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MEETING REPORTS

Advances in Therapeutics: Meeting Report from the 31st Annual Meeting of the American Society for Bone and Mineral Research

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There were advances in therapeutics at the 2009 ASBMR Annual Meeting, though not too many big ones, which is probably good as the big ones are usually wrong. As always, the data are presented for information here; I avoid inferences because these studies are unpublished and have not been peer-reviewed, and the reader should not necessarily take this information to be knowledge.

Anti-Resorptives

One study pooled two medical claims databases (1). The number of women with ≥ 80% medication possession ratio (MPR) on oral bisphosphonates grew from 533,226 in 2000 to 1,956,307 in 2007, totaling 13,243,448 person-years for the entire time period, with 3/4 of them in the 65+ age range. This amounts to 3.5% percent of the female population in the U.S. In total, an estimated cumulative 135,316 fractures were prevented from 2000-2007, within a range of 113,666 to 243,572, saving over $1.5 billion dollars.

Risedronate

Cortical porosity is an important cause of bone loss and bone fragility. In one investigation, women with osteoporosis were randomized to risedronate (5 mg/day, n = 28) or placebo (n = 21) and had paired trans-iliac biopsies at baseline and 5 years (2). In the risedronate group, pore area decreased in the 25-100 and 100-300 μm ranges by 18% and 25% but remained unchanged in the placebo group. Pore area at 5 years in the 25-100 μm range was 17% lower in the risedronate than placebo group. Pore number in the 25-100 mm range was also lower by 17% at 5 years in the risedronate group, compared to the placebo group. Reductions were found in pores > 300-500 μm but none were significant. Reduced intracortical porosity is likely to contribute to the slowing of progression and perhaps partial reversal of bone fragility.

Not all bisphosphonates are the same. Fracture risk reduction is higher against vertebral than nonvertebral fractures, and there are likely to be several reasons for this. High affinity binding to mineral may limit accessibility of the bisphosphonate to matrix deeper beneath the endosteal surface. The uptake of 14C-risedronate into the vertebral bodies and tibial shafts of four-month old rats was quantified (3). Two rats were given a single subcutaneous dose of risedronate 1.5 mg/kg and two were given 10 times this dose. Uptake into the vertebrae, with a higher proportion of trabecular bone, was three-fold higher than that into the cortical bone.

Zoledronic Acid

Investigators reported a pooled post-hoc analysis of two pivotal trials in 9375 women (4). Zoledronic acid 5 mg reduced fracture risk for all fracture types by 6 months, reduced clinical vertebral fracture risk by 12 months by 57% and reduced non-vertebral fractures by 18 months by 23%. Another study of zoledronic acid reported that the bisphosphonate reduced the risk of non-vertebral fractures by 25% (5). For the 6 non-vertebral fracture sites (wrist, hip, pelvis, humerus, leg and clavicle) fracture risk reduction was around 30% at 1 and 3 years. The incidence of fractures at these 6 non-vertebral fracture sites in the zoledronic acid 5 mg group, compared to the placebo group, was 2.3% and 3.2%, respectively, at

1 year and 5.9% and 8.8%, respectively, at 3 years.

Denosumab

Iliac crest histomorphometric data in patients from the FREEDOM study who underwent bone biopsy at 24 months (n = 68), 36 months (n = 47), and 23 at both times (evaluable number of biopsies = 62 in the placebo group and 53 in the denosumab group) were reported (6). Double-labeling in trabecular bone was observed in 94% of placebo biopsies but only in 19% of those treated with denosumab, slightly more (30%) on cortical bone surfaces. Measures of tissue level remodeling were suppressed. This is the desired effect in the shorter term but what about in the longer term? Another study reported that BMD continued to increase during 6 years of treatment with denosumab (7). Long-term remodeling suppression allows more complete secondary mineralization of bone that would otherwise have been remodeled, which is why BMD continues to increase – is this good or bad? It was also reported that among 286 subjects given denosumab 60 mg every 6 months for a total of 24 months, of 256 subjects stopping treatment, BMD decreased but remained higher than placebo at 24 months after discontinuation (8). Bone turnover markers increased above baseline within 3 months and returned to baseline.

