly decreases the amount of bone loss in patients with BMT, compared to those in the control group. Patients will be equally randomized to control or treatment groups at baseline. All transplant patients will receive oral calcium 500 mg and vitamin D 400 IU twice daily throughout the trial.

The primary endpoint is the percent reduction in bone mineral density (BMD) of the lumbar spine, femoral neck, and total hip measured at 12 month relative to baseline, which we denote here as Diff_BMD. Assuming that the mean Diff_BMD is 12% decrease in the control group and is 0.1% in the treatment (Ibandronate) group, a maximum of 120 patients (60 patients per group)

will be needed in order to have an 80% power to detect this difference at a two-sided significance level of 0.05, assuming a common standard deviation of 0.23. Assuming a drop-out rate of 40% for the patients due to mortality and relapse in the first year, a maximum of 200 patients will be enrolled into the study. The total accrual period will be 20 months, with 10 patients enrolled per month.

Two interim analyses are planned for the primary endpoint of the percent reduction in BMD between baseline and 12 months, when 40 and 80 patients have been accrued into the study and followed for one year, respectively. A Lan-DeMets spending function with O'Brian-Fleming stopping boundaries has been assumed. The two-sided Z-score cut-off values for rejecting the null hypothesis are ± 3.71 and ± 2.51 for the two interim looks, respectively.

The change of BMD between baseline and 12 months will be summarized by treatment and control groups. Data will be transformed as appropriate to satisfy the normality assumption. A two-sample t-test on the transformed data or Wilcoxon rank-sum test will be performed to compare the two groups in terms of percent change of BMD from baseline to 12 months.

The change of BMD between baseline and 6 months will also be summarized and the percent change in BMD over time will be plotted for all patients and by treatment group, respectively. A linear mixed-effect model will be fit for the data set to investigate if there is a treatment effect at different time points and if the pattern of BMD change over time differs between two groups. Similar analysis will also be performed for graft rate, serum C-telopeptide (CTX) measured over time, as well as for cytokines associated with bone loss. The incidence rate of fracture will be estimated for each arm and will be compared between the two arms using Fisher's exact test.

The change of BMD between baseline and 12 months will also be summarized for patients with and without additional steroid treatment for GVHD after allogeneic bone marrow transplant separately. Wilcoxon rank sum test will be used to assess the difference in BMD change between patients with and without prolonged steroid and other immunosuppressant use for the treatment of GVHD, either in all patients or by treatment group. A multiple linear model will be fit for the BMD at 12 months, adjusting for baseline BMD and using steroid doses in GVHD, treatment as well as steroid use in GVHD and treatment interaction as predictors.

We will summarize the change of BMD between baseline and 12 months by disease type (i.e., hematological malignancies vs. hematological disorders). Wilcoxon rank sum test will be used to assess the difference in BMD change between patients with hematological malignancies and those with hematological disorders. A multiple linear model will be fit for the BMD at 12 months, using baseline BMD, disease type, treatment arm, as well as the interaction between disease type and treatment as covariates. The fitted model will help us address the question whether or not the treatment effect is similar in these two disease types.

Based on already published data (9) on risk of skeletal-related events (SRE) with ibandronate, modeling will be conducted to determine cost-effectiveness ratio of cost per SRE avoided, with sensitivity analysis. Costs will include the potential cost of treating for SREs and the potential cost of treating adverse events due to i.v. Ibandronate. One-way sensitivity analysis varying the key assumption (SRE relative risk reduction rate from 0% to 50% in 5% intervals) over the base case will be conducted to determine if it might impact the cost-effectiveness ratio.

Incremental Cost Effectiveness Ratio (ICER):

1.
$$\frac{(\text{Cost}_{\text{treatment}} - \text{Cost}_{\text{control}})}{(\# \text{SREs}_{\text{treatment}} - \# \text{SREs}_{\text{control}})}$$
2.
$$\frac{(\text{Cost}_{\text{treatment}} - \text{Cost}_{\text{control}})}{(\text{Months free of SREs}_{\text{treatment}} - \text{Months free of SREs}_{\text{control}})}$$

TreeAge Pro 2007 by TreeAge Software Inc., will be utilized for the cost-effectiveness calculations. The analysis will compute per-patient costs and benefits for the 12 month study period, following an intent-to-treat approach, and produce a cost-effectiveness ratio. The primary outcomes are incremental cost per percent of reduction in BMD and incremental cost per patient within one or two SD of normal BMD.

