

## **MEETING REPORTS**

# **Advances in Therapeutics: Meeting Report from the 30th Annual Meeting of the American Society for Bone and Mineral Research**

**September 12-16, 2008 in Montréal, Québec, Canada**

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This report summarizes advances in therapeutics presented at ASBMR. There were many but the data have not been peer-reviewed so inferences are tentative.

### **Denosumab**

Results from a phase 3, randomized, double-blind trial revealed a reduction in vertebral, hip and nonvertebral fracture risk (1). 7,808 women with osteoporosis were randomized to placebo or treatment with denosumab (DmAb) for 3 years. Fracture risk was reduced at vertebral (70%), nonvertebral (20%) and proximal femoral sites (41%). The design and execution of the study were excellent with 83% of subjects completing the study, intention-to-treat analysis and no serious adverse events. We have a new treatment for osteoporosis.

Another study reported that DmAb and alendronate (ALN) reduced remodeling indices in monkeys and that transition from ALN to DmAb reduced remodeling further (2). Cortical porosity (rib, tibial diaphysis) was reduced with DmAb and with ALN-DmAb, but not with ALN alone. Peak load of L5-6 trabecular cores was greater in the DmAb and ALN-DmAb groups than controls but not with continuous ALN. Cortical porosity is an important cause of bone fragility and at this time no drug has been proven to reduce intracortical porosity. The drug is a powerful remodeling suppressant but the effects are rapidly reversible, which means that compliance will be critical.

### **SERMS and Nonvertebral Fractures**

After a long wait, the answer to the big

question of whether a SERM can reduce nonvertebral fractures is available: yes it can. The effects of lasofoxifene (LASO) were investigated in 8,556 women in the PEARL study (Postmenopausal Evaluation And Risk-reduction with LASO). Compared with placebo, LASO at 0.25 and 0.5 mg/d reduced vertebral fracture by 31% and 42%, respectively ( $P < 0.002$ ) (3). The 0.5 mg dose decreased the risk of non-vertebral fracture by 22% ( $P = 0.02$ ); the decrease was 14% with 0.25 mg/d ( $P = 0.13$ ). LASO at 0.25 mg/d and 0.5 mg/d reduced the risk of ER+ breast cancer by 84% and 67%, respectively, as well as the risk of stroke (-36%), but increased the risk of venous thromboembolic events (VTE). Two cases of endometrial cancer occurred in the placebo group, 2 in the 0.25 mg LASO group, and 1 in the 0.5 mg LASO group. Hot flushes, muscle spasm, vaginal discharge, candidiasis, uterine polyps and prolapse occurred more often, and back pain, arthralgia, insomnia, hyperlipidemia, hypertension, and gastritis occurred less often, with LASO.

Bazedoxifene reduced the risk of vertebral fractures in a recent phase 3 trial. Results of post hoc analyses of nonvertebral fracture incidence among women at higher risk for fracture were reported from that trial (femoral neck T score  $\leq -3.0$  and/or  $\geq 1$  moderate or  $\geq 2$  mild vertebral fractures;  $n = 1,772$ ) (4). Nonvertebral fracture rates were 4.9%, 6.5%, 8.4%, and 9.1% with bazedoxifene at 20 mg and 40 mg, raloxifene at 60 mg, and placebo, respectively. Bazedoxifene at 20 mg reduced nonvertebral fracture incidence relative to placebo and raloxifene at 60 mg

(50% and 44%, respectively;  $P < 0.05$ ). These results are interesting but post hoc analyses are hypothesis-generating, not hypothesis-testing.

### Antisclerostin Antibody

Sclerostin, a product of the *SOST* gene in osteocytes, inhibits bone formation. Overloading decreases sclerostin expression, thus facilitating bone formation, while disuse does the reverse. A study reported that anti-sclerostin antibody increased bone formation and decreased bone resorption in distal tibial metaphyseal trabecular bone in ovariectomized (OVX) rats (5). Anti-sclerostin antibody increased BV/TV at all doses (2.5, 5, 10, and 25 mg/kg). Increases occurred in mineralizing surface, mineral apposition rate and bone formation rate. Eroded surface/bone surface was decreased at all doses. Another study reported that anti-sclerostin antibodies administered to hindlimb immobilized male rats prevented the increased bone resorption and prevented the reduced mineral apposition and bone formation produced by immobilization (6). Not only were the effects of immobilization reversed, but treatment increased BV/TV, Tb.Th, mineralizing surface, MAR and BFR/BS above controls. Whether the dream – reduced bone resorption and increased bone formation – has come true, only time and experiments in human subjects will tell.

