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Strengthening the Bones in Primary Biliary Cirrhosis

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Hepatic osteodystrophy in the form of osteoporosis (i.e., low bone mass with microarchitectural disruption and skeletal fragility) resulting in an increased risk of fracture, particularly at the spine, hip, wrist, humerus, and pelvis is a well-known complication of primary biliary cirrhosis (PBC). Studies using dual-photon or dual-energy x-ray absorptiometry (DXA) had reported a prevalence of osteoporosis (i.e., t-score ≤ −2.5, that is, a value for bone mineral densitometry [BMD] 2.5 or more standard deviations below the young adult reference mean) in patients with PBC varying from 14% to 52%, with an additional 30% to 50% suffering from osteopenia (i.e., t-score between −1 and −2.5) [1–8]. The prevalence of osteoporosis among patients with PBC is significantly higher than in age- and sex-matched population [2,4,7,8], and thus BMD testing with DXA is recommended for all patients with PBC regardless of their age, sex and menopausal status. Studies had demonstrated that the prevalence of osteoporosis in PBC is higher in older postmenopausal women, and in those with lower body mass index, more advanced fibrosis on liver biopsy, and increasing severity and duration of PBC [2,4,7]. The prevalence of osteoporosis in PBC appears to be decreasing over time [9], likely related to improved treatment for PBC and the diagnosis of the liver disease made at earlier stages. Osteoporosis is usually a silent disease in patients with PBC until it is complicated by fractures – fractures that can occur following minimal trauma (fragility fractures or low-trauma fractures). Vertebral and nonvertebral fractures occur in 1 out of 4 or 5 patients with PBC [10]. When compared with the general population, the absolute increase in fracture risk in patients with PBC is moderately increased with an absolute excess fracture rate of 12.5 per 1000 person-years [11].

Prevention and treatment of osteoporosis in PBC consists of nondrug and drug or hormonal therapy. There are three components to the nondrug therapy of osteoporosis: diet (adequate intake of calories, calcium and vitamin D), exercise, and cessation of smoking. The above measures should be adopted universally in all patients with PBC, not only in postmenopausal women, to reduce bone loss. PBC patients with osteoporosis or at high risk for the disease should be considered for drug therapy. Particular attention should be paid to treating patients with a recent fracture, because they are at high risk for a second fracture. Patients with PBC with the highest risk of fracture are the ones most likely to benefit from drug therapy. Thus, selection of patients based upon fracture risk, as determined by a combination of both BMD and clinical risk factors, is desirable. The recommendations by the National Osteoporosis Foundation [12] to initiate drug therapy in those with hip or vertebral (clinical or asymptomatic) fractures apply to patients with PBC as it does the recommendation for drug therapy to those with a T-score ≤ −2.5 at the femoral neck, total hip or lumbar spine.

In patient with PBC with a T-score between −1.0 and −2.5 (osteopenia), the decision to initiate drug therapy is less clear, although this subgroup of patients most likely would

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benefit from drug therapy as well [10]. Guidelines from the National Osteoporosis Foundation [12] and the Endocrine Society [13] recommend drug therapy in postmenopausal women and men age 50 and older with osteopenia at the femoral neck, total hip or lumbar spine when there is a 10-year hip fracture probability ≥3% or a 10-year major osteoporosis related fracture probability ≥20% based on the World Health Organization (WHO) absolute fracture risk model or FRAX [14,15]. The Fracture Risk Assessment Tool (FRAX) was introduced by the WHO task force to estimate the 10-year probability of hip fracture and major osteoporotic fracture (hip, lumbar spine, proximal humerus, or forearm) for untreated patients between ages 40 and 90 years using easily obtainable clinical risk factors for fracture and femoral neck BMD (g/cm^2) using DXA [15]. However, the FRAX as a guide for drug therapy in osteopenic PBC patients has not been investigated.

A systematic review of 567 trials published between 2005 and 2011 confirmed the fracture prevention efficacy of multiple agents compared with placebo in the general population [16]. Bisphosphonates (alendronate, risedronate, zoledronic acid, ibandronate), denosumab, raloxifene, and teriparatide reduce the risk of vertebral fractures. Alendronate, risedronate, zoledronic acid, and denosumab reduce the risk of hip and other nonvertebral fractures. Unfortunately, data on efficacy and safety of these medications in patients with PBC are scarce or do not exist. In patients with PBC and osteoporosis, alendronate significantly improves bone density when compared to placebo and etidronate [17,18]. Other bisphosphonates had not been tested in patients with PBC until recently.

In this issue of Hepatology, Guanabens et al. report their results of a randomized trial comparing monthly ibandronate (150 mg) vs. weekly alendronate (70 mg) given orally for two years to patients with PBC and either osteoporosis, or with osteopenia plus a fragility fracture [19]. Forty-two patients were randomized but only 33 completed the two years of treatment. The primary end-point of the trial was adherence to treatment investigated by the Morisky-Green scale; at the end of the two-year treatment period adherence to treatment was significantly better with ibandronate than alendronate. In addition, at two years, BMD of lumbar spine increased significantly from baseline by 4.5% and 5.7% with alendronate and ibandronate, respectively. Although there was an increment in BMD of femoral neck and total hip from baseline with both bisphosphonates this increment was not statistically significant. The increment in bone mass in any of the three sites evaluated was not statistically different between the two groups. Several markers of bone turnover improved as well with both bisphosphonates. Both bisphosphonates were well tolerated and only one patient – in the alendronate group, developed a fracture.

The study is the first to evaluate ibandronate in PBC. The results are consistent with what has been reported in studies performed in the general population regarding the efficacy and safety of both bisphosphonates and the better compliance with ibandronate treatment given its once a month recommendation [16]. Unfortunately, the number of patients enrolled was too small and the study did not have power to detect a difference in efficacy between the two bisphosphonates. In addition, and as it has happened with every other treatment trial for osteoporosis in PBC, the duration of treatment and follow-up was too short to allow an assessment of the potential efficacy of these bisphosphonates in reducing the number of fractures in PBC. Knowing that there is an approximately twofold increase in risk of fractures for each standard deviation decrease in BMD [20], the increment in BMD achieved with both bisphosphonates would in theory reduce the risk of fractures; nevertheless, and as recognized by the authors, further larger studies with longer follow up are needed to determine the impact of bone mass increment with ibandronate in reducing the absolute fracture risk in PBC.

In summary, the study by Guanabens et al. has taken us a step further and provides the bases for further evaluation of ibandronate in the treatment of osteoporosis in PBC. Taken together the results of this clinical trial along with the extensive data on the safety and efficacy of ibandronate in the prevention of osteoporotic fractures in postmenopausal women from the general population, it seems tempting to recommend ibandronate as the first line therapy for osteoporosis in PBC.

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Abbreviations

PBC	primary biliary cirrhosis
DXA	dual-energy x-ray absorptiometry
BMD	bone mineral densitometry
FRAX	fracture risk assessment tool

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