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ORIGINAL ARTICLE

Treatment of osteoporosis after liver transplantation with ibandronate

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Summary

Osteoporosis is a major side-effect after liver transplantation (LTX). Therefore, the objective of the study was to evaluate the efficacy of ibandronate to reduce fractures after LTX. Seventy-four patients after LTX were included in the study and measurements of bone mineral density (BMD) of lumbar spine and proximal femur using dual energy X-ray absorptiometry (DEXA) were performed prior to and 3, 6, 12 and 24 months after surgery. The study group (IBA) consisted of 34 patients who received calcium (1 g/day), vitamin D3 (800–1000 IE/day) and ibandronate 2 mg every 3 months intravenously for 1 year. The control group consisted of 40 patients (CON) who received calcium and vitamin D3 at the same dosages. Prevalence of new fractures was predefined as primary endpoint. Changes of BMD and biochemical markers of bone metabolism were also investigated. In all patients, we found a reduction of BMD in the first few months after LTX. In the lumbar spine and the proximal femur the maximum reduction occurred 3 and 6 months post-LTX. One and 2 years after transplantation, the group receiving ibandronate demonstrated a better recovery from loss of BMD and a significantly lower prevalence of fractures (IBA 2 vs. CON 10 $P < 0.04$, χ^2). Ibandronate with calcium and vitamin D3 reduces the BMD-loss after LTX and decreases the rate of bone fractures significantly.

Introduction

The last 15 years have witnessed a steady improvement in graft and patient survival after undergoing liver transplantation (LTX), making the postoperative quality of life a concern with increased significance. Osteoporosis with its train of vertebral body and peripheral fractures features largely among the long-term side-effects of LTX and adds substantially to its financial and personal care burden.

Bone mineral density (BMD) studies have shown high rates of osteoporosis and osteopenia in liver disease [1,2]. Fracture rates up to 50% are noticed in liver transplant recipients [3]. Osteoporosis is not only the result of cholestatic disease [4,5]. Hepatitis B and C also as well as alcoholic cirrhosis are associated with osteopenia frequently [6,7]. Additionally immunosuppressive drugs (glucocorticoids, calcineurin inhibitors) are related to adverse effects on bone remodelling [8].

Decreased BMD and a resulting increase of fracture risk are long-term complications of almost all organ transplantations [4,9,10], although rates differ with the organ involved. Glucocorticoid-induced osteoporosis is a notable complication of LTX [11], potentiated by frequent pre-existing bone disease, especially following cholestatic liver failure [7,12]. Key pathogenetic factors in this regard may include imbalance of the osteoprotegerin (OPG), such as antiresorptive cytokine [13]/the receptor activator of nuclear factor kappa B (RANK)/RANK ligand (RANKL) system [14], as well as different cytokines [interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-12(IL-12), tumor necrosis factor α (TNF-α)] [15].

The aim of the present study was to evaluate the efficacy of ibandronate application (2 mg intravenously) in the prevention and treatment of post-transplantation-associated osteoporosis and related fractures.

