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ORIGINAL ARTICLE

Beneficial treatment with risedronate in long-term survivors after allogeneic stem cell transplantation for hematological malignancies

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Abstract In this prospective randomized study we evaluated the effect of risedronate, an aminobisphosphonate, on bone mass and turnover in patients who had undergone allogeneic stem cell transplant (SCT) for hematological malignancies. Thirty-four patients (18 females, 16 males, age 32 ± 10 years) with bone mineral density (BMD) ≤ -1.5 SD as a T-score at least 6 months after SCT were treated with calcium 1 g/day and vitamin D 800 IU/day and randomized to receive ($n = 17$, group 1) or not receive ($n = 17$, group 2) oral risedronate 5 mg/day. The duration of treatment was 12 months. After 6 months, lumbar BMD increased by $4.4 \pm 1.6\%$ in patients of group 1 and decreased by $4.3 \pm 1.5\%$ in those of group 2 ($P < 0.05$); at the femoral neck, BMD did not change significantly in patients of group 1 ($+1.2 \pm 1.2\%$), while it decreased in those of group 2 ($-4.3 \pm 2.1\%$; $P < 0.05$). After 12 months, lumbar BMD further increased ($+5.9 \pm 1.7\%$, $P < 0.05$), compared to baseline in group 1 and slightly increased ($+1.1 \pm 1.4\%$) in group 2. No further changes were observed at femoral neck in both groups. In conclusion, treatment with risedronate for 12 months increased BMD significantly at the lumbar spine and prevented further bone loss at the femoral neck in long-term survivors after allo-SCT.

Keywords Allogeneic stem cell transplant · DEXA · Osteocalcin · Osteoporosis · Risedronate

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Introduction

Osteoporosis is a relatively common and early complication after allogeneic stem cell transplantation (allo-SCT). The pathogenesis of bone loss related to allo-SCT is complex and still incompletely understood [1]. Major risk factors include myeloablative conditioning regimens, huge cytokine release at the time of transplant, long-lasting high-dose steroids and cyclosporin-A (CsA) therapy, reduced mobility and frequent gonadal failure [1, 2]. Additionally, altered kidney, liver and bowel function result in reduced intake and abnormal metabolism of calcium and vitamin D [1, 3]. Recently, post-transplant number and function of osteoblastic precursors within the stromal stem cell compartment were found to be severely and persistently deficient, suggesting that the inability to regenerate a normal osteogenic cell compartment may partly explain the severe bone damage after allogeneic SCT [4, 5, 6, 7].

Välimäki et al. [8] found that patients undergoing allo-SCT have bone loss at both the lumbar spine (5.7%) and femoral neck (6.1–8.6%) after the first 6 months from allo-SCT. In a larger case series, Stern et al. [9] found a significant BMD decrease at the lumbar spine and femoral neck even 3 months after SCT in users of hormone replacement therapy (HRT). BMD further decreased by 2.5% at total hip within 12 months [9]. Other studies in smaller cohorts have also described bone loss that was prevalent at the femoral neck within a few months after SCT [10, 11, 12, 13, 14]. A persistent

decrease in femoral BMD was confirmed in two cross-sectional studies evaluating BMD up to 13 years after SCT [4, 15].

The treatment of osteoporosis in allo-SCT patients has been poorly investigated. Calcium supplementation with or without calcitonin for 12 months did not prevent bone loss within the 1st year after SCT [8], while increase in lumbar BMD by 9% was found in 13 women treated for 1 year with HRT [16].

Bisphosphonates are currently employed in the treatment of postmenopausal osteoporosis with high success rates [17, 18, 19]. These compounds are also effective in patients with severe bone loss such as in endogenous or exogenous hypercortisolism [20, 21, 22]. Since steroids are widely used in hematological malignancies before and after SCT, bisphosphonates might be considered as the most indicated approach to treat osteoporosis in such patients. Risedronate is a bisphosphonate for oral administration approved in Italy for the prevention and treatment of osteoporosis and is reported to be well tolerated in long-term treatments [17, 20, 23, 24].

The aim of this open, prospective and randomized study was to investigate the effectiveness of a treatment with risedronate on bone metabolism in allo-SCT recipients.

