MEETING REPORT

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TREATMENT OF OSTEOPOROSIS

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Advances have taken place in therapeutics. The most impressive are new forms of therapy that seem to have bone-forming effects on one or both periosteal and endosteal surfaces and no anti-resorptive effect or an inhibitory effect on resorption. Some of these studies are summarized below. Inferences must await scrutiny of the published work.

Anti-Sclerostin Antibodies

One study reported that antisclerostin antibodies (5 or 25 mg/kg twice weekly for five weeks) given to rats increased BMD by 16 and 27% (lumbar spine), 15% and 20% (distal femur), and 9% and 11% (femur-tibia) (1). Osteocalcin increased with no change in CTX, and trabecular bone volume increased by 133% and 166%, respectively. Osteoblast but not osteoclast surface increased with other evidence of increased bone formation, including mineralizing surface, apposition rate and bone formation rate. Greater increases in mineralizing surface (383% versus 130%) and bone formation rate (852% versus 285%) were found on the endocortical than on the periosteal surfaces.

Anti-sclerostin antibody studies also examined rats aged six months and left untreated for 5 months following oophorectomy (2). 5 weeks of anti-sclerostin antibody increased trabecular bone volume of the second lumbar vertebra with increases in osteoblast surfaces, but not osteoclast surfaces, relative to oophorectomized animals. Increases in bone formation surfaces occurred without prior resorption. Mineralizing surfaces increased by 76%-288%, mineral apposition rate by 8%-60%, and bone formation rate by 100%-546%, relative to oophorectomized controls.

Sclerostin inhibition was also found to increase periosteal and endocortical bone formation and to decrease cortical porosity in six-month-old female rats oophorectomized and left for 13 months and then treated with sclerostin antibody 25 mg/kg twice weekly for five weeks (3). Marrow cavity area decreased by 17% and cortical bone area increased by 14%, compared with oophorectomized controls. Mineralizing surfaces increased by 155%, mineral apposition rate by 84%, bone formation rate by 339%, and on the endocortical surface the respective increases were 372%, 145% and 913% compared with oophorectomized controls. Cortical porosity was examined and expressed as a percentage of total cortical area. Porosity decreased relative to oophorectomized controls with increased intracortical surface bone formation parameters.

In a study of 48 healthy postmenopausal women, treatment with varying doses of a sclerostin antibody resulted in increases in P1NP, osteocalcin and bone specific alkaline phosphatase of 60-100% at 3 mg/kg by 21 days (4).

Remodeling Suppressants

Several advances have taken place using drugs that reduce the birth rate of new remodeling units. It is a little misleading to call these drugs resorption inhibitors – they are of course – but whether they reduce the volume of bone resorbed in the reduced numbers of remodeling units remains unclear. Evidence for this is best for estrogen but no data is available for bisphosphonates. One of the most powerful remodeling rate suppressants appears to be denosumab, a drug that inhibits the
synthesis of bone-resorbing osteoclasts and the activity of existing osteoclasts.

Denosumab

Studies in oophorectomized monkeys found that denosumab (25 or 50 mg/kg for 16 months) increased bone mass by ~20-25% at the femoral neck and spine and increased peak tolerated loads by 54% at the spine and by 19-34% at the femoral neck, compared to oophorectomized controls (5). Stiffness increased 39-46% at the vertebra and by 20-25% at the femoral neck, compared to oophorectomized controls. Another group reported the effects of denosumab after 48 months in postmenopausal women (6). In 229 patients, 48 months of continuous treatment increased spine bone density by 10.6% and hip bone density by 5.8%. Cessation resulted in a fall in bone density to near baseline while rechallenging increased bone density. Bone turnover markers were decreased with continuous therapy and increased upon discontinuation.

In male mice, denosumab was also reported to prevent cortical bone thinning, induced by prednisolone, which was the result of increased resorption as reflected in increased DPD excretion and increased serum and bone TRAP5b activity (7).

Bisphosphonates

Advances in the study of the bisphosphonates have also been made. In the first study of the prevention of fractures in women with hip fractures, 1065 patients were assigned to yearly intravenous zoledronic acid (5 mg), and 1062 patients were assigned to placebo during a median of 1.9 years (8). The respective rates of any new clinical fracture were 8.6% vs 13.9% (a 35% risk reduction, \( P = 0.001 \)), rates of new clinical vertebral fracture were 1.7% vs 3.8% (\( P = 0.02 \)), and rates of new non-vertebral fractures were 7.6% vs 10.7% (\( P = 0.03 \)). 101 of 1054 patients (9.6%) and 141 of 1057 patients (13.3%) died, a reduction of 28% (\( P = 0.01 \)).