Patients and methods

Between 1998 and 2004, 74 LTX patients (38 women, 36 men) between 19 and 70 years of age (mean: 51.7 ± 12.9 years) were included in a prospective study of osteoporosis prophylaxis. The participants were randomly divided (1:1) into two groups, the first being the ibandronate group and the second representing the control group. The ibandronate group (n = 34; 20 women, 14 men; mean age: 51.5 ± 14.0 years) received calcium 1 g/day per os (p.o.), vitamin D3 800–1000 IE/day p.o. and ibandronate 2 mg intravenously (i.v.) every 3 months for 1 year. The ibandronate infusion was injected on the day of LTX; the calcium and vitamin D3 administration was realized as the patients resumed oral feeding. The control group (n = 40; 12 women, 28 men; mean age: 50.9 ± 11.2 years) received calcium 1 g/day p.o. and vitamin D3 800–1000 IE/day p.o. only, also beginning when the oral feeding was possible. Informed consent was obtained of each patient before transplantation and during observation of the clinical course. Duration of post-operative immobilization was similar in both groups (data not shown). All patients received quadruple immunosuppression post-LTX with cyclosporin, corticosteroids, mycophenolate mofetil (MMF) and anti-thymocyte globulin (ATG) according to international standards. Cyclosporin was administered according to a therapeutic drug monitoring (TDM) schedule. MMF dosage was 500 mg twice a day. 500 mg prednisolone was administered intraoperativly followed by a reduction according to the body weight. To exclude non post-transplantation aetiologies of osteoporosis, the following exclusion criteria were strictly applied before transplantation: hyperparathyroidism, prior long-term steroid therapy (>6 months), renal impairment (creatinine clearance <60 ml/min, creatinine >300 μmol/l, hepatorenal syndrome), prior osteoporosis treatment, T-score > − 3 at lumbar spine and pre-existing osteoporotic fracture (biplanar lumbar and thoracic spinal X-rays).

All patients underwent bone densitometry pre- and 3, 6, 12 and 24 months post-LTX. Lumbar spine and femoral neck BMD was measured using the World Health Organization (WHO)-preferred method, dual energy X-ray absorptiometry (DEXA), on the same densitometer (QDR 4500, Hologic; http://www.hologic.com; quoted precision error 2.8 at 95% confidence interval). After a fracture occurred a symptomatic and orthopaedic treatment was initiated. All patients continued with the investigation. Laboratory parameters determined during the study included calcium, phosphate, osteocalcin, bone-specific alkaline phosphatase (BAP) and isoenzymes, 25-hydroxy-vitamin D, parathyroid hormone, and thyroid stimulating hormone (TSH) prior and 3, 6, 12 and 24 months after LTX. BAP and urinary excretion of pyridinoline and desoxypyridinoline were measured 24 months post-LTX for the retrospective assessment of osteoblast and osteoclast activity respectively.

Statistical analyses

Group sample size of 30 in both groups was found to achieve 71% power to detect a difference between the group proportions of −0.26. The significance level was targeted at 0.05. The significance level actually achieved by design was 0.047. The sample size was based on the estimated difference in the prevalence of fractures between two groups. Differences in the primary endpoint (fracture prevalence) were evaluated by chi-squared test. Changes in BMD and biochemical markers were analysed by using the Student's t-test or Wilcoxon test respectively, categorical variables were compared by the chi-squared test and/or one-way-ANOVA. Data are presented as median and/or means ± SD with regard to the statistical spread. The SPSS 15.0 for Windows statistics program (http://www.spss.com) was used for data analysis.

Results

Patient baseline characteristics

From 1998 to 2004, 182 patients were liver transplanted in our centre. Seventy-four patients were randomized to the study, considering the exclusion criteria (Table 1). Sixteen patients (seven of the IBA and nine of CON group) had to be excluded (death, noncompliance, rejection, renal impairment with a creatinine clearance <60 ml/min) within 24 months after LTX.

Focussing on the indications for LTX (Table 1), cholestatic disease [primary biliary cirrhosis (PBC), primary

Table 1. Baseline characteristics.

	IBA group, n = 34	CON group, n = 40	P-value
Female/Male	20/14	12/28	0.01
Age	51.5 ± 14.0	50.9 ± 11.2	0.84
Cholestatic liver diseases	5	2	0.04
Ethyl-toxic-liver diseases	15	12	0.19
Hepatitis B/C	5	9	0.19
Other liver diseases	9	17	0.01
T-score LWS	−1.76 ± 1.08	−1.20 ± 1.6	0.27
T-score Neck	−1.92 ± 1.12	−1.44 ± 1.28	0.22

