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CORRESPONDENCE

Effects of Parathyroid Hormone and Alendronate Alone or in Combination in Osteoporosis

TO THE EDITOR: Both Black et al.[1] and Finkelstein et al.[2] (Sept. 25 issue) measured markers of bone turnover, but neither group took osteoprotegerin into consideration as a possibly relevant player in bone remodeling. Osteoprotegerin, a secreted member of the family of tumor necrosis factor receptors, is a potent inhibitor of osteoclast activation and differentiation.[3,4] In patients with osteoporosis, osteoprotegerin has been found to correlate strongly with markers of bone turnover[5] — a finding that may point toward a higher level of osteoprotegerin expression in patients with a higher level of these markers.

In limited experimental settings, the serum osteoprotegerin level has been found to be increased in Paget's disease and to be decreased after treatment with tiludronate, a common bisphosphonate.[6] Osteoprotegerin and receptor activator of nuclear factor-κB (RANK) have been identified as important determinants of increased bone resorption induced by estrogen deficiency.[7] Taking these relevant findings into consideration, we suspect that there is a potential interaction among bone mineral density, changes in the serum alkaline phosphate level, other possible markers of bone turnover, and the serum level of osteoprotegerin — an interaction that perhaps should be considered in further studies on this issue.

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TO THE EDITOR: Bone resorption and bone formation are coupled, and alendronate, which decreases bone turnover, impairs the anabolic effect of para-

THIS WEEK'S LETTERS

thyroid hormone, which increases bone turnover.[1-3] Thus, combination therapy with the use of a drug that does not affect bone turnover might be a good choice. The serum vitamin K level decreases as a person gets older, and undercarboxylated osteocalcin is a marker of skeletal fragility in elderly persons. Vitamin K has been approved for the treatment of osteoporosis in Japan and has been reported to reduce the risk of vertebral and hip fracture without changing bone turnover or increasing bone mineral density. Although the mechanisms remain unclear, this vitamin might improve bone material properties by promoting the incorporation of osteocalcin into bone[4] or might induce increases in bone size by increasing periosteal bone formation.[5] Because of the limited efficacy of drugs and their potential toxicity, combination therapy with drugs that have different mechanisms of action is considered to reduce the risk of fracture. Vitamin K has a very wide safety range, and we propose combination therapy with the use of vitamin K as an essential supplement for the management of osteoporosis.

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TO THE EDITOR: Black et al. and Finkelstein et al., as well as Khosla, in an accompanying editorial,[1] suggest that combining parathyroid hormone with bisphosphonates is a bad idea. I believe that this suggestion is premature. Neither Black et al. nor Finkelstein et al. tested the currently approved recombinant human parathyroid hormone (1–34), and neither present any fracture or biopsy data. Spinal bone mineral density increased to a similar extent with parathyroid hormone and combination therapy in the study by Black et al. and increased an impressive 14.8 percent (at the posteroanterior spine) with combination therapy in the study by Finkelstein et al. The total-hip bone mineral density, as measured by dual-energy x-ray absorptiometry, increased to a similar or greater extent with combination therapy. The meaning of data obtained from quantitative computed tomography (CT) with regard to reduction of the risk of fracture is unclear. Parathyroid hormone–mediated decreases in forearm bone mineral density are due to increases in bone area.[2]

Bisphosphonates reduce the risk of hip fractures. It is unknown whether parathyroid hormone reduces the risk of hip fractures. The clinical meaning of the inhibition of parathyroid hormone–mediated increases in bone-formation markers by alendronate is also unknown. Markers of bone formation reflect osteoblast activity, not necessarily bone formation.[3] Additional evidence that we do not understand the meaning of the biomarker changes is the observation made by Finkelstein et al. that after 12 months of parathyroid hormone administration, levels of bone-formation markers decline, yet bone mineral density continues to improve. It is too soon to make judgments about parathyroid hormone–bisphosphonate combinations from the available data.