In another study, minodronate was given to 359 postmenopausal Japanese women aged between 55 and 80 years, while 345 received placebo for 26 months (9). Vertebral fracture rate was reduced by 58.9% (CI 36.6%-73.3%). Fractures occurred in 10.4% of treated patients versus 24% of placebo recipients. Effects on non-vertebral fractures were not reported.

Differences in bisphosphonates that affect the response to anabolic therapy were also reported (10). In 146 post-ridgedronate- and 146 post-alendronate-treated subjects treated with 20 \( \mu \)g of PTH(1-34) for 12 months, the former had a greater response in bone turnover markers (before and after adjusting for higher baseline values in the post-ridgedronate group). There was a 76% greater increase in QCT of trabecular bone at the spine (24.1% versus 13.7%, \( p = 0.02 \)).

A greater absolute increase in P1NP for the post-ridgedronate than post-alendronate group during months 1-5 was also reported (11). Similar results were found for other markers. The increases post-ridgedronate occurred earlier but became similar after 12 months.

If a drug makes BMU balance positive, it is of interest to increase the rate of remodeling, or to at least avoid suppressing it, as the net effect should be reconstruction of the skeleton. It was reported that a bisphosphonate analog (IG9402) without remodeling suppressant activity prevented osteocyte and osteoblast apoptosis and the loss of strength induced by corticosteroid therapy (12). IG9402 did not reduce markers of remodeling while alendronate did. Alendronate decreased bone formation, but this was not found with the drug.

SERMS

In a phase 3 study, women with osteoporosis with or without prevalent fractures were treated with 20 mg or 40 mg/day of bazedoxifene (BZA), compared with 60 mg of raloxifene or placebo (13). Among 7492 women after three years, incidences of new vertebral fractures were 2.3%, 2.5%, 2.3% and 4.1% in the BZA 20 mg, BZA 40 mg, raloxifene 60 mg and placebo groups, respectively, with statistically significant risk reductions for new vertebral fracture of 42%, 37% and 42%, respectively, compared with placebo. There was no effect on non-vertebral fractures. In the post hoc analysis of those patients with a T score \( \leq -3 \) SD or one or more moderate or multiple vertebral fractures (\( n=1782 \)), nonvertebral fracture incidence was 3%, 3.8%, 5.9% and 6.3% in the BZA 20 mg, BZA 40 mg, raloxifene 60 mg, and placebo groups, respectively. This resulted in the 20 mg dose of BZA reducing...
nonvertebral fractures by 52%, a significant reduction.

Finally, in 1583 postmenopausal women with a mean age of 57 years treated with BZA, prevention of bone loss and a reduction in bone remodeling markers in the order of around 20-25% was found, similar to that found with raloxifene (14).

**Cysteine Protease Inhibition**

The cysteine protease inhibitor MK-0822 was evaluated in a dose-ranging study in 399 postmenopausal women randomized to placebo or one of four doses (15). The highest dose increased spine BMD by 3.4% and femoral neck BMD by 2.5%, and was associated with a 58% reduction in urinary NTx.

**Parathyroid Hormone**

In 7 women with osteoporosis, 12 months of 20 µg of parathyroid hormone increased BV/TV by 6.9%. Two-thirds of of the increase was due to an increase in trabecular thickness and one-third of the increase was due to an increase in trabecular number (16). There was a trend towards a decrease in cortical thickness and cortical vBMD.

An increase in microcrack density was reported in patients treated with alendronate compared to untreated controls (17). Sixty-six postmenopausal women with osteoporosis were treated with 20 µg daily of PTH(1-34) for two years. Thirty-eight stopped alendronate and were treated with PTH while 28 were treatment-naïve. Paired biopsies were available in 13 treatment-naïve and 18 alendronate-treated subjects. Crack surface density and crack length decreased in previously alendronate-treated patients while only crack length was reduced in formerly treatment-naïve patients. The authors infer that PTH(1-34) reduced microdamage accumulation.

