Transplant International

LETTER TO THE EDITOR

Non-persistent effect of short-term bisphosphonate treatment in preventing fractures after liver transplantation

doi:10.1111/j.1432-2277.2009.00918.x

Bone disease is one of the most common complications after transplantation, affecting many transplant patients; some of them have recurrent fractures.

We recently showed that high-dose zoledronic acid (ZOL) prevents bone fractures after orthotopic liver transplantation (OLT) [1]. The anti-re-absorptive action of ZOL became evident after 6 months, resulting in a beneficial outcome on bone matrix mineralization [2]. Renal function was not affected by bisphosphonate therapy.

This study was carried out to determine whether a high-dose bisphosphonate treatment within the first 12 months exerted long-term beneficial effects on bone mineralization and turnover, preventing fractures. For this purpose, all subjects received conventional X-ray, bone mineral density (BMD) measurements and determination of serologic markers of bone turnover 3 years after transplantation. The long-term consequence of this treatment is yet to be investigated.

Baseline characteristics, cumulative steroid dose, creatinine values and liver function parameters did not differ significantly. A total of 96 patients underwent randomization (49 patients in the control (CON) group and 47 in the ZOL group) at the beginning of the trial and 29 patients were analysed in the CON and 28 in the ZOL group after 36 months of engraftment. The ZOL and CON groups did not differ significantly in major baseline characteristics (Table 1).

Three new fractures at 12 months after OLT occurred in the ZOL group (total numbers over 36 months: $n = 7$), these 'late' fractures were asymptomatic and detected by X-ray: no further fractures could be seen after 12 months in the CON group (total numbers over 36 months: $n = 11$). Two patients with 'late' fractures had a normal BMD after 12 months. The third patient had osteopenia at the lumbar spine after 1 year of transplantation. All fractures were vertebral fractures. No clinical sign or biochemical parameter could be detected to predict these late fractures. The preventive effect of bisphosphonate treatment after engraftment for fractures was not sustained from 12 months to 3 years ($P = 0.076$) (Fig. 1).

BMD of the femoral neck and lumbar spine increased significantly in both groups ($P < 0.001$) from the time of transplantation until the third year after OLT. The increase in BMD *t*-scores of the lumbar spine in the same time interval also reached statistical significance in both groups ($P = 0.006$). No statistically significant differences could be detected in BMD *t*-scores of the femoral neck in both groups 36 months after OLT ($P = 0.125$).

Osteoprotegerin, C-telopeptide, calcitonin, iPTH, osteocalcin and bone specific alkaline phosphatase were not significantly different at 12 and 36 months after OLT between both groups. Accordingly, adequate conversion of 25OH-VitD to bioactive 1,25 (OH)-VitD occurred within 12 months in both groups and continued to be sufficient in the following years. Serum calcium and phosphate levels were similar in both groups at every time point (Table 2).

One patient suffered from osteonecrosis of the jaw 25 months after OLT and 13 months after the last ZOL infusion.

CON-, but not ZOL, -treated patients lost bone mineral density at femoral neck in the first 6 months. From the sixth month onwards, femoral neck BMD increased in both groups, being statistically higher at 3 years than at 12 months. The BMD of the lumbar spine increased in the ZOL the CON group in the first 12 months without a statistically significant difference between the groups. After 1 year, the BMD of lumbar spine increased and was statistically higher at 3 years than that at 12 months. This effect is most likely driven by the fact that the corticosteroid doses are significantly higher early after transplantation than doses used for the maintenance of immunosuppression after the first year.

Millonig *et al.* [3] used a study protocol involving alendronate in combination with calcium/VitD to prevent bone loss after OLT. The study was not powered to assess fractures. In this trial, patients were stratified by BMD before transplantation and patients with osteopenia or osteoporosis received alendronate after OLT. Similar to like their results, we found that patients who received bisphosphonate did not experience significant bone loss in the lumbar spine in the early phase after OLT. We could even demonstrate a significant increase of BMD in femo-

Table 1. Patient baseline characteristics at 36 months post-OLT.

