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Efficacy and Safety of 3-Year Denosumab Therapy for Osteoporosis in Patients With Autoimmune Liver Diseases

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Osteoporosis is a major complication in patients with primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH). Denosumab, a fully human monoclonal antibody against the receptor activator of nuclear factor-dB ligand (RANKL), increases bone mineral density (BMD) by inhibiting development and activity of osteoclasts and decreasing bone resorption. We have already reported the efficacy and safety of short-term (1-year) denosumab therapy for osteoporosis in patients with PBC or AIH,[1] but the effect of long-term administration remains unknown. In this study, we aimed to clarify the efficacy and safety of long-term denosumab therapy for osteoporosis in patients with PBC or AIH.

Case Series

We enrolled 10 consecutive PBC (n = 6, 5; stage I or II, 1; stage IV) or AIH (n = 4) patients with osteoporosis who received subcutaneous denosumab treatment at a dose of 60 mg every 6 months for 36 months or more between November 2014 and September 2018, whose BMD at the lumbar spine by dual-energy X-ray absorptiometry was less than 2.5 SD below the mean of young adult population (expressed as a T score). All patients were postmenopausal women with a median age of 68.5 (range: 59-79) years who had not received bone resorption inhibitors. The PBC and AIH patients had been treated for more than 6 months with ursodeoxycholic acid (600 mg/day) and small doses of prednisolone (3 or 5 mg/day), respectively, without any signs of cholestasis or liver failure. All patients received supplementation with oral calcium (305 mg/day) and vitamin D (200 IU/day) in addition to these drugs.

The BMD (T score) gradually and significantly improved with denosumab treatment over 36 months (Fig. 1A). Serum tartrate-resistant acid phosphatase 5b (TRACP-5b) and alkaline phosphatase 3

Abbreviations: AIH, autoimmune hepatitis; ALP3, alkaline phosphatase 3; BMD, bone mineral density; PBC, primary biliary cholangitis; RANKL, receptor activator of nuclear factor-dB ligand; TRACP-5b, tartrate-resistant acid phosphatase 5b.

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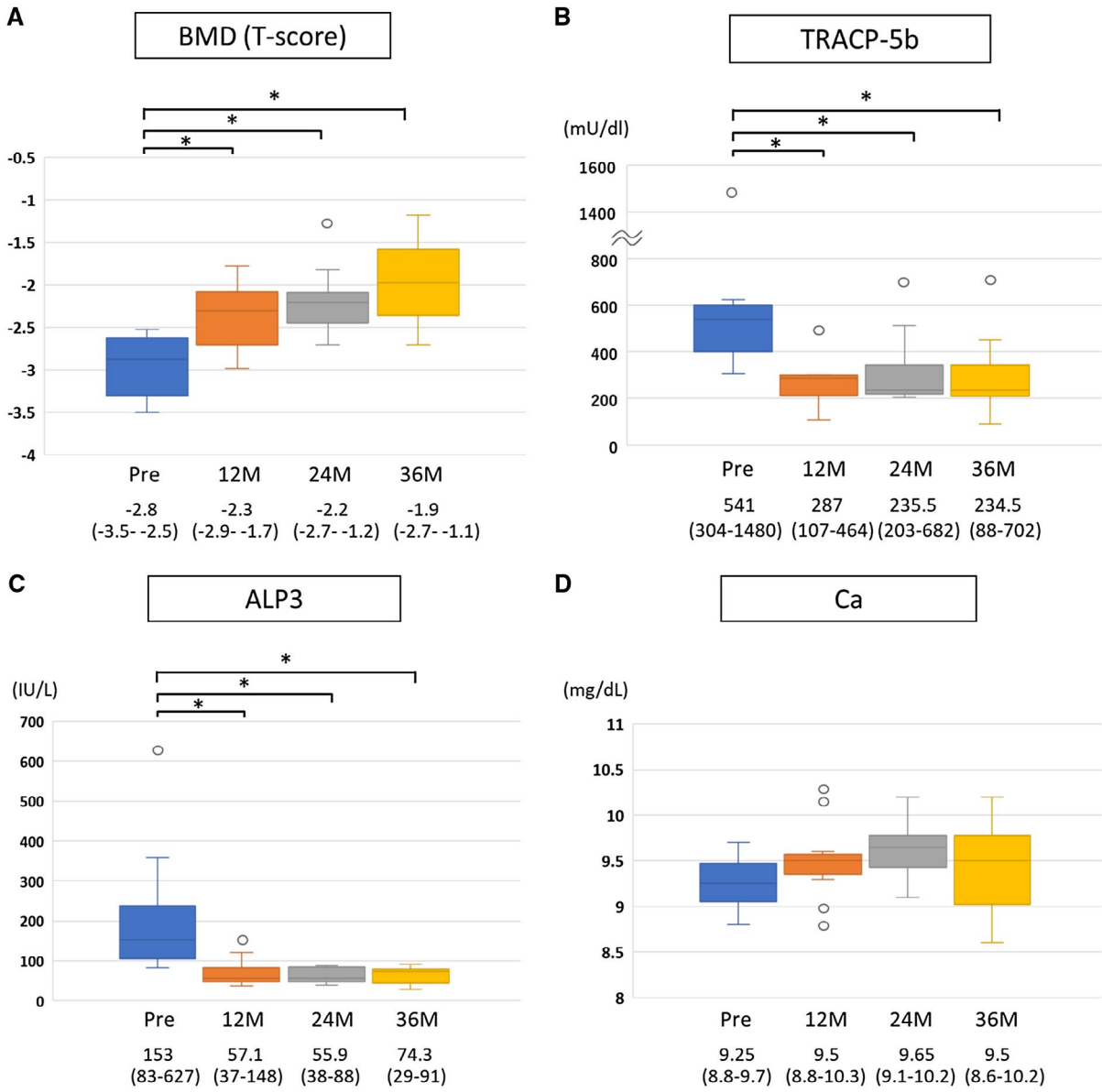