Subjects and methods

Fifty-five consecutive patients who had undergone allo-SCT in our institution were evaluated for BMD at the lumbar spine, total hip and femoral neck, serum osteocalcin levels and urinary hydroxyproline excretion at least 6 months after SCT. Normal BMD values were present in 14 patients, while 41 (22 females and 19 males, aged 33 ± 9.5 years; range, 20–51) had a BMD T-score of at least -1 SD at one or more skeletal sites. In patients with osteoporosis affected by gastrointestinal graft vs. host disease (GVHD) ($n = 3$), i.v. treatment with zoledronic acid was initiated; they were thus not included in this study. Thirty-four patients (18 females and 16 males, aged 32 ± 10 years; range, 20–51) with a T-score < -1.5 SD at the lumbar spine and/or femoral neck were enrolled in this study. All of them had been successfully allo-transplanted with unmanipulated marrow from an HLA-identical sibling. Reasons for transplant included acute myeloid leukemia ($n = 14$), chronic myeloid leukemia ($n = 9$), acute lymphoblastic leukemia ($n = 7$) and Hodgkin's lymphoma ($n = 4$). All patients had been conditioned with the BU-CY2 regimen (busulphan 16 mg/kg and cyclophosphamide 120 mg/kg) and had received CsA (1 mg/kg per day by continuous i.v. infusion from day -1 to day $+20$ and then 8 mg/kg per day orally) plus short-course methotrexate as prophylaxis for GVHD. The median cumulative dose of steroids given to this cohort of patients prior to study entry was equivalent to 5.7 g/kg of prednisone (range 0.8–21.2) for 3–30 months. Eleven patients were continuing glucocorticoid therapy (1–2.5 mg /kg per day of prednisone equivalent) because of persistent chronic GVHD for 2–7 months during the study.

Thirty-four healthy subjects matched for gender, age and body mass index (BMI) were also studied as controls; for ethical reasons, they underwent a single biochemical and densitometric evaluation (Table 1). None of the controls received drugs interfering with bone metabolism. Informed consent was obtained from all patients in accordance with institutional guidelines, and the study design was made in accordance with the Helsinki II Declaration.

At study entry, bone metabolism, bone density and gonadal status was evaluated in all subjects, and BMI in kg/m^2 was calculated. None of the patients had received any previous treatment for osteopenia/osteoporosis. Then, the patients were randomized to receive treatment with risedronate 5 mg orally once daily at 7.30–8.00 a.m., at least 30 min before breakfast with at least 200 cc of water, calcium 1 g and vitamin D 800 IU once daily orally at 18.00–19.00 daily for 6 months ($n = 17$, group 1) or the same treatment with calcium and vitamin D without risedronate ($n = 17$, group 2). Randomization was performed according to the program at the website www.randomization.com; the randomization sequence was stored by one of the investigators (A.C.), who was not directly involved in the treatment or in the follow-up of the patients, and was inaccessible to the other investigators.

Table 1 Clinical, biochemical and densitometric characteristics of patients and controls at study entry. Values are expressed as means ± SD. *BMI* body mass index, *SCT* stem cell transplantation, *BMD* bone mineral density. Normal range: *Ca* 2.2–2.6, *P* 0.7–1.35, *ALP* 98–275 U/l, *creatinine* < 133 μmol/l; *albumin* 3.6–5.2 g/dl, *osteocalcin* 2–22 ng/ml, *iPTH* 10–75 ng/l; *hydroxyproline excretion* 60–190 μmol/m^2

