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NOT TO BE MISSED

Clinical and Basic Research Papers – October 2011

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Cancer and Bone

Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinshaw R, Keane M, Gil M, Houston SJ, Grieve RJ, Barrett-Lee PJ, Ritchie D, Pugh J, Gaunt C, Rea U, Peterson J, Davies C, Hiley V, Gregory W, Bell R; for the AZURE Investigators. Breast-cancer adjuvant therapy with zoledronic acid. *N Eng J Med*. 2011 Sep 25. [Epub ahead of print] [Abstract] [Full Text]

A recent IBMS BoneKEy webinar, The Anti-cancer Activity of Bisphosphonates in the Clinic, examined the evidence in favor of using bisphosphonates in the clinical cancer setting (click here for a news summary of the webinar). Newly published work, from webinar presenter Robert Coleman (University of Sheffield, UK) and colleagues, now provides both disappointing and intriguing data regarding the use of zoledronic acid (ZA) in breast cancer.

The new work, published ahead-of-print in The New England Journal of Medicine, presents findings from the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial. In this randomized, controlled, open-label phase 3 clinical trial, patients with early-stage breast cancer were randomized to receive either standard adjuvant therapy alone or with 4 mg of intravenous ZA; subjects received 6 doses of the drug every 3-4 weeks, followed by 8 doses every 3 months, followed by 5 doses every 6 months, for a total treatment duration of 5 years. Results showed that, compared to controls on standard adjuvant therapy alone, those also receiving ZA did not exhibit any statistically significant differences in the rate of disease-free survival (DFS), the study's primary end point, as similar numbers of patients in each group had recurrent disease or had died at the study's 5 year follow-up. Likewise, no between-group differences were found in the secondary end point of invasive-DFS events (which include ipsilateral invasive breast tumor recurrence, regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, contralateral invasive breast cancer, and second primary nonbreast invasive cancer), with similar numbers of patients in each group alive and without invasive disease, nor were there differences in the secondary end point of overall survival. Thus the authors conclude that their findings do not bolster the case for using ZA in the adjuvant early-stage breast cancer setting.

Interestingly, though, in a subgroup analysis, the study did document statistically significant differences between groups when classifying patients according to menopausal status. Now, patients taking ZA who were postmenopausal for more than 5 years exhibited increased rates of invasive DFS compared to controls (78.2% vs. 71.0%, respectively), with an adjusted hazard ratio of 0.75 (95% CI, 0.59-0.96;

p=0.02), while no such differences were found between patients taking ZA who were premenopausal, perimenopausal, or whose menopausal status was unknown and controls. Similar findings were documented for overall survival: postmenopausal patients on ZA had higher 5-year overall survival compared to controls (84.6% vs. 78.7%, respectively), with an adjusted hazard ratio of 0.74 (95% CI, 0.55 to 0.98; p=0.04), while no differences were found between patients taking ZA who were premenopausal, perimenopausal, or whose menopausal status was unknown and controls. Furthermore, the study found that, in terms of distant skeletal recurrence, there was no difference in the effects of ZA between the two menopausal groups, but there was a difference for the other aspects of invasive-DFS (e.g., loco-regional recurrence and non-skeletal distant recurrence), with an apparent benefit seen in the postmenopausal group and potential harm in the other menopausal group. Based on these subgroup findings, the authors call for more research into possible interaction between ZA and reproductive hormones. —Neil Andrews

Clinical Studies and Drug Effects

Adie S, Harris IA, Naylor JM, Rae H, Dao A, Yong S, Ying V. Pulsed electromagnetic field stimulation for acute tibial shaft fractures: a multicenter, double-blind, randomized trial. *J Bone Joint Surg Am*. 2011 Sep 7;93(17):1569-76. [Abstract]

Here is a double-blind randomized controlled trial of pulsed electromagnetic fields for acute tibial fractures. No difference is seen either in intention to treat or when allowing for compliance. The authors do not recommend use of this therapy, which is commonplace because of its non-invasiveness. —DGL

