Summary
Liver transplant is now well established in the management of chronic terminal hepatopathy. With the follow up of these patients, we are getting to know pathologies derived from their earlier diseases and those from the organ transplant, among which are those produced by the immunosuppression (cyclosporine, FK506, sirolimus, glucocorticoids) necessary for their treatment. Among these complications with affect the quality of life in these patients are osteoporosis and fractures, which can appear mainly in the first 6-12 months after transplant, but which can continue to a lesser extent in the following years. Vertebral fractures, and those of the ribs, are the most frequent, in 65% and 24% of patients, with negative prognostic factors such as age and primary biliary cirrhosis. So, it is a severe form of osteoporosis which is analysed in this work, and to which we bring our therapeutic experience. With antiresorptive drugs, positive results have been reported for the prevention and treatment of this bone loss.

Key words: Osteoporosis, Liver transplant, Biphosphonates, Steroids.
Introduction
In this review the factors which can influence the loss of bone mass after transplant, at least in patients with chronic hepatopathy, are outlined. The review goes on to study the factors which intervene in the post-transplant loss of bone mass and in the appearance of fractures. Finally we analyse the management of those patients at risk of post-transplant osteoporosis and review the current scientific evidence for antiresorptive treatment in this scenario.

Pre-transplant bone pathology
Loss of bone is a frequent complication of chronic hepatopathy, its prevalence being higher among those patients on the waiting list for a liver transplant, especially in cholestatic hepatopathy. There are multiple associated risk factors, among which are: hypogonadism, vitamin D deficiency, malabsorption, low weight, reduced physical activity, and in some cases, previous steroid treatment.

The last two decades have brought significant changes in the management of chronic hepatopathy, in immunosuppression regimes, in waiting times for liver transplants, and in the nutritional status of patients. Some authors have observed an improvement in lumbar bone mineral density (BMD) with pre-transplant T-scores increasing from -2.5 before 1990 to -1.7 after 1996.

Bone mass in the post-transplant period
After the transplant an accelerated loss of bone takes place in the first 3-6 months, increasing considerably the incidence of osteoporosis and osteopenia. A number of studies show that this early loss of bone is followed by a recuperation of bone metabolism which starts just a few months after the transplant. There are multiple associated risk factors, among which are: hypogonadism, vitamin D deficiency, malabsorption, low weight, reduced physical activity, and in some cases, previous steroid treatment.

The potential impact of the dose of GC as a determinant of the loss of bone is supported by the absence of bone loss in the lumbar and proximal femoral regions found in patients with renal transplants treated with low doses of steroids and tacrolimus. In addition, in the work of Martínez et al., the withdrawal of GC after the transplant accelerated the recuperation of lumbar BMD (Z-score -0.44 in the group with early withdrawal of prednisone vs Z-score of -0.99 in patients in whom treatment with prednisone was maintained; p< 0.05), without adverse effects on tolerance of the graft. On the other hand, the higher rates of fracture which are present after heart and lung transplants in which greater doses of steroids are used, would be consistent with the role which they play in the pathogenesis of post-transplant osteoporosis.

Factors implicated in the loss of bone mass

**Glucocorticoids**
Given that the early loss of bone mass has been observed in all transplants of solid organs, it has traditionally been assumed that the high doses of glucocorticoids (GC) necessary for immunosuppression played a principal role in this loss.

The potential impact of the dose of GC as a determinant of the loss of bone is supported by the absence of bone loss in the lumbar and proximal femoral regions found in patients with renal transplants treated with low doses of steroids and tacrolimus. In addition, in the work of Martínez et al., the withdrawal of GC after the transplant accelerated the recuperation of lumbar BMD (Z-score -0.44 in the group with early withdrawal of prednisone vs Z-score of -0.99 in patients in whom treatment with prednisone was maintained; p< 0.05), without adverse effects on tolerance of the graft. On the other hand, the higher rates of fracture which are present after heart and lung transplants in which greater doses of steroids are used, would be consistent with the role which they play in the pathogenesis of post-transplant osteoporosis.