	Patients ($n = 34$)	Controls ($n = 34$)	*P*
Gender (M/F)	16/18	16/18	NS
Age (years)	32.7 ± 10	32.8 ± 9.5	NS
BMI (kg/m^2)	25.6 ± 2.2	25.5 ± 2.4	NS
Time from SCT (months)	17.5 ± 7	–	
Calcium (mmol/l)	2.36 ± 0.13	2.34 ± 0.11	NS
Phosphorus (mmol/l)	1.08 ± 0.17	1.09 ± 0.18	NS
Alkaline phosphatase (U/l)	91 ± 32	88 ± 20	NS
Creatinine (μmol/l)	86 ± 8.6	80 ± 10	NS
Albumin (g/dl)	4.2 ± 0.36	4.3 ± 0.3	NS
Osteocalcin (ng/ml)	13.9 ± 4.3	15.9 ± 2.5	0.04
iPTH (ng/l)	39.7 ± 10.9	36.9 ± 10.7	NS
Urinary hydroxyproline excretion (μmol/l/m^2)	133.6 ± 32	122 ± 16	0.046
Urinary hydroxyproline/creatinine	9.14 ± 0.8	9.3 ± 0.7	NS
BMD at lumbar spine (g/cm^2)	0.88 ± 0.1	1.05 ± 0.08	< 0.001
T-score (SD)	-1.715 ± 1.0	-0.2 ± 0.93	< 0.001
BMD at total hip (g/cm^2)	0.82 ± 0.08	0.92 ± 0.1	< 0.001
T-score (SD)	-1.55 ± 0.78	0.05 ± 0.95	< 0.001
BMD at femoral neck (g/cm^2)	0.77 ± 0.1	0.92 ± 0.105	< 0.001
T-score (SD)	-1.53 ± 1.0	-0.1 ± 0.9	< 0.001

Gonadal status assessment

In all subjects at study entry serum FSH, LH and 17-β-estradiol/testosterone were measured in a single sample at 8.00 a.m. In the patients, but not in the controls, the evaluation was repeated after 6 months.

Bone metabolism assessment

In both patient groups, at study entry and after 3, 6 and 12 months, serum calcium, phosphorus, creatinine, alkaline phosphatase, intact PTH and osteocalcin values were determined in a single blood sample, and urinary calcium, phosphorus and hydroxyproline were assayed in the 24-h urinary collection. Blood samples were collected in the morning after a 12-h fast.

Bone density assessment

In both patient groups, bone density was determined by dual-energy X-ray absorptiometry (DEXA) simultaneously at two different skeletal sites, the lumbar spine (L1-L4), total hip and femoral

neck (FN), using Hologic QDR 1000 densitometer (Hologic, Inc., Waltham, Mass.). Individual BMD values were considered as g/cm^2 and T-score. BMD measurement has been performed at baseline and after 6 and 12–13 (median, 12.3) months of treatment. The changes are expressed as a percentage of the baseline value. Quality control was maintained by daily scanning of an anthropomorphic spine phantom. The coefficient of variation was 1.7% for the lumbar spine and 2.1% for the hip. The reference population adopted in this study was the international pooled sample provided by the manufacturer; their data did not differ significantly from those obtained on a local sample in a study performed when the device was set up [25].

Assays

All measurements were performed by commercially available kits: FSH and LH with radioimmunoassay (RIA, Biodata, Rimini), testosterone and estradiol using solid phase chemoluminescent enzyme immunoassay (DPC, Los Angeles, Calif.). Intact PTH and serum osteocalcin levels were measured by RIA (Nichols Institute Diagnostics, Calif.), the detection limit of the latter being 0.35 mg/l. Hydroxyproline excretion was measured with high pressure liquid chromatography. The blood chemistry profile, including levels of Ca, P, ALP, 24-h urinary Ca excretion and creatinine, was analyzed using a standard autoanalyzer.

Statistical analysis

Data are reported as mean ± SD. Statistical analysis was performed by the Student's *t* test for unpaired data for the intrergroup differences. Friedman's test was used to compare the variables within the same group. Linear regression was used to analyze the relationship between increments of bone density and baseline BMD expressed both as absolute values and Z-score. The significance was set at 5%.

Results

After randomization, both groups were similar in terms of age, time from transplant, BMI, gender (Table 2) and previous treatment history. All men had normal testosterone levels, although it was in the lower third of the normal range in five of them. On the other hand, all but one woman had had ovarian failure after SCT. Six female patients (three in each group) were not receiving HRT, while all other women were on standard HRT during the whole treatment period; the treatment had been started 6–10 months after SCT. Five patients in group 1 and six in group 2 continued corticosteroid treatment; all of them stopped the treatment during the study. Another patient in group 2 had steroid plus CsA treatment initiated at the 7th month because of GVHD exacerbation. Similar daily doses were used in both groups (Table 2). Cyclosporine A was continued in nine patients (four in group 1 and five in group 2). Steroids were used for 2–7 months (median, 3.6 and 4.1 months for groups 1 and 2, respectively) during the study, whereas treatment periods for CsA lasted 3–7.5 months (median, 4.6 and 4.9 months for groups 1 and 2, respectively).

