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MEETING REPORT

Osteoporosis Management: clinical highlights of ASBMR 2015

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Fracture Risk Assessment

A new concept with clinical relevance emerged in this congress: risk of imminent fracture, or the probability of suffering a fragility fracture within 12–24 months following medical evaluation. A retrospective cohort study (Abstract #1066) from a large American database of more than 1.3 M individuals older than 50 years showed that the risk for imminent fracture was significantly associated with recent falls (odds ratio (OR) 6.67), use of psychoactive medications (OR for narcotics 2.11 and for selective serotonin reuptake inhibitor 1.47), age per every additional decade (OR 2.00), wheelchair use (OR 1.79), Charlson Index >4 (OR 1.46) or above 3 (OR 1.40), mobility impairment (OR 1.46), central nervous system disease (OR 1.41) and use of muscle relaxants (OR 1.40). A second paper (Abstract#LB-SA0032) showed that in the first year after a major osteoporotic fracture the OR of a subsequent fracture is 2.9 (95% confidence interval (CI): 2.5–3.3). This increase in risk remains up to 10 years (risk ratio 1.8 (95% CI: 1.5–2.3). Overall, individuals at risk for imminent fracture might benefit from prompt treatment to minimize this increased risk.

A national observational study in Denmark (Abstract #LB-SA0034) showed that long-term treatment with alendronate (10 or more doses per year) was associated with a significant 25% reduction in the risk for hip fracture but, importantly, with no significant risk for subthrochanteric/femoral shaft fracture (OR 0.70, 95% CI 0.44–1.11).

Elderly men with type 2 diabetes mellitus do not have increased risk for either prevalent or incident vertebral fracture (Abstract #1067). In elderly men with chronic kidney disease, FRAX underestimates the risk for hip fracture (Abstract #1138). Furthermore, common medical conditions such as end-stage renal disease, Parkinson's disease, HIV infection, recent stroke, type 1 diabetes and heart failure are associated with an increased risk for hip fracture and deserve assessment and intervention (Abstract #LB-MO0024). The use of reference point indentation improves the fracture risk assessment at the femoral neck both as an independent predictor (area under the curve (AUC)=0.88–0.93) and further when combined with bone mineral density (BMD) and FRAX (AUC=0.95–0.99). Finally, a meta-regression analysis of a number of drug trials shows that DXA hip BMD strongly predicts hip fracture risk reduction with appropriate treatment, suggesting that this can be a valid surrogate marker of efficacy as well as a potential treatment target (Abstract #1145).

Treatment of Osteoporosis

Bisphosphonates are the standard of care in osteoporosis for their long record of use and low cost. New data from the FIT (Alendronate) and HORIZON-PFT (Zoledronic acid) studies were presented, based on an individual *post hoc* analysis showing that these drugs reduce the risk for fracture in patients with type 2 diabetes (Abstract #1141). Moreover, in an observational 8-year study, bisphosphonates prescribed to patients after a fragility fracture were associated with lower risk for subsequent fragility fracture (HR=0.59) and mortality (HR=0.79), after adjusting for baseline characteristics (Abstract #LB-1153).

Vitamin D is a must for the treatment regimens in osteoporosis. A genome-wide association studies analysis from the SUNLIGHT Consortium in 34 915 Caucasian men and women detected an interaction between single-nucleotide variants and vitamin D intake in the achieved levels of the hormone (Abstract #1088). Supplementation of vitamin D during pregnancy in winter months increases newborn bone mass (Abstract #FR0052). A randomized clinical trial assessed different regimens of vitamin D supplementation in postmenopausal women, concluding that 20 ng ml^{-1} of 25 (OH) D is the desirable goal; higher values (above 30 ng ml^{-1}) increased calcium absorption but did not affect BMD (Abstract #1090). Another randomized trial (Abstract #1091) demonstrated that high-dose vitamin D supplementation does not improve insulin resistance indices in elderly overweight subjects.

Denosumab, the anti-RANKL antibody, is approved and used in clinics. Analysis of biopsies taken in the pivotal FREEDOM trial (Abstract #1054) showed an increase in matrix mineralization with reduced tissue heterogeneity, as could be predicted from their potent antiresorptive action. If the drug is used after teriparatide, denosumab increases cortical volumetric BMD and thickness, whereas if teriparatide is administered

after denosumab the effect is the opposite, perhaps because fresh undermineralized bone interferes with the measurements. However, the greatest increases in peripheral cortical bone measurements are obtained by combining both drugs (Abstract #1055), suggesting a very potent regime for treating severe osteoporosis.