In spite of the fact that few works have successfully shown an association between the cumulative dose of GC and the loss of bone mass in the post-transplant period, Guichelaar et al., confirmed this relationship by means of a histomorphometric analysis. In this work, the accumulated dose of steroids at one month and 4 months post-transplant, was positively correlated with the loss of bone volume, and inversely with the parameters of formation. In addition, this histomorphometric study indicated that the principal incident which drives the loss of bone mass happens very early in the post-transplant period and, probably, is found to be related to a reduction in bone formation. These findings are consistent with the known effect of steroids on the osteoblasts and on bone formation.

For the same reason, the transitory inhibition of the formation can play a key role in the loss of bone following transplants.

The same group, in a study or 33 patients with chronic cholestatic hepatopathy found that despite a decrease in BMD 4 months after transplant, biopsies of the iliac crest at 4 months showed histomorphometric improvement, increasing significantly the static and dynamic parameters from low levels at the moment of transplant to values in the range of normality 4 months after the transplant. At the same time, the measurements at four months of the parameters for bone resorption showed the same increase, but in a range similar to those values obtained immediately post-transplant. These histomorphometric findings indicate that despite the post-transplant loss of bone, at 4 months the bone metabolism had improved, with an increase in bone formation and a more closely matched balance of formation and resorption.

The current evidence, for the same reason, suggests that the loss of bone after liver transplant is caused by an initial increase in bone resorption, together with a decrease in formation. Later, the bone formation increases and may overtake the resorption. These changes could be consistent with the rapid decrease in BMD observed in the first months post-transplant, and the later recuperation towards baseline values, found in the majority of studies.

Other immunosuppressive drugs
The role played by other immunosuppressive drugs in the post-transplant loss of bone mass is not well known. Tacrolimus induces severe loss of trabecular bone in rats, although it seems to be less severe in humans. With respect to cyclospo-
Vitamin D

Numerous works in the literature found low levels of 25-OH vitamin D in hepatopathic patients. Although it has been suggested that the decreased levels of vitamin D in patients with hepatopathies might be due in part to a lower production of transport proteins (DBP and albumin)\textsuperscript{25,26}, to a change in the 25 hydroxylation of vitamin D\textsuperscript{27-29}, or to the malabsorption of liposoluble vitamins in cholestatic hepato-pathies\textsuperscript{30}, it seems that the lower levels of vitamin D in chronic hepato-pathies are related, with great probability, to a deficient supply of vitamin D due to environmental and dietary factors.

Some authors found that the levels of 25-OH vitamin D are independent predictors of the BMD in the hips of patients with cirrhosis\textsuperscript{31}. Crosbie et al. found a correlation between levels of 25-OH vitamin D at 3 months after liver transplant and an increase in BMD at 6 months, which suggests that the normalisation of levels of vitamin D can exert a positive effect on BMD\textsuperscript{32}.

Fractures in the post-transplant period

In patients receiving a liver transplant, the most frequent fractures are vertebral fractures. The following risk factors for fractures occurring after transplants have been identified: advanced age\textsuperscript{2}; pre-transplant vertebral fractures\textsuperscript{33}; chronic cholestatic hepato-pathies\textsuperscript{34}. Similarly to that which was the case with bone mass, few authors have found a relationship between the dose of glucocorticoids and the risk of fracture in patients receiving a liver transplant\textsuperscript{35}.

Guichelaar et al. studied, in 360 patients with chronic cholestatic hepatopathy between 1985 and 2001, the incidence and predictive variables of fractures (vertebral and non-vertebral) pre- and post-transplant, from the pre-transplant period, up to 8 years after\textsuperscript{36}. The accumulated incidence of fractures was 30% in the first year post-transplant and 46% at 8 years after the transplant. Differently from other studies, there was a similar incidence of vertebral and non-vertebral post-transplant fractures. The majority of fractures occurred in trabecular bone, with the spinal column and the ribs making up over 90% of the total fractures. The principal risk factors for the appearance of fractures post-transplant were the presence of fractures pre-transplant, a lower BMD, the dose of glucocorticoids post-transplant and primary biliary cirrhosis. Neither the loss of bone in the first 4 months post-transplant, nor the later bone gain were correlated with fractures.