Table 2 Variations after 12-month treatment. Group 1 received risedronate, calcium and vitamin D; group 2 only calcium and vitamin D. Values are expressed as means ± SD. No.: 15 and 16 patients completed 6-month treatment in group 1 and 2, respectively; [§]considered only in patients on treatment. Normal range: *Ca*2.2–2.6, *P* 0.7–1.35, *ALP*98–275 U/l, *creatinine* < 133 μmol/l; *albumin* 3.6–5.2 g/dl, *osteocalcin* 2–22 ng/ml, *iPTH* 10–75 ng/l; *hydroxyproline excretion* 60–190 μmol/m^2

	Group 1		Group 2	
	Basal	12-month #	Basal	12-month #
Evaluable number (M/F)	8/9	7/8	8/9	8/8
Age (years)	32.5 ± 10.2		33.2 ± 10.4	
Time since SCT (months)	17 ± 7		18 ± 6	
BMI (kg/m^2)	25.3 ± 2.3	25.15 ± 2.3	25.7 ± 2.2	25.55 ± 2.25
Patients continuing steroid treatment during the study	5	–	6	1
Average daily dose of corticosteroids (mg)[§]	45.6 ± 16	–	55.4 ± 12	12.5
Patients continuing cyclosporine A treatment	4		5	1
Cyclosporine A average daily dose (mg) [§]	119.2 ± 40	–	124 ± 36	50
Women on standard HRT	6/9	5/8	6/9	5/8
Calcium (mmol/l)	2.37 ± 0.12	2.39 ± 0.11	2.36 ± 0.13	2.4 ± 0.12
Phosphorus (mmol/l)	1.07 ± 0.16	1.06 ± 0.2	1.08 ± 0.17	1.07 ± 0.15
Alkaline phosphatase (U/l)	93 ± 25	96 ± 28	90 ± 33	93 ± 28
Creatinine (μmol/l)	86 ± 8.5	88 ± 8	87 ± 9	87.5 ± 9.5
Albumin (g/dl)	4.2 ± 0.4	4.2 ± 0.5	4.15 ± 0.35	4.2 ± 0.4
Osteocalcin (ng/ml)	14 ± 4.4	14.6 ± 5.2	13.9 ± 4.3	14.1 ± 4.1
iPTH (ng/l)	40 ± 10	38.5 ± 9	39.5 ± 11.2	38.4 ± 10.1
Urinary hydroxyproline excretion (μmol/l/m^2)	135 ± 31	113.3 ± 25*	132 ± 33.3	126 ± 34
Urinary hydroxyproline/creatinine	9.2 ± 0.8	8.8 ± 0.68	9.1 ± 0.76	9.0 ± 0.74
BMD at lumbar spine (g/cm^2)	0.88 ± 0.075	0.93 ± 0.092*	0.89 ± 0.09	0.864 ± 0.1[a]
T-score (SD)	−1.71 ± 0.85	−1.35 ± 0.9	−1.7 ± 1.0	−1.85 ± 0.95
BMD at total hip (g/cm^2)	0.842 ± 0.05	0.853 ± 0.06	0.84 ± 0.08	0.806 ± 0.09[*a]
T-score (SD)	−1.5 ± 0.62	−1.46 ± 0.6	−1.49 ± 0.7	−1.78 ± 0.89
BMD at femoral neck (g/cm^2)	0.77 ± 0.1	0.78 ± 0.1	0.78 ± 0.08	0.747 ± 0.087[*a]
T-score (SD)	−1.59 ± 1.0	−1.486 ± 0.9	−1.5 ± 0.65	−1.8 ± 0.8

*$P < 0.05$ vs. baseline; [a]$P < 0.05$ vs. group 1

Bone metabolism

Serum and urinary calcium, serum phosphorus, creatinine and alkaline phosphatase were normal in all patients both at study entry and during the follow-up (Table 2). At baseline, osteocalcin levels were lower ($P = 0.04$) and hydroxyproline excretion higher ($P = 0.046$) in patients than in controls. Urinary hydroxyproline excretion was similar in groups 1 and 2 at baseline, and decreased by $11.3 \pm 3.7\%$ after 3 months ($P = 0.042$) and by $16.8 \pm 3.8\%$ ($P = 0.025$) at 12 months in patients of group 1. Serum osteocalcin values were similar in groups 1 and 2 at baseline and after 3, 6 and 12 months, without any significant change during the study period (Table 2).