Discontinuation of anti-sclerostin antibody treatment in rats resulted in reversal of the benefits derived during treatment (7). This is interesting for the same reason that stopping PTH results in loss of anabolic effects unless an antiresorptive agent is administered. We don't know why this occurs since the authors did not report markers of bone turnover or histomorphometry in rats post-sclerostin.

Anti-sclerostin antibody was compared with ALN to determine whether there was blunting of the anabolic effect as seen when PTH is given to ALN-treated patients, and results showed there was not (8). In OVX rats treated after 3.5 months, for 6 weeks

ALN prevented bone loss. Anti-sclerostin antibody prevented trabecular bone loss and restored trabecular bone volume and architecture and cortical area of the vertebra to sham levels. Results with anti-sclerostin antibody alone and with ALN did not differ, so no blunting of the restorative effects of the anti-sclerostin antibody in OVX rats occurred. Increased mineralizing surface, mineral apposition rate and bone formation rate, on the periosteal and the endocortical surface of the tibial shaft, were reported.

### Parathyroid Hormone

Responses in BMD and remodeling markers are blunted when PTH is given to individuals treated with ALN. PTH(1-34) increased histomorphometric indices of remodeling similarly in 38 women who stopped ALN and 28 treatment-naive women (9). Baseline biopsies showed suppressed remodeling but the percentage increase after PTH was greater except for mineralizing surfaces which remained below untreated women. The authors infer that a cellular response to PTH does occur but the birth rate of remodeling units is blunted.

The cellular mechanism responsible for the blunted anabolic effect of PTH in bisphosphonate-treated subjects was examined (10). In ALN-treated women, mineral apposition rate increased by about twice that in alendronate-naive women but the baseline apposition rate was lower in the former. Mineralized perimeter increased in both groups but less so in the ALN group in which it was also more suppressed at baseline. PTH(1-34) stimulates new bone formation but limitation of actively remodeling surface blunts the effect.

It was reported that calcitonin attenuates the anabolic effect of PTH *in vivo* and upregulates sclerostin expression (11). 3-week-old rats were treated with hPTH(1-34) (30  $\mu\text{g}/\text{kg}$ ) and 0.5  $\mu\text{g}/\text{kg}$  of salmon calcitonin (sCT) to inhibit osteoclast activation without a prolonged effect on resorption. The anabolic effect of PTH was impaired with a reduction of PTH induced suppression of sclerostin mRNA needed for

its anabolic effect. sCT reduced mRNA for other osteocytic gene products including MEPE and DMP-1. Calcitonin can promote sclerostin production, blunting the anabolic effect of PTH.

The antifracture efficacy of PTH(1-34) versus ALN in corticosteroid therapy during 3 years was presented (12). Fewer patients given PTH(1-34) had new radiographic vertebral fractures (3/173, 1.7%) compared to those given ALN (13/169, 7.7%) ( $p=0.007$ ). Nonvertebral fracture incidence did not differ (PTH(1-34) 16/214 (7.5%), ALN 15/214 (7.0%)).

Results were reported for transdermal delivery of hPTH(1-34) (TD) to 48 healthy, post-menopausal women aged 65 years randomly allocated to 50, 70, or 90  $\mu\text{g}$  TD or a daily SC dose of 20  $\mu\text{g}$  (13). Serum hPTH(1-34) was quantifiable 1.5-3.5 hours longer after TD dosing than after 20  $\mu\text{g}$  SC dosing. The bioavailability of TD hPTH(1-34) was ~40% of SC injection. Following 6 days of hPTH(1-34), serum PINP increased in each group.

### Zoledronic Acid

Zoledronic acid (ZOL) given to patients following hip fracture is associated with a 28% lower mortality. A greater absolute reduction in males than females (6.4% vs. 2.8%) and fewer cardiac deaths (2.9% vs. 7.7%) were reported (14). Subsequent fractures increased the risk of death by 72% but only 2% more of the overall association between treatment and mortality was accounted for by further fractures so the causes of the reduction in mortality remain unclear.

A study reported that ZOL reduces remodeling intensity, and the decreases in bone remodeling markers but not the increases in BMD predict fracture risk reduction (15). A 1 standard deviation reduction in P1NP at 12 months was associated with a fracture risk reduction of 34% (any clinical fracture), 27% (nonvertebral fractures), 64% (hip fractures) and 40% (morphometric fractures). What

combination of morphological and biochemical surrogates of bone strength account for the remaining ~50-60% of the risk reduction?