The estimates of fragility-related fracture post-transplant varied widely according to the studies. In various works the percentages of fractures referred varied between 25-35%, mainly in the first 6 months after the transplant\textsuperscript{37,38,39}, while other authors found a lower rate of fractures (6-8%)\textsuperscript{40,41}. These differences in the incidence of fractures referred to in the different studies could be due to a number of factors: the selection of the patients, treatment with immunosuppressors, criteria used for the diagnosis of vertebral fractures. However, in general, the highest rates of fractures appear in the literature in the earlier works, while more recent works report lower rates. Compston found an incidence of 27% for vertebral fractures in the first three months after transplant in a study of 37 patients receiving a liver transplant between 1993 and 1995\textsuperscript{42}. In a later study of the same group carried out between 1995 and 1998 the incidence of fractures in the first year was only 5%\textsuperscript{43}. Between these studies there was a significant reduction in the dose and duration of treatment with glucocorticoids, although the use of cyclosporine and tacrolimus was hardly modified.

Thus, it appears that the natural history of post-transplant osteoporosis has been improving in the last few years. Other factors which might explain this apparent reduction on the frequency of osteoporotic post-transplant fractures as well as the reduction in the doses of glucocorticoids (and possibly the use of cyclosporine A, which has been substituted by other immunosuppressant drugs), could be that in some countries transplants nowadays take place at an earlier stage of hepatopathy, which diminishes the prevalence of pre-transplant bone pathology. In addition, the spectrum of hepato-pathies in which transplants are carried out has changed over the years. Thus, in Europe primary biliary cirrhosis represented 57% of the transplants in 1983, whilst in 1999 this was only 20%, with an increase in patients receiving transplants due to viral hepatitis (principally VHC) and alcoholic cirrhosis.
Evaluation of patients at risk of post-transplant osteoporosis

The adequate management of post-transplant bone pathology implies both the optimisation of bone health before transplant and the prevention of bone loss after transplant. In summary, the following paths of intervention are recommended.[36]

1. Pre-transplant period

Table 1 summarises the initial evaluation of a patient with chronic hepatopathy on the waiting list for a liver transplant. The following biochemical analyses are carried out: calcium, phosphorus, total and bone phosphatase, creatinine, calcidiol, PTH, TSH, proteinogram, total testosterone, bio-available testosterone and LH or oestradiol and FSH, as well as calcium in urine in 24 hours. Annual bone densitometry before transplant. Lateral X-ray of the dorsolumbar spinal column. Moderate physical exercise is recommended. The maintenance of a good nutritional state. Ensure an adequate intake of calcium (1500 mg/day) and vitamin D (400-800 UI/day) (ensure adequate blood levels of 25-OH vitamin D). Prevent hypercalcemia (if a patient who does not take loop diuretics has hypercalciuria, add 25 mg/day of hydrochlorothiazide). Treat hypogonadism if present and not contraindicated.

After a first evaluation, the follow up of the patient should be oriented around the results of the BMD, the existence or not, of fractures, as well as other associate risk factors.

2. Prevention of bone loss post-transplant

In general, for the prevention and treatment of post-transplant osteoporosis the use of bisphosphonates is recommended.[36] While there are contradictory data for both oral and intravenous bisphosphonates, many studies with favourable results for bisphosphonates were carried out without randomisation, without a control group and with a small number of patients, such that the beneficial effect can be attributed incorrectly to the treatment and is due to the general improvement in the state of the patient which takes place after the transplant.