Two Incremental Cost Effectiveness Ratios (ICER) will be calculated:

1.
$$\frac{(\text{Cost}_{\text{treatment}} - \text{Cost}_{\text{control}})}{(\% \text{BMD reduction}_{\text{treatment}} - \% \text{BMD reduction}_{\text{control}})}$$
2.
$$\frac{(\text{Cost}_{\text{treatment}} - \text{Cost}_{\text{control}})}{(\# \text{Patients with normal BMD}_{\text{treatment}} - \# \text{Patients with normal BMD}_{\text{control}})}$$

5.1 Data and Protocol Management

A standard procedure to ensure participant confidentiality will be established. Personal identification information will be kept confidential and will be available only to the PI and relevant study staff. The study database will also be kept confidential and will be password protected. The results of this study will be reported by group results only and no individual results will be reported.

5.2 Safety Monitoring

In addition, a safety monitoring rule will be implemented using the method of Thall, Simon and Estey (1995, 1996). We define the adverse event (AE) as “the percent reduction in BMD is greater than or equal to 15% from baseline to 6 months” and denote its probability as p. The trial will be stopped if, for any arm, there is more than 95% chance that p is greater than 30%, ie, stop the trial if $\text{Prob}(p > 20\% \mid \text{data}) > 0.95$. For each arm, assuming a beta (1, 1) prior and applying the above stopping rule when every 10 patients have been treated and evaluated after 1-year follow-up, the stopping boundaries are as follows: The trial will be stopped if for any one of the two arms, $[\# \text{ patients with AE}] / [\# \text{ patients evaluated at 6 months}] \geq 6/10, 10/20, 14/30, 17/40, 21/50, 24/60$.

Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. All patients will have dental screening for jaw osteonecrosis at baseline and every 6 months thereafter. Patients with recent tooth extraction and signs of incomplete healing and/or uncontrolled infection will be excluded. During the trial, any dental condition should be treated immediately but conservatively, avoiding any invasive surgical procedure.

5.3 Suspected Unexpected Serious Adverse Reactions (SUSAR) Reporting

All suspected Unexpected Serious Adverse Reaction (SUSAR) must be reported to Roche. Any adverse event that is both serious and unexpected (SUSAR), as defined in, and in accordance with the time frame indicated in 21 CFR Part 312. Adverse events will be deemed unexpected if not identified in the Safety Reference Document for **Compound®** (FDA approved Package Insert / Investigator's Brochure), and must be reported by the principal investigator to FDA and Roche by telephone or by fax. For **fatal or life-threatening SUSARs, principal investigator must notify FDA within 7 calendar days** of becoming aware of the event. The initial report must be followed by a completed FDA Form 3500A MedWatch Report faxed to FDA **within 15 calendar days** of becoming aware of the event. For Non-fatal/life-threatening SUSARs, principal investigator should notify FDA by fax using FDA Form 3500A MedWatch Report **within 15 calendar days** of becoming aware of the event. The completed FDA Form 3500 Medwatch Report should be simultaneously transmitted by fax **directly** to Roche Pharma Development Medical Safety Central Operations (PDMS-COps) using the Roche Supported Trials Safety Fax Cover Sheet. PDMS COps faxes receipt acknowledgement and MCN (Manufacture Control Number) to site. The responsible Institutional Review Board should be notified in accordance with Good Clinical Practice and all local laws and institutional regulations. If a SUSAR occurs within the context of a multi-center clinical trial, the principle investigator must provide a copy of the completed FDA Form 3500A to all participating investigators **within the timelines outlined above.** The MedWatch form can be accessed at: <http://www.accessdata.fda.gov/scripts/MedWatch/>.

Contact Information:

FDA:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)

Roche:

Pharma Development Medical Safety Central Operations (PDMS – COps)
Fax: 011-44-1707-373793

The principal investigator will provide Roche PDMS COps with subsequent follow-up information as soon as it becomes available using the Roche Supported Trials Safety Fax Cover Sheet. The coversheet must have the Manufacturer Control Number (MCN) associated with the SUSAR, provided by PDMS COps upon receipt of the FDA Form 3500A MedWatch Report, and ensure that the follow-up box is checked. Roche may conduct an independent assessment of the SUSAR(s) and in such circumstances the principal investigator and participating institution will provide any additional information required to complete the assessment.

5.4 Benefit

Bone marrow transplantation is performed with increasing frequency and success, with the majority of patients surviving for many years. In this context, bone loss is a common and serious

post-transplant complication. Bone loss, occurs early and most rapidly during the first three to six months after the transplantation, and is often more severe at the femoral neck. This study will address the issue of whether bisphosphonates given immediately following the transplant can prevent the early bone loss. Since bone loss is tightly correlated with the fracture risk, early prevention of bone loss potentially prevent the fracture later in patient's life.

We plan on presenting our findings at national and international meetings and publishing these in peer-reviewed journals. This work will contribute to the management of post-transplant bone loss and may facilitate other intervention studies to address such issues.

5.5 Home Care

Patients in treatment group receive Ibandronate once every three months. If the patient is unable to receive it at MD Anderson, the PI or PI designated personnel will contact the patient's home MD directly to have the infusion done in their office.

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