	CON	ZOL	*P* value
Female/Male	7/22	7/21	0.94
post-menopausal	3	2	0.54
Age	59 ± 8.9	56 ± 7.7	0.28
BMI (BW kg/m^2)	30.4 ± 3.2	30.1 ± 2.8	0.67
Indications for LT			
Viral	2	3	0.76
Alcoholic	13	15	0.41
Cholestatic	2	2	1.0
Hepatocellular Carcinoma	6	6	1.0
others	6	2	0.11
Femoral neck *z*-score*	−0.68 ± 0.89	−0.06 ± 0.86	0.11
Femoral neck *t*-score*	−1.16 ± 1.27	−0.77 ± 1.11	0.24
Lumbar spine *z*-score*	0.11 ± 1.41	0.41 ± 1.34	0.62
Lumbar spine *t*-score*	−0.52 ± 1.45	−0.08 ± 1.44	0.26

Data are presented as mean ± SD or as counts when appropriate (*t*-test, Fisher's exact test).
BMI, Body Mass Index kg/m^2.
*36 months post-liver transplantation data (bone mineral density: *Z*-score, *T*-score).

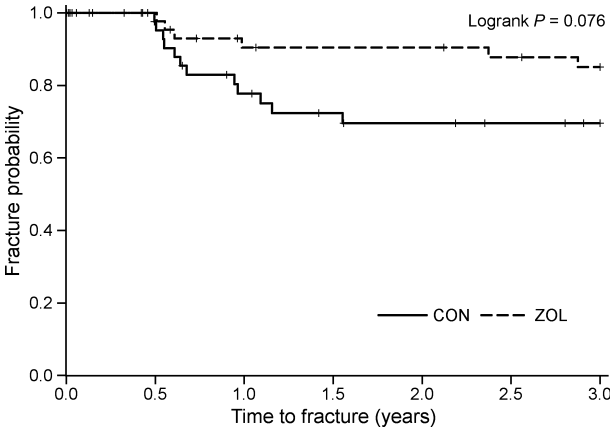

Figure 1 Primary study endpoint: fracture.

ral neck in the ZOL-treated patients. Many investigators have shown that bisphosphonate can prevent bone loss, but the trials were also not powered to assess fractures after transplantation [1,4–8]. It is not clear if bisphosphonates should be given before or only after OLT; also the dosages have not been defined, i.e., how often and how long this treatment should be administered.

As indicated by biochemical resolution of osteoclast inhibition after the first 12 months in the ZOL group, it may be worth investigating if longer-term bisphosphonate therapy exhibits additional beneficial effects on steroid minimization and on BMD in the long term, preventing fractures after transplantation. Because of the lack of published evidence, no clear recommendation currently exists on the use of bisphosphonates in the short and long term after liver transplantation. Bisphosphonates predominantly inhibit osteoclasts and, to a lesser extent, osteoblasts. The treatment with bisphosphonates should lead to a positive bone balance, despite the presence of low bone turnover before transplantation. Indeed, as shown in our previous trial, none of our study patients exhibited signs of adynamic bone disease or osteomalacia in the follow-up bone biopsy at 6 months [2].

Crawford *et al.* [5] recently showed that 1 year after liver transplant, bone loss can be prevented by ZOL at 3, 6 and 12 months. Long-term follow-up data on these patients are not available yet, although using hard end points such as fracture rates is also missing in this trial.

Zoledronic acid dosage of 2 mg should be set every 3 months after engraftment, because of the time when fractures after transplantation appear.

We have shown that a short-term benefit of high-dose bisphosphonate therapy did not result in persistent prevention of bone fractures in our liver transplant population. We recommend a less high bisphosphonate dose as we used in this trial, for over 2 years after engraftment.

Table 2. Biochemical bone markers.