McClung MR, Miller PD, Brown JP, Zanchetta J, Bolognese MA, Benhamou CL, Balske A, Burgio DE, Sarley J, McCullough LK, Recker RR. Efficacy and safety of a novel delayed-release risedronate 35 mg once-a-week tablet. *Osteoporos Int*. 2011 Sep 27. [Epub ahead of print] [Abstract]

The inconvenience of taking oral bisphosphonates on an empty stomach may contribute to the poor compliance with these drugs. This is the first oral formulation of a delayed-release bisphosphonate, namely, weekly risedronate, that could free patients from such a hassle, allowing them to take the drug after breakfast. The study shows that the new formulation taken under these conditions inhibits bone turnover markers and increases aBMD similarly to the 5 mg daily administration in standard conditions (i.e., at least 30 minutes before breakfast). —SF

Peichl P, Holzer LA, Maier R, Holzer G. Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. *J Bone Joint Surg Am*. 2011 Sep 7;93(17):1583-7. [Abstract]

In this controlled but not truly randomized study, 21 patients (every 3rd patient) presenting with pelvic fractures confirmed on CT received 100 µg of PTH 1-84 starting within two days after admission. All patients were treated with vitamin D and calcium. CT scans were repeated every 4 weeks. At 8 weeks, all the PTH-treated patients had healed their fractures, whereas only 9% of controls had healed. At 12 weeks, only 68% of controls had healed. Both the visual analog scale score for pain and the result of the Timed "Up and Go" test improved in the study group. Although not a truly double-blind study, the evidence is exciting enough to be explored further. —DGL

Bone Modeling, Remodeling, and Repair

Doi Y, Miyazaki M, Yoshiiwa T, Hara K, Kataoka M, Tsumura H. Manipulation of the anabolic and catabolic responses with BMP-2 and zoledronic acid in a rat femoral fracture model. *Bone*. 2011 Oct;49(4):777-82. [Abstract]

> *Rat femoral osteotomies were treated with a MedGEL carrier alone, carrier containing 1 µg rhBMP-2, carrier and a subcutaneous systemic zoledronic acid (ZA) injection 2 weeks after surgery, or carrier containing 1-µg rhBMP-2 and ZA 2 weeks after surgery. The combination group showed increased union rate (93% vs. 29-57%). Ultimate load, stiffness and energy absorption were all increased 3-fold or more over controls with combination therapy.* —DGL

Li YF, Zhou CC, Li JH, Luo E, Zhu SS, Feng G, Hu J. The effects of combined human parathyroid hormone (1-34) and zoledronic acid treatment on fracture healing in osteoporotic rats. *Osteoporos Int*. 2011 Sep 3. [Epub ahead of print] [Abstract]

> *Ovariectomized (OVX) rats with tibial fractures received vehicle, ZA, PTH, or ZA plus PTH treatment for 4 and 8 weeks. Doses were ZA 1.5 µg/kg weekly, and PTH 60 µg/kg, three times a week. All treatments increased callus formation and strength over control; ZA + PTH showed the strongest effects on percent bone volume (BV/TV), trabecular thickness, total fluorescence-marked callus area, and biomechanical strength (>100% increase in strength at 8 weeks). No difference in bone mineral density and BV/TV of the contralateral tibiae was observed between treated groups.*
> —DGL

Xiong J, Onal M, Jilka RL, Weinstein RS, Manolagas SC, O'Brien CA. Matrix-embedded cells control osteoclast formation. *Nat Med*. 2011 Sep 11. [Epub ahead of print] [Abstract]

Nakashima T, Hayashi M, Fukunaga T, Kurata K, Oh-Hora M, Feng JQ, Bonewald LF, Kodama T, Wutz A, Wagner EF, Penninger JM, Takayanagi H. Evidence for osteocyte regulation of bone homeostasis through RANKL expression. *Nat Med*. 2011 Sep 11. [Epub ahead of print] [Abstract]