Given the accelerate loss of bone mass which occurs immediately after transplant, many experts recommend preventative treatment for all patients receiving transplant of solid organs, independently of the BMD pre-transplant.[33,35-37] This approach is based on observational data which show an overlap in pre-transplant BMD values between patients who present post-transplant fracture and those who do not.[38] Another approach for the management of patients receiving transplants is to apply clinical guides used for the prevention of osteoporosis induced by glucocorticoids.

Preventive measures and antiresorptive treatment after liver transplant. Current evidence.

The studies around the efficacy of treatment with vitamin D in patients with cirrhosis have a number of shortcomings: lack of randomisation and control group, low numbers of patients, predominance of primary bilial cirrhosis, poor representation of viral hepatitis, absence of data on fractures.[38] Although the works published to date do not allow the conclusion to be drawn that treatment with vitamin D influences the progression of bone disease in patients with cirrhosis, almost all authors, including the American Association of Gastroenterology, recommend supplementation with calcium and vitamin D in this type of patient.[26,30] Supplementation with calcium and vitamin D is also recommended during the post-transplant period. Table 2 summarises characteristics and results of the main studies on which we are going to comment.

Hay et al. found that subcutaneous calcitonin (100 UI/day) was not successful in preventing bone loss or fractures in patients with primary bilial cirrhosis or primary schlerosing cholangitis receiving liver transplants.[29] In another work of Guichaar et al., in those with liver transplants histomorphometric analysis showed that calcitonin (n= 14 calcitonin, n= 19 control) was not effective, either directly (number of osteoclasts, area of erosion) or indirectly (trabecular thickness, number and separation) on the parameters for bone resorption.[30]

Valero et al.[41] studied the effects of calcitriol vs cyclical etidronate on the lumbar BMD in 40 patients with liver transplants. There was a significant increase in BMD in both groups, but greater in the group with etidronate.[42] Another study with cyclical etidronate, combined with alphacalcidol and calcium, carried out in 53 patients did not find prevention of bone loss in the lumbar or femoral region, although neither was there a control group.[17]

With respect to pamidronate, the results are contradictory. One non-randomised study found a positive effect in the reduction of vertebral fractures in 13 patients with liver transplants.[42] In Dodidou et al.[17] patients with liver transplants and 13 with heart transplants with high levels of loss of bone mass or osteoporotic fractures occurring in the first two years after the transplant received 30 mg/3 months of intravenous pamidronate over two years, along with 1000 mg of calcium and 1000 UI/day of vitamin D.[43] A historic control group of 58 patients treated with calcium and vitamin D was used. The BMD increased significantly in the lumbar spinal column and femoral neck among those patients treated, in spite of the fact that the treatment was not initiated immediately after the transplant. Another non-randomised study with pamidronate carried out by Pennisi et al. involved 85 patients receiving liver transplants. 47 of these patients, who presented with pre-transplant osteopenia or osteoporosis, received 30 mg of i.v. pamidronate every 3 months for one year after the transplant. The rest of the patients were used as the control group. A significant increase in BMD in the lumbar region was observed in patients treated with pamidronate as opposed to the control group. The BMD in the femoral neck reduced in both groups. The authors concluded that pamidronate appears to have a...
limited effect on trabecular bone without modifying the cortical structure of the femur. Ninkovic et al., in a controlled and randomised study in 99 patients with liver transplants, an i.v. infusion of 60 mg of pamidronate, administered preoperatively, had no significant effect on the loss of bone mass, or on the rate of fractures one year after the transplant. An unexpected finding of this study was the absence of loss of lumbar bone mass and the low rate of fractures (8%) in the non-treated patients, although there was significant loss of bone in the femoral neck, which pamidronate could also not prevent. In a recent multi-centred study by Monegal et al., with 79 patients, two infusions of 90 mg of i.v. pamidronate (in the first two weeks, and 3 months after liver transplant) prevented the loss of bone mass in the lumbar region during the first year. Pamidronate did not manage to reduce the loss of bone in the femoral neck or the incidence of post-transplant fractures.