From the 10-year extension of the FREEDOM trial, two new sets of data have emerged, showing a relationship between total hip T-score after 8 years and the degree of nonvertebral fracture risk reduction (Abstract #1146), which suggests BMD as a practical target for treatment, at least when denosumab is used, and second, a continuous increase in BMD over 10 years with low fracture incidence (Abstract #LB-1157).

Additional results on abaloparatide, a PTHrP analog with osteoanabolic effects, were presented from the ACTIVE pivotal trial (Abstract #1053). The main results were previously reported at the Endocrine Society meeting earlier this year; here, the effect on major osteoporotic fractures was analyzed. After 18 months of treatment, the authors reported a significant BMD increase in the spine and hip, with a 67% (HR=0.33, 95% CI: 0.16, 0.68) reduction in the incidence of major osteoporotic fractures, compared with the placebo group. Something new in this analysis is that fractures of the upper arm, forearm (including wrist), hip, shoulder and/or vertebral spine (spine and/or tailbone) were included as 'major fractures'. Surprisingly, the teriparatide arm showed no significant differences vs placebo.

Odanacatib, a cathepsin K inhibitor that has completed the phase 3 trial, has positive effects on bone density assessed by QCT, reflected in a significant improvement in bone strength at the spine and the hip by finite-element analysis (Abstract #1056). Moreover, in a subgroup analysis of the pivotal LOFT trial, the effect on fracture incidence (new and worsening vertebral, hip and non-hip) in postmenopausal women was consistent among predefined groups by the presence/absence of vertebral fractures at baseline, age above or below 70, or bisphosphonates tolerance (Abstract #1144).

Sclerostin antibody romosozumab, a potent anabolic agent currently in phase 3 trial, increases bone strength at the spine and hip in postmenopausal women assessed by finite-element analysis in postmenopausal women participating in the phase 2 study (Abstract #1143), and this effect was superior to teriparatide treatment. Two preclinical papers with clinical relevance assessed the positive effect of the drug on bone mass and strength in cynomolgus monkeys (Abstract #1019) and in a mouse model of osteogenesis imperfecta caused by Wnt1 mutation (Abstract #1018).

Other Musculoskeletal Problems

Osteoarthritis and chronic back pain are predictors of falls in postmenopausal women (Abstract #1007). A new method has been developed for assessing articular damage in osteoarthritis using joint space width and fractal analysis of the subchondral bone texture (Abstract #1009). Finally, an experimental drug, atsttritin, an engineering protein derived from progranulin growth factor, displays potent anti-inflammatory effect and prevents progression of the disease by local injection in a murine model (Abstract #LB-SU0006).

According to the results of the PRISM-EZ trial, bisphosphonate treatment of Paget disease of bone should be directed to controlling clinical symptoms and not to the normalization of alkaline phosphatase levels within normal range, which increases the risk for fracture and need for orthopedic procedures (Abstract #1069). A new option, an oral PTH (1–34), has been tested for the treatment of hypoparathyroidism (Abstract #LB-SU).

Sarcopenia is a common condition in frail patients and is associated with increased mortality (Abstract #1142) and predicts fracture risk in healthy 65-year-old community dwellers (Abstract #1115). A better grip strength is associated with increased cortical thickness (Abstract #1114), and treatment with vitamin K1 has shown positive effects on body balance and the ability of muscular use (Abstract #FR310).

Rare Diseases

In adults with X-linked hypophosphatemia, treatment prevents dentition problems but not enthesopathy (Abstract #1070). Asfotase alfa is effective and well tolerated in a 5-year treatment regime in children with hypophosphatasia (Abstract #1074). In a cohort of 372 patients with fibrous dysplasia (Abstract #1074), the polyostotic form was the only independent predictor of fragility fracture. Vorositide, a C-type natriuretic peptide in subcutaneous injection, was safe, effective and well tolerated in a phase 2 treatment trial in children with achondroplasia and open growth plates (Abstract #LB-1154). For autosomal dominant hypocalcemia, the rare form of hypoparathyroidism, the calcilytic NPSP795 increased PTH levels while maintaining fasting calcium levels (Abstract #LB-SA0002). Finally, zoledronic acid showed beneficial effects in the bone lesions of three children with langerhans cell histiocytosis (Abstract #LB-SA0010).

Miscellaneous

Black tea consumption is associated with a decreased risk for osteoporotic fracture including the hip (Abstract #FR0309). The FGF-inhibitor NVP-BGJ398 has anti-tumor effects and controls tumor-induced osteomalacia in malignant mesenchymal tumors (Abstract #LB-SA0035). Finally, older home-dwelling men with low sclerostin and high DKK1 levels showed a fivefold increase in cardiovascular risk compared with the opposite combination (Abstract #LB-SU0029).

Conflict of Interest

The author declares no conflict of interest.