> *These two seminal papers highlight the central role of osteocytes producing RANKL in bone remodeling. The first study uses a set of promoter-Cre constructs to target RANKL deletion in mesenchymal stem cells of the limbs, early osteoblasts and late-proliferating chondrocytes, differentiated osteoblasts, and osteocytes (the latter through Dmp1-Cre). All deletions led to an osteopetrotic phenotype, similar to RANK and RANKL KO mice previously described, with the exception of the osteocyte RANKL KO, which developed higher bone mass only with growth. Moreover, these mice were resistant to bone loss induced by tail-suspension (disuse limbs). It is, however, curious that RANKL mRNA expression in total bones was not lower in osteocytic KO mice, whereas osteocytes are the most abundant cell type in the skeleton. This would argue against a high level of RANKL expression in these cells under normal conditions.*
>
> *The second study directly demonstrates a high level of RANKL expression in purified osteocytes. Deletion of RANKL specifically in T cells led to no bone phenotype. Consistent with the previous study (above), the high bone mass phenotype in the osteocytic KO developed only after birth.* —SF

Physiology and Metabolism

Baliram R, Latif R, Berkowitz J, Frid S, Colaianni G, Sun L, Zaidi M, Davies TF. Thyroid-stimulating hormone induces a Wnt-dependent, feed-forward loop for osteoblastogenesis in embryonic stem cell cultures. *Proc Natl Acad Sci U S A*. 2011 Sep 27;108(39):16277-82. [Abstract] [Full Text]

> *Growth hormone, follicle-stimulating hormone, and thyroid-stimulating hormone: bone appears as a target organ for a number of pituitary hormones. Here a direct influence of thyroid-stimulating hormone on osteoblast differentiation is shown using embryonic stem cells in vitro.* —SF

Wu RW, Lin TP, Ko JY, Yeh DW, Chen MW, Ke HC, Wu SL, Wang FS. Cannabinoid receptor 1 regulates ERK and GSK-3β-dependent glucocorticoid inhibition of osteoblast differentiation in murine MC3T3-E1 cells. *Bone*. 2011 Aug 30. [Epub ahead of print] [Abstract]

Sophocleous A, Landao-Bassonga E, Van't Hof RJ, Idris AI, Ralston SH. The type 2 cannabinoid receptor regulates bone mass and ovariectomy-induced bone loss by affecting osteoblast differentiation and bone formation. *Endocrinology*. 2011 Jun;152(6):2141-9. [Abstract] [Full Text]

> *The type 1 and type 2 cannabinoid receptors (CB1 and CB2, respectively) have been reported to regulate bone mass and bone turnover. Wu et al. point out that CB1 regulation of ERK and GSK-3β-dependent pathways participates in inhibition of Runx2 signaling and osteoblast differentiation by glucocorticoid. The authors thus propose CB1 blockade as a strategy for alleviating the adverse actions of glucocorticoid on osteoblastic activities.*
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> *The second study investigated the role of the CB2 pathway in bone metabolism using a combination of genetic and pharmacological approaches. Bone mass and turnover were normal in young CB2(-/-) mice, but by 12 months of age, the mice had developed high-turnover osteoporosis; primary osteoblasts from CB2(-/-) mice had a reduced capacity to form bone nodules in vitro and had impaired PTH-induced alkaline phosphatase (ALP) activity. It seems that cannabinoid receptors regulate osteoblast differentiation in vitro and bone formation in vivo.* —DK

Yoshikawa Y, Kode A, Xu L, Mosialou I, Silva BC, Ferron M, Clemens TL, Economides AN, Kousteni S. Genetic evidence points to an osteocalcin-independent influence of osteoblasts on energy metabolism. *J Bone Miner Res*. 2011 Sep;26(9):2012-25. [Abstract]

> *Osteocalcin KO mice develop insulin insensitivity and a metabolic syndrome. This study shows that partial ablation of the osteoblastic population using targeted diphtheria toxin expression mimicked the effects of a lack of osteocalcin; however, energy expenditure was increased. These results emphasize the role of bone cells in fat metabolic control and suggest that other osteoblastic factors could also contribute to it.* —SF