### Bisphosphonates and Tissue Properties

It was reported that 32 patients taking ALN and 13 taking risedronate (RIS) for 3 to 12 years (mean 6.5) had higher tissue mineral density than controls (ALN  $1.13 \pm 0.07$ , RIS  $1.10 \pm 0.07$ , controls  $1.09 \pm 0.08$ , placebo  $1.07 \pm 0.06$ ) but lower tissue mineral density than patients taking ALN for 3 years ( $1.19 \pm 0.06$ ) (16). There was no difference by treatment. The authors infer that tissue mineralization increases during the first 3 years of therapy and then declines despite the persistence of low remodeling. The data are difficult to interpret because of small sample sizes.

Compared to controls, twice the accumulation of pentosidine in trabecular bone in patients receiving ALN for 2 years was reported (17). Changes in cortical bone were not observed. Accumulation was higher with greater suppression of remodeling (reflected by activation frequency, bone formation rate and mineralizing surfaces). The contribution of these changes to overall bone strength accounting for effects of structural changes and tissue mineral changes remains to be determined.

An association between remodeling suppression and osteocyte viability was observed from bone biopsies from 8 women with low bone turnover treated with ALN for more than 5 years and 8 controls (18). Treated patients had more empty lacunae and reduced osteocyte density and enhanced heterogeneity of osteocyte distribution due to an increase in trabeculae with no osteocytes. The reduction in osteocytes may reduce damage detection and removal and may be a form of damage itself as the tissue stiffness around empty lacunae may increase, forming a region liable to incur damage (as it cannot absorb energy).

### **Bisphosphonates and Rapidity of Onset**

4-month-old female rabbits treated with vehicle (VEH), low or high dose RIS (1.2 or 2.4 µg/kg), or ALN (2.4 µg/kg) subcutaneously 3 times a week for 5 weeks were examined (19). Relative to the amount of labeled surface at week 1, there was less percent labeled surface at weeks 2 and 3 in the RIS 1.2 µg/kg (-8%) and RIS 2.4 µg/kg (-11%) groups compared to both VEH and ALN; there was no difference between VEH and ALN. At week 4, only the RIS 1.2 µg/kg group was different from VEH and ALN. RIS exerts a more rapid onset of remodeling suppression than ALN in vertebral trabecular bone.

1-year-old intact female beagles treated for 3 months with VEH, ALN 0.2 mg/kg/day or ZOL 0.06 mg/kg/month were studied (20). Intracortical bone remodeling was reduced with ZOL in the alveolar bone of the mandible (-92%), the non-alveolar bone of the mandible (-83%) and the rib (-85%), compared to VEH. These reductions of remodeling in ZOL-treated animals were also more profound than with ALN at the three sites (-56%, -55%, and -57%, respectively). Levels of intracortical remodeling were not different between ALN and VEH at any of the sites and there was no difference in the number of labeled osteons among any of the treatment groups in the tibia.

### **Vitamin D Meta-Analysis**

When trials are not designed well enough to produce answers, resort to meta-analysis; this is the case for studies of vitamin D, calcium or both. A meta-analysis was performed on the efficacy of vitamin D in preventing non-vertebral and hip fractures in individuals over the age of 65 (21). 12 randomized controlled trials (RCTs) for non-vertebral fractures (n = 42,279) and 8 RCTs for hip fractures (n = 40,886) gave a pooled relative risk (RR) for non-vertebral fractures of 0.86 (95% CI, 0.77-0.96) and a pooled RR for hip fractures of 0.91 (95% CI, 0.78-1.05). With higher doses, the pooled RR for any non-vertebral fractures from 9 trials was

0.80 (95% CI, 0.72-0.89; n = 33,265) and the pooled RR for hip fracture from 5 trials was 0.82 (95% CI, 0.69-0.97; n = 31,872). For the higher doses, non-vertebral fracture reduction was significant in community-dwelling (-29%) and institutionalized (-15%) individuals, independent of calcium supplementation.