sclerosing cholangitis (PSC)] was distributed predominantly in the ibandronate group, while alcoholic and hepatitic cirrhosis was distributed equally between the two groups. Thirty-four patients were assigned to the study (IBA) group and 40 patients (CON) to the control group. Both groups did differ significantly in some baseline characteristics. The gender distribution showed significantly more women in the IBA-group (IBA 58.8% vs. CON 30.0%; $P < 0.01$) and we noted a significant difference in the distribution of liver diseases (Table 1). The most common liver diseases were ethyl-toxic-liver disease (IBA 15 vs. CON 12; $P = 0.19$) followed by other liver diseases (haemochromatosis, hepatocellular carcinoma, Wilson's disease, autoimmune hepatitis, cryptogenic cirrhosis) IBA 9 vs. CON 17; $P = 0.01$, third, hepatitis B/C IBA 5 vs. CON 9; 0.19, cholestatic diseases were unequally arranged IBA 5 vs. CON 2 with statistical significance ($P = 0.04$). Both groups showed similar cumulative prednisolone doses (IBA 2776 mg vs. 2426 mg; $P = 0.82$) after 12 months.

The study group (IBA) demonstrated higher T-scores (lower BMD) than the control group at the lumbar spine (IBA −1.75 vs. CON −1.46; $P = 0.14$) and the neck (IBA−2.01 vs. CON −.54; $P = 0.53$) prior to transplantation (Table 2).

Lumbar spine

Both groups illustrated a clear impaired median T-score (IBA −1.75 vs. CON −1.46 $P = 0.28$) before transplantation (Figs 1 and 2). Three months after LTX, the bone mineral loss resumed for both groups (IBA −4.89% vs. CON −2.04%; $P = 0.54$). At 6 months the IBA group continued the reduction of bone mineral loss whereas the CON group nearly stopped (IBA −4.03% vs. CON −0.45%; $P = 0.51$). At 12 months postsurgery the groups changed significantly (IBA −0.23% vs. CON −3.19%; $P = 0.04$). At 24 months the IBA group registered an increase of +4.42% whereas the CON group listed a loss of BMD −1.80% (IBA +4.42% vs. CON −1.80%; $P = 0.13$).

Table 2. Changes of bone mineral density (BMD) during the course of investigation.

	Pre-LTX	3 months	6 months	12 months	24 months
LWS T-score					
Ibandronate	−1.75	−2.24	−1.86	−1.34	−1.82
Control	−1.46	−1.91	−1.72	−1.79	−2.61
P-value	0.27	0.97	0.55	0.50	0.44
LWS changes of BMD in (%) from baseline (g/cm^2)					
Ibandronate		−4.89	−4.03	−0.23	+4.42
Control		−2.04	−0.45	−3.19	−1.80
P-value		0.83	0.78	0.76	0.13
Neck T-score					
Ibandronate	−2.01	−2.24	−2.41	−1.94	−2.23
Control	−1.54	−1.98	−1.80	−1.63	−2.66
P-value	0.22	0.73	0.28	0.90	0.77
Neck changes of BMD in (%) from baseline (g/cm^2)					
Ibandronate		−8.21	−3.02	−2.21	+0.60
Control		−4.04	−4.61	−4.07	−3.89
P-value		0.11	0.95	0.24	0.33

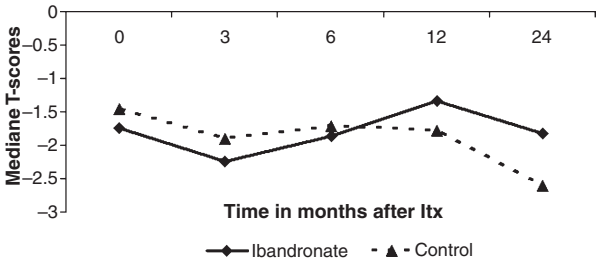

Figure 1 T-score at the lumbar spine.