Intracortical formation and resorption, expressed as % haversian labeled perimeter (HLPm) and % cortical porosity (CtPo), respectively, were assessed (9). Trabecular bone formation and resorption were assessed as % mineralizing surface (MS) and % eroded surface (ES), respectively. Cortical HLPm, CtPo, and trabecular MS were increased in ovariectomized (OVX) monkeys. Denosumab reduced HLPm, CtPo, MS and ES. In another OVX study, sequential biopsies showed that denosumab reduced each remodeling parameter in the rib and ilium. Reductions in rib HLPm and CtPo were proportional to increases in cortical vBMD of the tibia (R^2=0.44 and 0.55, respectively). Reductions in MS and ES in the iliac crest were proportional to increases in lumbar spine BMD (R^2=0.42 and 0.60, respectively). CtPo and trabecular ES were reduced by denosumab.

Further analysis from the pivotal trial using denosumab was also provided (10). Nonvertebral fractures were reduced by 20%. The effect was greater in women with low BMI, femoral neck BMD T-score ≤ -2.5, and those without prevalent vertebral fracture, but did not differ by age or prior nonvertebral fracture. Denosumab decreased the risk of new vertebral fracture by 68%. This effect did not differ by age, prevalent vertebral fracture, prior nonvertebral fracture and BMI (P >0.29 for all potential interactions). Denosumab reduced the risk of new vertebral fractures in women with osteoporosis to a similar degree in all subgroups tested.

Bazedoxifene

Bazedoxifene (BZA) reduced new vertebral fracture risk in postmenopausal women with osteoporosis during 3 years (11). 4,216 subjects were enrolled in the extension study. At 5 years, the incidence of new vertebral fractures was reduced with BZA 20 mg (4.5%) and BZA 40/20 mg (3.9%) compared with placebo (6.8%), corresponding to relative risk reductions of 35% (P = 0.014) and 40% (P = 0.005), respectively. There was no difference in nonvertebral fracture rates.

Bone Formation

Human anti-DKK1 Antibodies

Osteopenic OVX rhesus monkeys treated with DKK-1 mAb-A had increased markers of bone formation and vBMD at the lumbar spine, distal radius and tibia (12). In another study, rhesus macaque monkeys (age ~13-18 years, 8+ years post-OVX) treated with DKK1-mAB-A for 9-months had increases in bone density and trabecular vBMD at the spine and other sites (13).

PTH

hPTH(1-34) was given for 18 months to OVX adult female cynomolgus monkeys (14). Weekly hPTH-(1-34) increased BMD, cancellous BV/TV, trabecular thickness,

calcium/phosphorous content, collagen content, the amount of immature cross-links, and mechanical strength, improved trabecular bone pattern factor (TBPf) and structure model index, but decreased pentosidine in cancellous bone. BMD, BV/TV, Tb.Th, calcium content, phosphorous content, collagen content and enzymatic cross-link formation correlated with mechanical properties. TBPf, structure model index (SMI), pentosidine and the ratio of pentosidine to total enzymatic cross-links negatively correlated with mechanical properties. Ultimate load and breaking energy were predicted by cancellous BV/TV, Tb.Th, calcium content and the ratio of pentosidine to enzymatic cross-links, independently. Stiffness was only predicted by the ratio of pentosidine to enzymatic crosslinks. hPTH-(1-34) increased bone strength in vertebrae by increasing enzymatic crosslinks, BMD, BV/TV, Tb.Th, calcium content, collagen content, and by improving microarchitecture of cancellous bone.

It is difficult to make inferences based on surrogates of bone formation and strength. Teriparatide (20 μg daily; n=71) and PTH(1-84) (100 μg daily; n=71) during 18-months were compared (15). After PTH(1-84) there were about two-fold greater increases in osteocalcin and beta Cross-Laps at 6, 12 and 18 months than with teriparatide but spine BMD at 18 months increased similarly in PTH(1-84) (4.9%) and teriparatide-treated patients (7%); femur BMD increased similarly with PTH(1-84) (1.8%) and with teriparatide (1.1%).