Other Studies of Potential Interest

Chen GQ, Wang S, Hu SY. Osteoporosis increases chondrocyte proliferation without a change in apoptosis during fracture healing in an ovariectomized rat model. *Mol Med Report*. 2011 Sep 22. [Epub ahead of print] [Abstract]

Conforti AS, Gallo ME, Saraví FD. Yerba Mate (Ilex paraguariensis) consumption is associated with higher bone mineral density in postmenopausal women. *Bone*. 2011 Sep 3. [Epub ahead of print] [Abstract]

Duren DL, Blangero J, Sherwood RJ, Seselj M, Dyer T, Cole SA, Lee M, Choh AC, Chumlea WC, Siervogel RM, Czerwinski SA, Towne B. Cortical bone health shows significant linkage to chromosomes 2p, 3p, and 17q in 10-year-old children. *Bone*. 2011 Aug 31. [Epub ahead of print] [Abstract]

El-Hoss J, Sullivan K, Cheng T, Yu NY, Bobyn JD, Peacock L, Mikulec K, Baldock P, Alexander IE, Schindeler A, Little DG. A murine model of neurofibromatosis type 1 tibial pseudarthrosis featuring proliferative fibrous tissue and osteoclast-like cells. *J Bone Miner Res*. 2011 Sep 28. [Epub ahead of print] [Abstract]

Fitzpatrick LA, Smith PL, McBride TA, Fries MA, Hossain M, Dabrowski CE, Gordon DN. Ronacaleret, a calcium-sensing receptor antagonist, has no significant effect on radial fracture healing time: Results of a randomized, double-blinded, placebo-controlled Phase II clinical trial. *Bone*. 2011 Oct;49(4):845-52. [Abstract]

Granero-Moltó F, Myers TJ, Weis JA, Longobardi L, Li T, Yan Y, Case N, Rubin J, Spagnoli A. Mesenchymal stem cells expressing insulin-like growth factor-I (MSC^{IGF}) promote fracture healing and restore new bone formation in Irs1 knockout mice: analyses of MSC^{IGF} autocrine and paracrine regenerative effects. *Stem Cells*. 2011 Oct;29(10):1537-48. [Abstract]

Katiyar SK, Raman C. Green tea: a new option for the prevention or control of osteoarthritis. *Arthritis Res Ther*. 2011 Aug 10;13(4):121. [Epub ahead of print] [Abstract]

Li GH, Cheung CL, Xiao SM, Lau KS, Gao Y, Bow CH, Huang QY, Sham PC, Kung AW. Identification of QTL genes for BMD variation using both linkage and gene-based association approaches. *Hum Genet*. 2011 Oct;130(4):539-46. [Abstract]

Wang CY, Yang HB, Hsu HS, Chen LL, Tsai CC, Tsai KS, Yew TL, Kao YH, Hung SC. Mesenchymal stem cell-conditioned medium facilitates angiogenesis and fracture healing in diabetic rats. *J Tissue Eng Regen Med*. 2011 Sep 13. [Epub ahead of print] [Abstract]

Yang DC, Yang MH, Tsai CC, Huang TF, Chen YH, Hung SC. Hypoxia inhibits osteogenesis in human mesenchymal stem cells through direct regulation of RUNX2 by TWIST. *PLoS One*. 2011;6(9):e23965. [Abstract]

Conflict of Interest: Dr. Clézardin reports receiving research support from Novartis (Basel, Switzerland) and honoraria for advisory work and speaking engagements from Novartis and Amgen. Dr. Ferrari reports that he receives research support from Amgen and Merck Sharp & Dohme, and is an advisory committee member and lectures occasionally at conference symposia for the Alliance for Better Bone Health (sanofi aventis/P&G), Amgen, Merck Sharp & Dohme, Eli Lilly, Servier, and Novartis. Dr. Little reports that he receives royalties, research funds and consultancy fees from Novartis Pharma, as well as research support from Stryker Biotech. 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. Dr. Matsumoto reports that he is a member of the advisory board for Eli Lilly, and receives consultancy fees from Chugai, Astellas, Teijin, JT, and Daiichi-Sankyo. Dr. Karasik reports no conflicts of interest.