	CON (*n* = 29)			ZOL (*n* = 28)		
Variable + (Normal range)	12 m	36 m	*P* value	12 m	36 m	*P* value
Osteoclast differentiation-inhibition						
Osteoprotegerin (4.0–6.0 pmol/l)	5.2 ± 2.1	6.4 ± 2.6	0.12	4.5 ± 2.1	5.2 ± 2.3	0.32
C-telopeptide (0.08–0.44 ng/ml)	1.8 ± 3.0	0.5 ± 2.9	0.06	0.4 ± 5.0	0.3 ± 2.6	0.46
Calcitonin (<8 pg/ml)	5.3 ± 3.9	5.7 ± 3.0	0.64	5.2 ± 4.5	5.4 ± 3.9	0.86
iPTH (15–65 pg/ml)	44.6 ± 22.1	59.8 ± 29.9	0.06	50.7 ± 24.5	73.7 ± 63.4	0.09
Vitamin D3 (25–66 pg/ml)	37.9 ± 16.6	34.5 ± 10.1	0.42	34.5 ± 13.3	37.6 ± 19.6	0.60
Osteoblast activity						
Osteocalcin (14–46 ng/ml)	47.3 ± 22.5	31.4 ± 21.9	0.02	25.4 ± 17.9	27.8 ± 16.8	0.66
Bone spec. al. phosph. (15–41 U/l)	30.5 ± 12.6	27.1 ± 11.4	0.33	17.8 ± 8.2	23.7 ± 7.5	0.01
Serum calcium (2.1–2.65 mmol/l)	2.3 ± 1.5	2.4 ± 1.4	0.17	2.3 ± 1.6	2.4 ± 1.3	0.10
Serum phosphate (0.8–1.6 mmol/l)	1.2 ± 0.2	1.1 ± 0.2	0.09	1.1 ± 0.3	1.1 ± 0.2	0.84

Data are median and range. *P* values between 12 and 36 months in each group (Wilcoxon signed-rank test).

Martin Bodingbauer,[1] Bita Pakrah,[2] Ivan Kristo,[1]
Julian Marschalek,[1] Christopher Burghuber,[1]
Georg Györi,[1] Alexander Kainz,[3]
Susanne Rasoul-Rockenschaub,[1]
Klaus Klaushofer,[4]
Ferdinand Muehlbacher[1] and Rainer Oberbauer[3]
1 Division of Transplantation,
Department of Surgery,
Medical University of Vienna, Austria
2 Department of Neurosurgery,
KA Rudolfstiftung,
Vienna, Austria
3 Department of Internal Medicine III,
Division of Nephrology,
Medical University of Vienna,
and KH Elisabethinen, Linz, Austria
4 Ludwig Boltzmann Institute of Osteology at Hanusch
Hospital of WGKK and AUVA Trauma Centre Meidling,
4th Medical Department Hanusch Hospital,
Vienna, Austria

References

1. Bodingbauer M, Wekerle T, Pakrah B, *et al.* Prophylactic bisphosphonate treatment prevents bone fractures after liver transplantation. *Am J Transplant* 2007; **7**: 1763.
2. Misof BM, Bodingbauer M, Roschger P, *et al.* Short-term effects of high-dose zoledronic acid treatment on bone mineralization density distribution after orthotopic liver transplantation. *Calcif Tissue Int* 2008; **83**: 167.
3. Millonig G, Graziadei IW, Eichler D, *et al.* Alendronate in combination with calcium and vitamin D prevents bone loss after orthotopic liver transplantation: a prospective single-center study. *Liver Transpl* 2005; **11**: 960.
4. Ebeling PR, Burr DB. Positive effects of intravenous zoledronic acid on bone remodeling and structure: are different effects on osteoblast activity to other oral bisphosphonates responsible? *J Bone Miner Res* 2008; **23**: 2.
5. Crawford BA, Kam C, Pavlovic J, *et al.* Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2006; **144**: 239.
6. Mitterbauer C, Schwarz C, Haas M, Oberbauer R. Effects of bisphosphonates on bone loss in the first year after renal transplantation – a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant* 2006; **21**: 2275.
7. Pennisi P, Trombetti A, Giostra E, Mentha G, Rizzoli R, Fiore CE. Pamidronate and osteoporosis prevention in liver transplant recipients. *Rheumatol Int* 2007; **27**: 251.
8. Reeves HL, Francis RM, Manas DM, Hudson M, Day CP. Intravenous bisphosphonate prevents symptomatic osteoporotic vertebral collapse in patients after liver transplantation. *Liver Transpl Surg* 1998; **4**: 404.