Bone mineral density

At study entry, BMD was significantly lower in patients than in controls at each skeletal site ($P < 0.001$; Table 1). After randomization, BMD was similar in groups 1 and 2 at all skeletal sites considered (Table 2). Osteoporosis (T-score < -2.5 SD) was found at the femoral neck in three patients of group 1 and three of group 2, while at the lumbar spine it was found in four patients of group 1 and two of group 2.

After 6 months, lumbar BMD increased by $4.4 \pm 1.6\%$ in patients of group 1 and decreased by $4.3 \pm 1.5\%$ in those of group 2 ($P < 0.05$); at the femoral neck, BMD did not change significantly in patients of group 1 ($+1.2 \pm 1.2\%$), while it decreased in those of group 2 ($-4.3 \pm 2.1\%$; $P < 0.05$). Similar findings were observed at total hip, no change in group 1 and BMD decrease (1.22 ± 1.1 vs. $-4.1 \pm 1.6\%$; $P < 0.05$) in group 2.

Between the 6th and the 12th months, lumbar BMD further increased slightly in both groups: in group 1 by $5.9 \pm 1.7\%$ of the baseline value ($P < 0.05$) and in group 2 by $1.1 \pm 1.4\%$, reaching $-3.1 \pm 1.4\%$ of the baseline value. At the femoral neck, BMD did not change significantly in patients of both groups between the 6th and the 12th months. However, the percentage of BMD change between the two groups was significantly different (1.3 ± 1.2 vs. $-4.2 \pm 2.0\%$ from the baseline; $P < 0.05$) at this skeletal site. Similar BMD behavior was observed at total hip (1.35 ± 1.1 vs. $-4.1 \pm 1.6\%$ of the baseline; $P < 0.05$; Table 2).

Densitometric values at baseline and after 6 and 12 months are shown in Fig. 1. The major increase in BMD at the lumbar spine occurred within the first 6 months of treatment, as the mean increase was 4.4%, then continued a slower rise. The percent increment of lumbar BMD during antiresorptive therapy was inversely correlated with baseline BMD values and Z-scores at the same site ($r = -0.71$, $P = 0.049$ and $r = -0.73$, $P = 0.043$, respectively).