Calcilytic JTT-305

Calcilytics inhibit signals through the calcium-sensing receptor and increase endogenous PTH. A study of the novel calcilytic JTT-305 reported results from 154 patients who were randomized to placebo or 10 or 20 mg of JTT-305 daily for 12 weeks (16). PINP decreased by 13.3% in the placebo group and increased by 19.8% in the 10 mg group and 61.2% in the 20 mg group. Changes in lumbar spine BMD were 0.9%, 2.3% and 1.8% with the placebo, 10, and 20 mg groups, respectively.

Sclerostin Antibody

A sclerostin antibody (Scl-Ab) study reported that the antibody increased fracture callus density and strength, in a non-human primate fracture model, in 3-5-year-old male cynomolgus monkeys who underwent bilateral, transverse fibular osteotomies (17). Animals were injected biweekly with vehicle or 30 mg/kg Scl-Ab for 10 weeks. Scl-Ab increased serum P1NP and osteocalcin, BFR/BS at the L2 vertebra and femur shaft, BMD at the lumbar spine, hip, and distal radius, and increased lumbar vertebral strength. At the fracture site, Scl-Ab increased mean callus BMC. Scl-Ab-treated calluses were more mature and had 48% greater mean torsional stiffness.

Combining Anti-resorptives and Anabolics

One plus one does not always equal two**.** A combination therapy study reported that zoledronic acid does not blunt the effect of PTH on spine BMD and results in a greater increment in total hip BMD than PTH alone (18). Why blunting is reported with alendronate (ALN), not zoledronic acid, drugs that bind strongly to hydroxyapatite, is not clear. The effect of the combination at the hip was greater than either alone, perhaps because the antiresorptive prevents the transient increase in intracortical remodeling and porosity reported with PTH.

The anabolic agent of our dreams has not been found; it's not proven to be PTH for a range of reasons. Could it be an anti-sclerostin antibody? A study reported that an anti-sclerostin antibody given to mature, aged, osteopenic and OVX osteoporotic female nude mice increased bone formation (19). The benefit was preserved by zoledronic acid. The combination resulted in additive or synergistic effects depending on the parameter evaluated.

Another investigation reported that anti-sclerostin antibody increased bone formation, mass and strength in OVX rats (20). Scl-Ab given after ALN was equally effective in restoring BV/TV and increasing trabecular thickness (Tb.Th), MS/BS, MAR and BFR/BS at the vertebrae and increasing

serum osteocalcin. BV/TV, Tb.Th, trabecular and cortical formation parameters, and serum osteocalcin did not differ between Scl-Ab or Scl-Ab plus ALN in OVX rats pretreated with ALN.

It was also reported that anti-sclerostin antibody increases modeling-based bone formation in OVX rats and that this is not inhibited by ALN (21). Scl-Ab alone or with ALN restored trabecular BV/TV and increased trabecular thickness (Tb.Th) above the sham. ALN alone only prevented trabecular bone loss. BV/TV and Tb.Th did not differ in Scl-Ab alone and Scl-Ab plus ALN groups so ALN did not blunt the effects of Scl-Ab, but co-treatment reduced the percentage of double label (not single label) surface compared with Scl-Ab alone. Scl-Ab alone and Scl-Ab plus ALN equally increased modeling-based MS/BS. ALN alone decreased remodeling-based MS/BS. Remodeling-based MS/BS did not differ between Scl-Ab plus ALN and vehicle-treated OVX rats. The increase in modeling-based bone formation resulting from treatment with sclerostin antibody was not blunted by ALN.

It has been reported that in women continuing ALN, cyclic teriparatide (TPTD) (daily, 3 months on/3 months off) for 15 months had similar BMD effects to daily continued TPTD, despite the fact that only 60% of the total TPTD dose was given. In a further study reported at the meeting, 139 women with osteoporosis were untreated (n=67) or had prior ALN (n=72) (22). In 69 women completing 15 months, there were no differences in BMD change between the cyclic and daily treatments, suggesting that the cyclic approach may be appropriate.

Another combination study reported that, in postmenopausal women treated previously with either risedronate or ALN, in the entire subset of patients studied, teriparatide increased vertebral stiffness in 88% and ultimate load in 85% of subjects after 12 months (23). The increase in stiffness was greater in the risedronate (24.6%) than in the ALN group (14.4%). The increase in ultimate load was also greater in the risedronate (27.2%) than in the ALN group (15.3%).