With respect to the data on alendronate, Millonig et al. studied, for an average of 27.6 months, 136 patients who had received liver transplants. All the patients received 1000 mg of calcium and 400 UI of vitamin D. In addition, those who presented with osteopenia or osteoporosis took alendronate weekly. The BMD in the lumbar region and in the femoral neck increased in the patients with osteoporosis. Atamaz et al., in the first randomised study with a control group carried out with alendronate weekly, in 98 patients with liver transplants, during 24 months of follow up, observed that alendronate (70 mg weekly) significantly increased bone mass in the lumbar region, in the femoral neck and in the whole hip, as opposed to calcium (1000 mg) and calcitriol (0.5 μg), however it did not appear to exert a protective effect against fractures.

As far as zoledronate is concerned, in a study by Crawford, 62 patients with liver transplants were referred, randomly, to receive zoledronic acid (4 mg i.v.) or a placebo 7 days after transplant and at 3 and 9 months post-transplant. All the patients received 600 mg/day of calcium carbonate and 1000 UI/day of vitamin D. The group with zoledronic acid lost significantly less bone mass in the hip. In the lumbar region, the group with zoledronic acid lost less bone mass at three months, but the significant difference between the two groups had disappeared at 12 months. A notable finding of this study was the recuperation of the lumbar BMD at 6 months in the placebo group, which almost reached baseline levels after a transitory reduction at 3 months. At 12 months, the values of BMD superseded baseline levels in both the placebo group as well as in the group receiving zoledronate. This spontaneous improvement in BMD in the placebo group could be related to a general improvement in the state of those patients, mobility, muscle mass and nutrition, as a consequence of an improved liver function. In the same study, Crawford observed a higher loss of bone mass in the hip than in the lumbar region in the placebo group, reaching the nadir 6 months after the transplant with partial recuperation later. The patients who received treatment with zoledronate did not show loss of bone mass in the hip. In another study by Bolingbauer, the patients received treatment with 8 infusions of 4 mg of zoledronic acid i.v., over the first 12 months after their liver transplant (one infusion per month for the first 6 months, another at 9 months and another at 12 months), in addition to calcium carbonate (1000 mg/day) and vitamin D (800 UI/day). The main target of the study – fractures in the first 24 months after transplant – was found in 4 patients (8.5%) from the group with zoledronate (n=47), and in 11 patients (22.5%) in the control group (calcium + vitamin D) (n=49) (p<0.05). The densitometric parameters were significantly better in the femoral neck in the group with zoledronate only at 6 months, being similar in both groups later. In terms of the lumbar spinal column, no differences between the groups were found, neither at 6 nor at 12 months. The same group published a subsequent work, carried out with the same patients as in the earlier study in which they analysed through histomorphometry the parameters of distribution of the density of bone mineralization at the time of transplant. 39 patients were studied, 21 in the zoledronate group and 18 in the control group. Six months after the transplant, the treatment with 4 mg/month zoledronate i.v., showed a significant reduction in bone turnover compared with those patients treated with calcium and vitamin D (n=18) as well as a definite restoration in mineralization. This improvement in the bone-

<table>
<thead>
<tr>
<th>Initial pretransplant evaluation</th>
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<tbody>
<tr>
<td><strong>Biochemical determinations:</strong></td>
</tr>
<tr>
<td>- Calcium, phosphorus, total and bone alkaline phosphatase, creatinine, 25-OH vitamin D, PTH, TSH, proteinogram</td>
</tr>
<tr>
<td>- Total and bioavailable testosterone and LH/oes-tradiol and FSH</td>
</tr>
<tr>
<td>- Urinary calcium 24 h</td>
</tr>
<tr>
<td><strong>Lumbar and hip BMD annually</strong></td>
</tr>
<tr>
<td><strong>Lateral X-ray of dorsolumbar spinal column</strong></td>
</tr>
<tr>
<td><strong>Moderate physical exercise</strong></td>
</tr>
<tr>
<td><strong>Maintain good nutritional state and ensure adequa-te blood levels of 25-OH vitamin D</strong></td>
</tr>
<tr>
<td><strong>Prevent hypercalciuria</strong></td>
</tr>
<tr>
<td><strong>Treat hypogonadism if present and if there are no con-traindications</strong></td>
</tr>
<tr>
<td><strong>Initiate antiresorptive treatment according to BMD, fractures and other risk factors</strong></td>
</tr>
</tbody>
</table>
Table 2. Summary of main studies with biphosphonates in the liver transplant