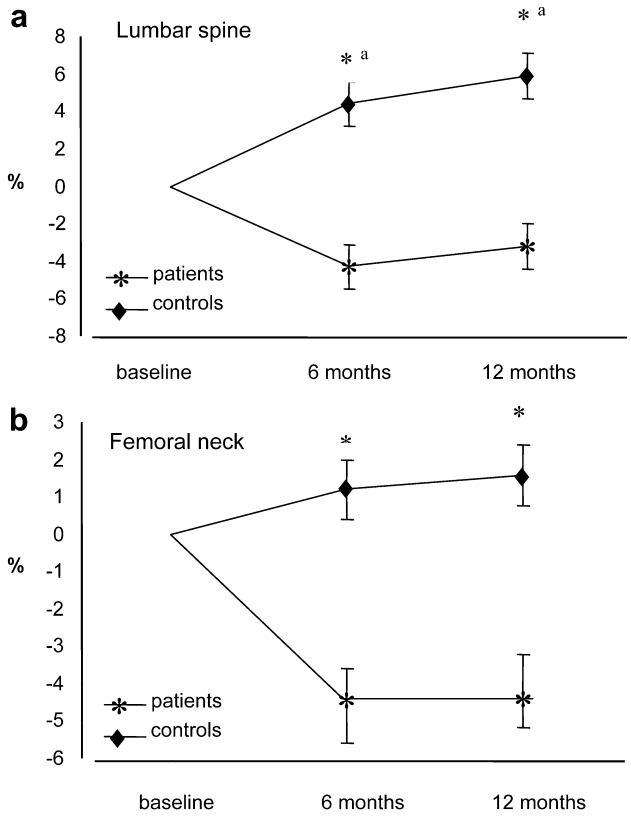

Fig. 1 Mean percent change of lumbar (**a**) and femoral (**b**) BMD in groups 1 and 2. Group 1 received risedronate 5 mg, calcium 1 g and vitamin D 800 U.I. daily, while group 2 was treated with calcium 1 g and vitamin D 800 U.I. daily. $^{*}P < 0.05$ vs. group 2; $^{a}P < 0.05$ vs. baseline

Tolerance to treatment

Two patients in group 1 and one patient in group 2 discontinued the treatment because of exacerbation of chronic gastrointestinal GVHD (one in each group) or of gastric intolerance. The treatment was withdrawn after 2–5 months in all three patients. Mild back pain and arthralgia occurred in three and four patients in group 1 and in two and three in group 2. Kidney function parameters did not change in any group over the study period (data not shown).

Discussion

This randomized prospective study demonstrates that oral administration of risedronate at the dose of 5 mg daily for 12 months significantly increased BMD (by 5.9%) at the lumbar spine and prevented bone loss at the femoral neck. Patients treated only by calcium and vitamin D supplementation lost approximately 4% of bone mass at the lumbar spine and femoral neck during the first 6 months, while between the 6th and 12th months of study they realized an increment of 1.3% at the lumbar spine. No significant change occurred at the femoral neck in the second 6-month period.

Nevertheless, changes in BMD at 6 and 12 months were significantly different between the two groups (treated by risedronate or supplementation only) at all skeletal sites.

These data confirm a previous observation of progressive bone loss up to 37 months after allo-SCT [4]. Nevertheless, both the initial BMD and subsequent bone loss in the group treated by calcium and vitamin D supplementation were similar at the lumbar spine and femoral neck during the first 6 months. These findings confirm those on insufficiency of standard prophylactic measures in the prevention of bone loss after allo-SCT [8, 26, 27]. In this respect, more effective therapeutic strategies may be necessary to prevent bone loss and treat osteoporosis in this particular patient population. It should be noted that the site of prevalent demineralization differs in our patient population compared to the findings of other groups, as the femoral neck has been the site of prevalent BMD decrease in previous studies [9, 15, 26]. In our cross-sectional study, only the patients evaluated at least 3 years after allo-SCT had a lower BMD at the femoral neck: we suggested that this finding is likely due to an improvement of lumbar BMD rather than continuous loss at the femoral neck [4]. In fact, lumbar BMD started to improve approximately 24 months after SCT in group 2. This is in agreement with a clinical observation that chronic GVHDs generally disappear, and immunosuppressive treatments are withdrawn 24–36 months after transplant. Differences in the populations enrolled in our and other studies can also be taken as partial explanation for the different sites of bone demineralization. In previous studies, hypogonadism was replaced early after SCT in all subjects, while six of our female patients were still hypogonadal because of contraindication to HRT or its refusal. To avoid adverse effects, we started HRT later (6–10 months after SCT) than previously described in other women, who received HRT as early as 60 days after SCT [9, 14, 15]. Moreover, 11 patients were on low-dose corticosteroid treatment for 2–7 months because of the persistent skin, ocular or liver cGVHDs that affect about 50% of allo-transplanted patients [28]. In this light, our observation is not surprising, as the lumbar spine represents an early principal target of bone damage induced by glucocorticoids and gonadal steroid decrease, given its prevalent trabecular structure. Additionally, the spine also represents a principal target of measurable bone mass improvement during antiresorptive treatments, sexual hormone replacement and general improvement of the patient's condition.