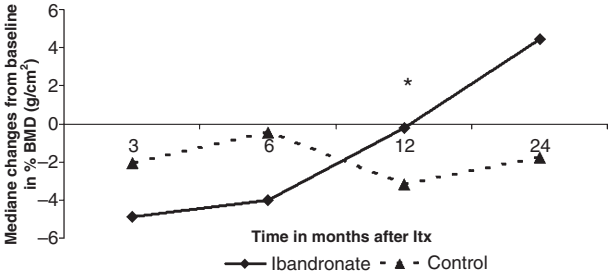

Figure 2 Median change of bone mineral density (BMD) from baseline pre-TX at the lumbar spine.

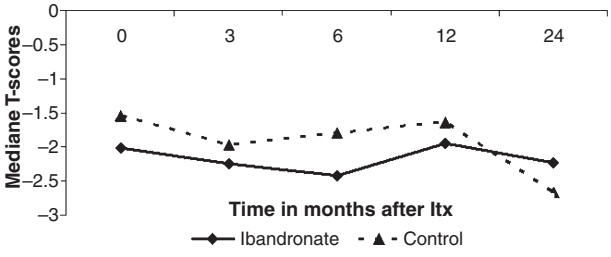

Figure 3 T-scores at the femoral neck.

Femoral neck

Pre-LTX BMD of the IBA group was slightly lower (−0.5 SD) compared with the control group (IBA −2.01 vs. −1.54; $P = 0.53$) (Figs 3 and 4). At 3 months both groups observed a high bone loss (IBA −8.21% vs. CON −4.04; $P = 0.99$). At 6 and 12 months the IBA group stabilized the BMD whereas the CON group stagnated (6 months IBA

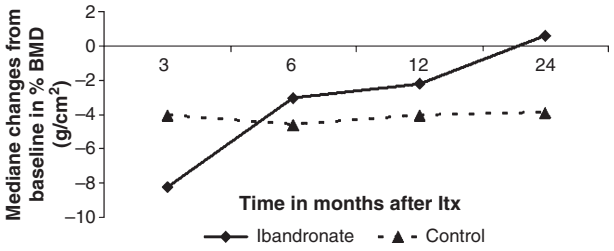

Figure 4 Median change of bone mineral density (BMD) from baseline pre-TX at the femoral neck.

−3.02% vs. −4.61; $P = 0.65$ 12 months IBA −2.21% vs. CON −4.07; $P = 0.17$). Up to the time of 24 months the IBA group continued the increase of BMD. The CON group did not show essential changes of BMD (24 months IBA +0.60% vs. CON −3.89; $P = 0.47$).

Fracture rates

The prevalence of clinical fractures up to 24 months post-LTX was 25.8% in the CON and 7.4% in the IBA group ($P = 0.04$) (Table 3). During the 24 months of investigation nine patients experienced 10 fractures. Two patients of the IBA group (one vertebral, one limb fracture) and seven patients of the CON group (one patient with two fractures extra- and vertebral). The extra-vertebral fractures consisted of limb, ribs and ankle fractures.

Bone-specific alkaline phosphatase/parathyroid hormone

The biochemical data are presented in Table 4. The biochemical markers did not display any significant difference in follow up. Only in case of bone-specific alkaline phosphatase (BAP), a trend could be noted after 3 months (IBA 1.03 ± 0.70 vs. CON 0.52 ± 0.35; $P = 0.053$). Within the parathyroid hormone level, a difference between IBA 68.86 ± 164.4 vs. CON 42.33 ± 31.32; $P = 0.08$ was documented pre-LTX.

Table 3. Fractures within 24 months post-transplantation.