Histomorphometric results following 20 µg of parathyroid hormone given to treatment-naïve and previously alendronate-treated subjects were also reported (18). After 2 years of treatment, bone biopsies demonstrated that activation frequency increased by 130% and 359% for 16 treatment-naïve and 29 alendronate-treated subjects, respectively. 3-D micro CT indicated an increase in trabecular and cortical thickness with no difference in the two groups, suggesting that prior alendronate treatment does not impair the morphological response to PTH. Trabecular thickness increased by 30% in both groups. For previously treatment-naïve and alendronate-treated groups, there were increases, respectively, of 36.7% and 12.7% in trabecular number, increases of 37.8% and 31.7% in cortical thickness, and increases of 28.2% and 42.8% in total cortical area.

The effects of cyclic and daily parathyroid hormone combined with OPG in 20-week-old mice treated for seven weeks was also reported (19). All treatments increased bone density. Daily PTH increased periosteal circumference by 4.9%, and the combination of daily PTH and OPG increased it by 4.2%. Cyclic PTH produced a 3.8% increase in periosteal circumference, while the combination of cyclic PTH and OPG produced an increase of 2.8%. OPG reduced endosteal circumference by 1.8%, and there was no effect on this measure from daily PTH. The combination of daily PTH and OPG reduced endosteal circumference by -5.4%, whereas cyclic PTH therapy increased it by 2.5%, and combination therapy of cyclic PTH plus OPG reduced it by -3.2%. Cortical thickness increased most with the combined daily PTH plus OPG treatment (+22%). Cyclic PTH plus OPG increased cortical thickness by 10.9%, daily PTH alone increased it by 14%, and cyclic PTH increased it by 6.2%.

Ostabolin-C, a cyclic analogue of PTH(1-31), has been shown to increase bone density in preclinical studies, and it is also now reported that, in 261 postmenopausal women treated by subcutaneous injection in a dose-ranging study, treatment with Ostabolin-C resulted in an increase in bone density within four months of treatment, with mean increases of around 11% within 12 months of treatment in the 45 µg group (20). These changes were accompanied by increases in biochemical measures of bone formation, with an increase in P1NP of over 120% and an increase in osteocalcin of over 100%.

**Calcium-Sensing Receptor**

Antagonism of the calcium-sensing receptor in the parathyroid gland results in an increase in endogenous PTH release, and investigators have now reported results in
healthy male volunteers given the calcium-sensing receptor antagonist SB-423557 (21). In a study comparing a range of doses, the authors report elevations in plasma PTH that lasted under eight hours. At doses of 100 mg of SB-423557 and above, PTH exposure was 10%-48% higher than placebo.

**Activin Fusion Protein**

A single dose of ACE-011 was reported to increase bone formation and decrease bone resorption markers in postmenopausal women (22). This fusion protein consists of an extracellular domain of human type II activin receptor IIA linked to the Fc portion of human IgG1. The fusion protein binds to activin and has been reported to improve architecture and bone strength as a result of an anabolic effect on bone. In this randomized, double-blind study of 48 women given a single dose of ACE-011 or placebo and followed for 120 days, treatment resulted in an increase in bone-specific alkaline phosphatase and a dose-dependent decrease in C-terminal type 1 collagen telopeptide and TRAP-5B.

ACE-011 was also reported to increase bone density and improve microarchitecture in monkeys given a single subcutaneous injection of up to 30 mg/kg, and monkeys given multiple doses at 10 mg/kg over three months. (23). Both doses were well-tolerated. Treatment bi-weekly for three months using 10 mg/kg per day increased BMD, trabecular bone density and structure. BMD of L5 by DXA increased by 13%, and micro-CT revealed that bone volume increased by 16% and trabecular number by 13%, and there was also a 7-fold decrease in structure model index. At the distal femur, similar observations were made, as there was an increase in trabecular density of 79%.

Finally, a study reported that a fusion protein combined with PTH prolongs PTH hormone action (24). This protein was synthesized by combining PTH(1-33) with the collagen binding domain of the CoH collagenase. The new drug resulted in stimulation of cyclic AMP accumulation, similar to that seen with PTH(1-34) in cell lines. Weekly injections in young female mice increased spinal bone density by 16% versus 7% for PTH(1-34). There was no evidence of hypercalcemia in the animals.

**Conflict of Interest:** The author 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.

**References**