Increase in lumbar BMD was greater in our study than that described in menopausal and corticosteroid induced osteoporosis (CIO). Lumbar BMD increased by 3.5–4.5% after 12 months of treatment in postmenopausal women [29, 30, 31] and by approximately 2% in patients on chronic steroid treatment [22, 32, 33]. Patients with CIO were on steroid therapy when treated with risedronate. Conversely, all but one of our patients had withdrawn high-dose (>7.5 mg of prednisone equivalent daily) corticosteroid treatment during the study or shortly before enrollment. As an increase in lumbar BMD ranging from 14 to 80% [34, 35] has been shown within 48 months in patients cured of Cushing's syndrome, we can hypothesize that a part of the BMD improvement observed in both groups was due to steroid withdrawal. In our cohort, baseline lumbar BMD was inversely correlated with percent BMD increment after antiresorptive therapy, a finding also observed in patients with CIO [22] and suggesting that the worse the baseline bone density is, the greater the BMD improvement can be.

The lack of BMD increase at the femoral site during risedronate treatment can be related to the short course of treatment and to the small number of patients included in the active treatment arm. However, also no significant BMD increase at the femoral neck was shown in patients with CIO after 1 year of treatment with risedronate [22, 32]. Additionally, in postmenopausal women the increment of bone density at the femoral neck was lower than at the lumbar spine after treatment with risedronate [28, 29, 30].

Hydroxyproline excretion significantly decreased in group 1 after 3 and 6 months, indicating reduced bone resorption. Indeed, aminobisphosphonates act by inhibiting bone resorption [36], although the complete mechanism of action has not yet been clarified. At the tissue level, an increase in BMD has been attributed to decreased bone turnover due to reduced frequency and resorption depth of the bone remodeling units [37]. At the cellular level, bisphosphonates have been shown to have direct and indirect inhibitory effects on osteoclasts [38, 39] and to stimulate proliferation and maturation of human osteoblasts [40]. We did not find any significant increase in circulating osteocalcin in patients treated by risedronate. However, this marker of bone formation was lower in patients than in controls at study entry, likely mirroring a decrease in osteoblast number and function as previously reported in allogeneic SCT recipients [4, 5, 6, 7]. Studies investigating osteoblast number and function in allo-SCT recipients during bisphosphonate treatment may be useful in order to explain the rapid BMD increase. Studies evaluating peri-transplant administration of bisphosphonates in patients undergoing allo-SCT can be useful.

Aminobisphosponates are widely considered to be an effective treatment of post-menopausal and glucocorticoid-induced osteoporosis [17, 18, 20, 23, 29, 30, 31, 32, 33]; both conditions present after allo-SCT. Risedronate is likely to improve bone turnover very early, as shown in patients treated for corticosteroid-induced osteoporosis in whom the increase in lumbar BMD was significant even at 3 months [22].

The gonadal status is an independent risk factor for osteoporosis, but the prevalence of women with gonadal insufficiency was similar in each group. Because of the small number of cases included in this pilot study, these conditions were not considered separately. Furthermore, male patients were considered to have normal gonadal function, although five of them had testosterone values

in the low-normal range. We do not know what their testosterone values were before the onset of the underlying disease and if the eventual change in gonadal secretion had contributed to the bone loss.

Risedronate was well tolerated in our patients, and the number of patients who withdrew because of adverse effects possibly related to the drug (dyspepsia, gastralgia) was minimal (1/17). These data agree with the results of a previous meta-analysis, showing that daily treatment by 5 mg of risedronate was not associated with increased frequency of adverse gastrointestinal tract effects, even among patients at high risk for these events [24]. Back pain and arthralgia, reported also by other authors during the risedronate treatment [22], were mostly self-limited and did not lead to discontinuation of the treatment.

The study has two main limitations: the study design, open and not masked, and the duration of follow-up. In fact, 12 months can be considered a relatively short period to determine any relevant effect on BMD. Moreover, patients were not evaluated before the transplant to detect the amount of bone loss closely related to the transplant procedure. It should be stated that the current main aim of the treatment with biphosphonates is to decrease the fracture rate, the most disabling complication of osteoporosis. However, because of the small size of each treatment arm and relatively short follow-up period, the fracture rate was not determined in this study.

In conclusion, the results of this study show that bone loss in long-term survivors of allo-SCT can be stopped and even reversed by risedronate associated with calcium and vitamin D, while the administration of only calcium and vitamin D is ineffective until GVHD disappears and immunosuppressive treatments are withdrawn. Longer studies are needed to confirm these data and to investigate whether higher doses, different ways of bisphosphonate administration and/or more prolonged treatment time may improve the results.

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