### **Strontium Ranelate**

Strontium ranelate (SR) reduces the risk of vertebral and nonvertebral fractures, but the mechanism responsible for this effect is not understood. It was previously reported that SR induced replication and differentiation, as well as increased the survival of primary human osteoblasts (HOBs). After treatment for 24 hours, 2 mM SR dose-dependently increased OPG mRNA expression up to 1.9-fold (22). The secretion of OPG was up-regulated while RANKL mRNA expression decreased by 75% after treatment with SR, and expression of RANKL at the HOB surface was also down-regulated. Knocking down the calcium-sensing receptor (CaSR) diminished the stimulatory effects by up to 46%. The increase in the production of OPG, and the decrease in the production of RANKL at the osteoblast surface supports the notion of a potential indirect inhibitory effect on osteoclastogenesis, but demonstration of this was not provided. The CaSR may be involved in the increase in osteoblast replication and osteoclast apoptosis induced by SR.

Another study reported that SR improves implant osseointegration (23). Rats received SR (625 mg/kg, 5/7 days, n=15), ALN (18 µg/kg/d, 2/7 days, n=15, positive control) or vehicles (n=15) for 8 weeks. The control, SR, and ALN groups had pull-out force (N) of 32.5, 43.5, and 48.4; hardness (mPa) of trabecular bone of 624, 721, and 654; and hardness of cortical bone of 837.3, 918.5, and 822.8, respectively. SR and ALN improved pull-out force, and both agents positively influenced microarchitecture, but intrinsic bone tissue quality improved with SR but not ALN. Tetracycline labeling along the implant was seen with SR, but not with ALN.

It was also found that SR promotes murine osteoblastic cell proliferation in part through activation of the CaSR (24). Mouse calvaria pre-osteoblasts from *CaSR*(+/+) and *CaSR*(-/-) mice were studied. IL-1 $\beta$  increased apoptosis in both *CaSR*(+/+) and *CaSR*(-/-) osteoblasts. SR (1-5 mM) blunted apoptosis induced by IL-1 $\beta$  or TNF $\alpha$  in both *CaSR*(+/+) and *CaSR*(-/-) osteoblasts and increased phospho-PI3K and phospho-Akt levels in both types of osteoblasts, suggesting the involvement of these pro-survival signaling cascades in the anti-apoptotic effect. The CaSR is not essential for the anti-apoptotic effect of SR.

### Other Agents

LRP5 and 6 are co-receptors for Wnt ligands and bind inhibitory Dickkopf (DKK) proteins. Neutralizing anti-DKK1 monoclonal antibodies blocked receptor-ligand interaction, neutralized DKK1 function in osteoblastic differentiation and blocked DKK1 inhibition of Wnt-signaling, resulting in increases in BMD in young mice at the femur and in serum-P1NP and new bone formation in adult mice at endocortical surfaces and trabecular bone regions (25).

1,389 men with prostate cancer were randomly assigned to 80 mg toremifene or placebo once daily for 24 months (26). All subjects were taking androgen deprivation therapy for 36 months. A 54% reduction in new morphometric vertebral fractures ( $p < 0.04$ ) in the intent-to-treat population was observed.

Odanacatib (ODN) is a selective inhibitor of cathepsin K. It was reported that ODN increases bone strength in estrogen-deficient monkeys (27). BMD was higher in ODN than in OVX only monkeys, suggesting prevention of bone loss. Measures of strength were also maintained. Results of a study in which rabbits were treated for 28 weeks with ODN were also presented (28). Treatment using ODN and ALN prevented bone loss induced by OVX. BV/TV of LV3 was higher (+13.4%,  $P < .05$ ) with ODN vs. OVX ( $P < .04$ ). MS/BS was lower with ALN compared to OVX but was the same or

higher than OVX with ODN. Cathepsin K inhibition was accompanied by no suppression of bone formation, while ALN was associated with inhibition of bone formation.

Finally, it was reported that transgenic mice expressing constitutively active PTH/PTHrP receptors in osteoblast lineage cells (PPR\*Tg) have increased trabecular bone, osteoclast numbers and cortical porosity (29). Three-month-old PPR\*Tg mice given OPG-Fc exhibited reduced osteoclast numbers by 80%, whereas ALN and ZOL caused no reductions. All treatments caused ~2-fold increases in trabecular bone volume. Bone marrow fibrosis was abrogated by OPG-Fc, whereas ALN or ZOL reduced fibrosis by 54% and 55%, respectively. A 10-fold increase in cortical porosity in PPR\*Tg mice was prevented with OPG-Fc. ALN reduced cortical porosity by 39% ( $p < 0.05$  vs. VEH), while ZOL caused no reduction in porosity. Only OPG caused marked reductions in osteoclast numbers and total abrogation of both marrow fibrosis and cortical porosity.

**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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