FIG. 1. Changes in (A) BMD (T score), (B) serum TRACP-5b, (C) ALP 3, and (D) calcium (Ca) levels before and 12, 24, and 36 months (M) after denosumab treatment. Data are presented as box-and-whisker plots and are expressed as a median with the interquartile range and maximum and minimum values. Dots represent outliers defined as values exceeding the 75th percentile plus 1.5 times the interquartile range. *$P < 0.01$ (Wilcoxon signed-rank test).

(ALP3, bone-related isozyme) levels were significantly reduced (Fig. 1B,C). In this study period, fresh vertebral fractures and denosumab-related adverse events including hypocalcemia, atypical femoral fractures, and osteonecrosis of the jaw were not observed (Fig. 1D).

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Discussion

This report shows the efficacy and safety of long-term denosumab therapy for osteoporosis in patients with autoimmune liver diseases. The BMD significantly increased after denosumab treatment compared with the baseline. The decline in serum level of TRACP-5b, a bone resorption marker, and ALP3 suggests the decrease in bone turnover by denosumab treatment.

PBC and AIH are refractory autoimmune liver diseases that predominantly occur in middle-aged women. PBC is associated with the development of osteoporosis—a relative risk of 2.79 for osteoporosis and an odds ratio of 1.86 for the development of bone fractures compared with non-PBC populations. The suggested mechanisms of increased risk of osteoporosis in PBC include impaired conversion to 25-OH vitamin D, releasing cytokines and deficiency of insulin-like growth factor-1.[2] Glucocorticoid induces RANKL expression, which leads to inappropriate bone remodeling with increase in osteoclastogenesis and decrease in osteoblastogenesis. Hence, the patients with AIH on maintenance corticosteroid therapy have a higher risk of osteoporosis and bone fractures.[3] Bisphosphonates are effective in preventing osteoporosis in patients with PBC or induced by glucocorticoid.[3,4]

Denosumab has different mechanisms of action and can be used as a first-line treatment or as an alternative to bisphosphonates. In postmenopausal women with osteoporosis previously treated with oral bisphosphonates, denosumab was well-tolerated and increased BMD at all measured skeletal sites and inhibited bone remodeling more effectively compared with once-yearly intravenous bisphosphonate therapy with zoledronic acid.[5] Furthermore, denosumab does not require dose adjustment according to the renal function, indicating superiority of denosumab to bisphosphonates.

In this pilot study, we showed that long-term denosumab therapy significantly increased BMD without any adverse effects in patients with autoimmune liver diseases. These results warrant a large-scale prospective study.

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