<table>
<thead>
<tr>
<th>Biphosphonate</th>
<th>Design</th>
<th>Type of patients</th>
<th>Start treatment</th>
<th>Duration of treatment</th>
<th>Biphosphonate group</th>
<th>Control group</th>
<th>BMD</th>
<th>Fracture incidents*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Non-controlled</td>
<td>55±9 years</td>
<td>0-4 months postx</td>
<td>Average</td>
<td>ALN 70 mg/week v.o.</td>
<td>(patients without OP or op)</td>
<td>Increase in DMO CL in osteoporotics at 24 months (% not specified)</td>
<td>total 5.8%</td>
</tr>
<tr>
<td>Milonig, 2005 (46)</td>
<td>136</td>
<td>Non-controlled</td>
<td>Patients with OP or OP receive ALN</td>
<td>27.6 months</td>
<td>1000mg calcium/d</td>
<td>1000mg calcium/d</td>
<td>(not specified by group)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-randomised</td>
<td>OP 23.5%</td>
<td></td>
<td></td>
<td>400 UI vitD/d</td>
<td>400 UI vitD/d</td>
<td>OP 34%</td>
<td>8.7±4.8% vs 0.6±4.5% p&lt;0.05</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Controlled</td>
<td>45 ±10 years</td>
<td>First month postx</td>
<td>24 months</td>
<td>ALN T-score</td>
<td>ALN 3</td>
<td>CL 24 months</td>
<td>ALN 3</td>
</tr>
<tr>
<td>Atamaz, 2006 (47)</td>
<td>98</td>
<td>Randomised</td>
<td>ALN T-score</td>
<td></td>
<td>1000mg calcium/d</td>
<td>0.5mcg calcitriol/d</td>
<td>8.9±5.7% vs 1.4±4.9% p&lt;0.05</td>
<td>cont 11</td>
</tr>
<tr>
<td></td>
<td>Open</td>
<td>CL -1.6±0.9</td>
<td></td>
<td></td>
<td>0.5mcg calcitriol/d</td>
<td></td>
<td>n.s.</td>
<td>cont 2</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Controlled</td>
<td>52±11 años</td>
<td>prex-3 months postx</td>
<td>12 months</td>
<td>PM 60 mg i.v, Single dose</td>
<td>No treatment</td>
<td>No difference between Groups</td>
<td>PM 4</td>
</tr>
<tr>
<td>Ninkovic, 2002 (11)</td>
<td>99</td>
<td>randomised</td>
<td>OP 34%</td>
<td></td>
<td></td>
<td></td>
<td>CL (vs baseline)</td>
<td>PM 4</td>
</tr>
<tr>
<td></td>
<td>Open</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>with +1.9% p&lt;0.01</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Controlled</td>
<td>54±10 años</td>
<td>Not specified</td>
<td>12 months</td>
<td>PM 30 mg i.v/3 months</td>
<td>calcium 1000mg/d</td>
<td>CL T-score (vs baseline)</td>
<td>PM 1</td>
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<tr>
<td>Pennisi, 2006 (45)</td>
<td>85</td>
<td>Non-randomised</td>
<td>% not specified</td>
<td></td>
<td></td>
<td>Calcium 1000mg/d</td>
<td>PM +1.07</td>
<td>PM 1</td>
</tr>
<tr>
<td></td>
<td>(OP or op)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.01</td>
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Table 2. Summary of main studies with bisphosphonates in the liver transplant (cont.)