	Ibandronate, *n* = 27	Control, *n* = 31	IBA + CON, *n* = 58	*P*-value
Total fractures	2 (7.4%)	8 (25.8%)	10 (17.2%)	<0.04
Peripheral fractures	1 (3.7%)	4 (12.9%)	5 (16.12%)	<0.17
Vertebral fractures	1 (3.7%)	4 (12.9%)	5 (16.12%)	<0.17

Discussion

Osteopenia or even osteoporosis was found in many patients prior to LTX particularly at the spine. This has also been observed in numerous studies [16,17]. Diverse studies suggest that bisphosphonates are the most promising drugs for post-transplantational bone loss therapy. In our study, we investigated the intravenous ibandronate (every 3 months) application after LTX as compared with a study population only treated with basic therapy (calcium, vitamin D). Our study illustrated the immediate post-LTX fall in BMD at all measured sites particularly with regard to the values 3 and 6 months post-LTX. This was also the case in the CON group after 12 and 24 months despite standard therapy. In the ibandronate group, BMD increased after 6 months, and continued to do so until it exceeded the pre-LTX baseline. The BMD increase continued successively from 6 months after LT up to 24 months in the IBA group at the lumbar spine and the femoral neck. Amazingly, the IBA group noted a higher BMD loss at the lumbar spine and the femoral neck in the first 3 and 6 months after transplantation. A possible reason could be the different structure of the groups with much more woman and patients with a worse bone status in the IBA group prior to LTX. Another theory could be that the worse bone status (lower T-score) was more dramatically degraded by the application of steroid drugs after LTX than patients with a less affected bone. There are few studies of BMD with the bisphosphonate ibandronate in liver transplant recipients [18]. Similar results of BMD are demonstrated by treatment with Zolendronic acid after orthotopic LTX by Bronwyn *et al.* [19]. As compared with earlier studies of Millonig *et al.* [16] and Pennisi *et al.* [20] who worked with Alendronic- and Pamidronic acid our study demon-

Table 4. Changes of bone-specific alkaline phosphatase (BAP) and parathyroid hormone (PTH).

	Pre-LTX	3 months	6 months	12 months	24 months
BAP					
Ibandronate	0.73 ± 0.42	1.03 ± 0.70	1.13 ± 0.63	0.71 ± 0.49	1.27 ± 0.27
Control	1.02 ± 0.55	0.52 ± 0.35	0.94 ± 0.78	1.51 ± 0.98	1.56 ± 0.70
PTH					
Ibandronate	68.86 ± 164.4	27.67 ± 11.3	37.33 ± 15.7	90.35 ± 102.6	
Control	42.33 ± 31.32	19.55 ± 1.2	54.00 ± 9.35	44.14 ± 24.70	

strated a better efficacy (ascent of BMD) at the spine, particularly, whereas the ascent at the femoral neck was achieved in a later period, after LTX at 24 months. Physical impairment features largely in post-LTX status and makes a satisfactory quality of life difficult to achieve [21]. Only in the last decade, attention has begun to focus on osteoporosis in organ transplant recipients [10,22–24]. They have shown that fracture rates are high after liver- and heart-TX and require appropriate and effective treatment. Calcium, vitamin D and exercise have only an adjuvant role in this regard [25]. Different studies have shown BMD as a weak predictor for the fracture risk [17,26–29]. Many studies recorded nonsignificant bone mineral loss but multiple fractures after LTX [16,17,30]. Our study emphasizes these results with nonsignificant bone loss but multiple fractures in the CON group.