Other Agents

Strontium ranelate

A study reported results from women treated with strontium ranelate up to 60 months; 32 iliac bone biopsies were taken (24). Strontium was present only in newly-formed bone corresponding to formation identified by active surfaces with tetracycline labels. The surfaces of bone containing strontium increased from 2 (2%) to 36 months (35%), followed by a smaller increment until 60 months (48%), more marked in cancellous (4, 44, 88%, respectively) than in cortical bone (1, 29, 44%, respectively). However, focal bone strontium content remained constant in the new bone from 2 to 60 months. The degree of mineralization of bone (DMB) was maintained and the distribution of DMB was heterogeneous in cortical and cancellous bone.

Strontium ranelate at 150 or 450 mg/kg/d po and TPTD at 5 or 15 μg/kg/d sc were compared in 8 month old rats OVX at age 6 months (25). TPTD elevated collagen 1a2, osteocalcin, alkaline phosphatase, bone sialoprotein (BSP), and Runx2 gene expression relative to OVX controls. Strontium ranelate had no effect on these genes. Neither compound affected OPG expression. Compared to OVX controls, 12 weeks of TPTD increased lumbar vertebral BMC and BMD while strontium ranelate 150 and 450 mg/kg/d po increased only BMC. TPTD increased lumbar vertebral strength and stiffness while neither strontium ranelate dose had an effect on strength, and only strontium ranelate 450 had a 27% effect on stiffness. Histomorphometry at the proximal tibial metaphysis showed dose-dependent effects of TPTD 5 and 15 μg/kg/d sc on trabecular thickness and number, and relative bone volume and formation rates.

Odanacatib

OVX rhesus monkeys treated with odanacatib (ODN) (6 or 30 mg/kg) for 21 months were studied (26). Porosity was not changed. Endocortical perimeter tended to decrease leading to a reduction in marrow volume and an increase in cortical thickness, cortical volume and BV/TV in the

high dose group. Periosteal MS/BS and BFR/BS tended to be higher with both doses but were not significantly so. Endocortical MS/BS was 8-fold higher, MAR was ~18% higher, and BFR/BS was also higher in the low dose group. Although endocortical MS/BS in the high dose group only trended higher, ODN did not suppress endocortical BFR/BS. ODN increased cortical thickness.

Intact and OVX rhesus monkeys (13-19 years) given ODN (6 and 30 mg/kg, q.d., p.o.) were also studied (27). BMD gains of 11% and 15% and peak-load increases of 17% and 19%, respectively, were observed for the two doses. In the trabecular femoral neck (FN), MS/BS and BFR were unaltered by the 6 mg/kg dose but trended lower with the 30 mg/kg dose. MAR, TbTh, TbN and TbSp. were unaffected. Periosteal MS/BS, MAR and BFR were not affected by the low dose, but trended higher with the 30 mg/kg ODN dose. Dose-dependent effects of ODN on periosteal FN BFR were clearly demonstrated by a long-term (LT) MAR increase of 1.5-fold and a 3.5-fold LTBFR increase with the 30 mg/kg dose vs. vehicle. ODN appeared to have differential effects on FN trabecular and cortical bone at doses that prevented bone loss. ODN inhibited trabecular bone remodeling while building cortical bone, at least in part via stimulating periosteal bone formation.

Finally, a study reported results from rhesus monkeys assigned to intact, OVX + vehicle or OVX + ODN (6 or 30 mg/kg) (28). ODN prevented OVX-induced bone loss at 6 mg/kg, and increased BMD at 30 mg/kg. MS/BS was not affected by 6 mg/kg, but was ~80% lower by 30 mg/kg without reducing MAR. ODN reduced trabecular osteoblast surface and osteoid area/BS. Osteoclast (Oc) number/BS increased ~5-fold in the 30 mg/kg group. ODN did not affect the average size or number of nuclei per Oc suggesting inhibition of cathepsin K maintains normal Oc fusion rate. ODN reduced bone formation on trabeculae at the high dose.

Conflict of Interest: Dr. Seeman reports that he is an advisory committee member for Sanofi-Aventis, Eli Lilly, Merck Sharp & Dohme, Novartis, and Servier, and that he lectures occasionally at conference symposia for those companies.

Peer Review: This article has been peer-reviewed.

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