<table>
<thead>
<tr>
<th>Design</th>
<th>Type of patients</th>
<th>Start treatment</th>
<th>Duration of treatment</th>
<th>Biphosphonate group</th>
<th>Control group</th>
<th>BMD</th>
<th>Fracture incidents*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate</td>
<td>Monegal, 2008 (12)</td>
<td>controlled randomised Double blind multicentric</td>
<td>53±11 years PM 55%op con 51%OP 57%OP</td>
<td>2 weeks postx 12 months</td>
<td>PM 90 mg i.v. (2 weeks postx 3 months postx) calcium 1000mg/d 25OHD 16000 UI/15d</td>
<td>CL DMO vs baseline PM +2.9% p&lt;0.02 CF DMO vs baseline PM -3.2% con -3.1% p&lt;0.01</td>
<td>cont 3 n.s.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>CL DMO vs baseline PM +2.9% p&lt;0.02 CF DMO vs baseline PM -3.2% con -3.1% p&lt;0.01</td>
<td>PM 7 con 3 n.s.</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>CL DMO vs baseline PM +2.9% p&lt;0.02 CF DMO vs baseline PM -3.2% con -3.1% p&lt;0.01</td>
<td>PM 7 con 3 n.s.</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>Crawford, 2006 (37)</td>
<td>controlled randomised Double blind 2 centres</td>
<td>47±10 ZLN 52%OP 18%OP control 50%op 10%OP</td>
<td>1 week postx 12 months</td>
<td>ZLN 4 mg i.v. (1 week months 1,3,6,9) calcium 600 mg/d vit D 1000 U/d</td>
<td>calcium 600 mg/d vit D 1000 U/d</td>
<td>% change DMO ZOL-con CL n.s CF n.s FT +2.4% p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CL n.s CF n.s FT +2.4% p&lt;0.05</td>
<td>ZLN 2 cont 2 n.s.</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>CL n.s CF n.s FT +2.4% p&lt;0.05</td>
<td>ZLN 2 cont 2 n.s.</td>
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<tr>
<td>Zoledronate</td>
<td>Boedingbauer, 2007(48)</td>
<td>controlled randomised open</td>
<td>52±8 ZOL T-score CL -1.20 CF -1.23 cont T-score CL -1.12 CF -1.41</td>
<td>1 month postx 24 months</td>
<td>ZLN 4 mg i.v. (months postx 1.2,5,4,5,6,9,12) calcium 1000mg/d vit D 800 U/d</td>
<td>calcium 1000mg/d vit D 800 U/d</td>
<td>Objective 2° no difference between groups Objective 1°</td>
</tr>
</tbody>
</table>

BMD: bone mineral density; OP: osteoporosis; op: osteopenia; ALN: alendronate; PM: pamidronate; ZLN: zoledronate; con: control; CL: lumbar spinal column; CF: femoral neck; FT: femur total.
*vertebral and non-vertebral fractures due to fragility
’s micro-architectural properties may explain the beneficial effect of treatment with zoleodonate on the risk of fracture observed two years after the transplant, despite not achieving an improvement in the BMD with respect to the control group.

In conclusion, although the transplant of organs, in particular liver transplants, have contributed to resolving the vital problem of terminal chronic hepatopathies, the combination of the previous disease, and the intervention with immunosuppressive measures, can facilitate the development of an accentuated bone loss, which is going to impact on the future quality of life of these patients. At present we count on effective drugs for the prevention and treatment of this osteoporosis. New anti-osteoporotic drugs which stimulate bone mass, should be studied and trialed in this pathology. Finally, a better knowledge of the mechanisms by which immunosuppressors induce this bone loss is going to be important for its better prevention and etiopathogenic treatment.

Bibliography

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