In the course of investigation, we evaluated the incidence of the cumulative clinical fractures up to 24 months. We reported two fractures in the IBA and eight fractures in the CON group, which were significant ($P < 0.04$). Leidig-Bruckner *et al.* [22] showed that the highest rate (21%) for vertebral fractures in LTX recipients are seen during the second year after LTX whereas Ninkovic *et al.* [31] reported that the first 3 months are critical as the steroid dosages are at the highest at this time. Fracture rates were distinctly lower in the ibandronate group after 24 months. Particularly the vertebral fractures were reduced in the IBA group. All patients in this study, from its inception in 1998, received basic calcium and vitamin D therapy from the day of LTX even though such prophylaxis had yet to become standard in all centres, i.e. even the control group received medication in advance of its time. Without such prophylaxis, BMD loss in the control group would undoubtedly have been greater [32]. In the last years various trials illustrated that calcium and vitamin D supplementation alone did not prevent post-transplant bone loss [16,33,34]. Our study confirms that calcium and vitamin D_3 represent a useful but inadequate approach to the post-LTX stabilization of BMD. Despite the small sample size, this study reveals fracture rates and BMD profiles that underline the indication for postoperative bisphosphonate therapy in LTX recipients. Osteoporotic fractures cannot be adequately controlled by basic therapy alone. Ibandronate has proved to be more potent as antiresorptive drug than etidronate, clodronate, pamidronate and alendronate [35,36]. It increases BMD and decreases fracture risk [18,37]. Injection of 2 mg i.v. every 3 months ensures good patient compliance [38,39]. Nephrotoxicity is also minimal as compared with other amino-bisphosphonates [40].

Most patients studied have been women in whom postmenopausal oestrogen deficiency is clearly an additional risk factor. In our study, most of these patients were randomized to the ibandronate group (IBA 16 CON 10 women). This randomized gender distribution together with the higher frequency of cholestatic disease in the ibandronate group could have contributed to the baseline difference in BMD.

Dual-energy X-ray absorptiometry (DEXA) is the WHO-preferred method for determining BMD and informing the T-score classifications of osteopenia and osteoporosis. In addition, the earliest and most frequent fractures post-LTX in our study were vertebral, confirming earlier observations [31,41,42]. The fact that the sites at greatest risk of fracture are the spine and hip explains why DEXA is the method of choice for monitoring fracture risk.

Our study nevertheless has some limitations. In the course of investigation of BMD using DEXA X-rays of spine were performed at 12 and 24 months. CT scans were initiated only when the patient showed clinical symptoms (e.g. back pain). As many vertebral fractures are asymptomatic, the real fracture rate could be higher in both groups. The long period of recruitment as well as different concurrent drugs that had been administered to transplant recipients were unpredictable factors, which could have influenced the results on either side. At the beginning of the study, there were no guidelines for the investigation of bone resorption markers, particularly pyridinoline and desoxypyridinoline in follow up. At the launch of the study in 1998, crosslinks monitoring (pyridinoline, desoxypyridinoline) was yet to be recommended as a valid parameter of bone resorption [43]. They have since proved useful for monitoring bisphosphonate therapy [44,45]. In most cases in our study, pyridinoline and desoxypyridinoline were measured at 24 months post-LTX, and all values were within the reference range.

The most important laboratory parameters to monitor with respect to osteoporosis, bisphosphonate therapy and liver disease are calcium, phosphate, vitamin D status, parathormone, creatinine, BAP and osteocalcin. Assuming intact coupling, we expected the ibandronate group to show decreased parameters of bone formation through measurements of BAP and bone resorption [46]. In the control group, we expected normal bone formation and normal-to-increased bone resorption. We confirmed the decrease in bone formation in the ibandronate group at 12 months; however, we could not demonstrate decreased bone resorption after an average of 24 months. In assessing these parameters due allowance must be made for age, gender, race, incidental fractures, circadian rhythm and small sample size [47]. The basic calcium and vitamin D therapy in both groups may also have contributed to this result.

In conclusion, the main findings of this prospective, randomized study were that the therapy with ibandronate including the supplementation of calcium and vitamin D_3 is able to significantly reduce post-transplantation bone loss and osteoporosis-associated fractures. The early therapy of post-transplantation osteopathy is an important component of the post-LTX after-care and contributes to better mobility and quality of life of transplant recipients.

Authorship

DK: performed the study, collected and analysed data and wrote the paper. GL: contributed important measurements, analysed data and wrote the paper. GW: contributed important measurements. US: performed the study and collected data. MH: designed and performed the study, collected and analysed data.

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