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TO THE EDITOR: Since osteoporosis is correlated with serum 25-hydroxyvitamin D status, analyses of treatments must take this measurement into account, both at base line and throughout a study. Black et al. mention only that their subjects took a daily multivitamin containing 400 IU of vitamin D. The subjects in the study by Finkelstein et al. also took a multivitamin, and 25-hydroxyvitamin D was measured at base line. Although other values were measured at six-month intervals, the serum level of 25-hydroxyvitamin D was not. Given that the serum 25-hydroxyvitamin D level is the best measurement of a person's vitamin D status, and given the importance of adequate levels of vitamin D to bone

health,[1] it would be appropriate for all studies of bone metabolism to include measurements of serum 25-hydroxyvitamin D at base line, during the study, and at its conclusion. Attempting to determine the efficacy of treatment options related to osteoporosis without also taking into account concurrent serum 25-hydroxyvitamin D status is problematic.

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DR. BLACK AND COLLEAGUES REPLY: Dr. Miller makes some interesting points regarding our study of parathyroid hormone and alendronate, although we certainly do not suggest in our article that combination therapy with parathyroid hormone and bisphosphonate is a bad idea. In fact, we discuss virtually all the limitations mentioned by Dr. Miller. As he states, combination therapy does increase bone mineral density, and this increase was more evident in the two-year study by Finkelstein et al. than in our one-year study. However, we hypothesized that the combination would have an additive or synergistic effect, and in neither study was there evidence that the combination was superior to the better of the two agents given alone. There is obviously a great need for more data with regard both to recombinant human parathyroid hormone (1–34) (teriparatide), which was used by Finkelstein et al., and to the full-length molecule, recombinant human parathyroid hormone (1–84), which we used. However, the results of these two studies, along with data presented at the September 2003 meeting of the American Society for Bone and Mineral Research, suggest that parathyroid hormone (1–84) and parathyroid hormone (1–34) interact with alendronate in similar ways. As we discuss in our article, the results with alendronate cannot necessarily be generalized to combination therapy with other bisphosphonates or other antiresorptive drugs. The implications of quantitative CT and biochemical-marker end points with respect to bone strength and the risk of fracture are not entirely clear, and final judgment awaits more definitive trials. However, with that caveat, we believe that the data that are currently available support the notion that responses to parathyroid hormone therapy are maximized when bone turnover is not being suppressed during the course of treatment.

In response to Dr. Sugiyama and colleagues: Although our study did not provide evidence of a synergistic effect of parathyroid hormone and alendronate, it is entirely possible that other combinations of anabolic and antiresorptive agents would have other results. In addition, other combinations, including combinations with vitamin K, might be useful to study.

In response to Dr. Vegni and colleagues: Osteoprotegerin is a potentially useful surrogate marker that might provide distinct information. We agree that it should be included in future studies.

In response to Dr. Fuller: Our patients had sufficient vitamin D levels, according to measurements made at base line. Because their dietary intake of vitamin D was supplemented with 400 IU daily (as recommended by the Food and Drug Administration), it is highly unlikely that our patients became vitamin D–deficient during the study. We agree that this nutrient is important in therapeutic regimens for osteoporosis. We look forward to seeing analyses (from our own study and others) of the effect of base-line vitamin D levels on the effect of parathyroid hormone.

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DR. FINKELSTEIN AND COLLEAGUES REPLY: Dr. Vegni and colleagues note the importance of osteoprotegerin as an inhibitor of osteoclastic bone resorption. Although the meaning of circulating osteoprotegerin levels is still unclear, we are measuring serum osteoprotegerin levels in stored samples from our patients and will analyze these data.

Dr. Sugiyama and colleagues suggest that combining vitamin K with parathyroid hormone might be useful in the treatment of osteoporosis. Randomized, controlled clinical trials are needed to test this interesting idea.

Dr. Miller notes that we did not use the currently approved formulation of recombinant human parathyroid hormone (1–34). Our formulation of human parathyroid hormone (1–34), made by solid-phase synthesis, is identical to the recombinant molecule and produces results indistinguishable from those obtained with the recombinant molecule in animals and humans. Dr. Miller also notes that we did not report the incidence of fracture and cannot be certain how the observed changes in bone density and bone turnover will affect the risk of fracture. For that reason, we were careful to state in our conclusions that "additional studies are needed before combinations of antiresorptive agents and parathyroid hormone can be recommended for the treatment of men with osteoporosis." As Dr. Miller notes, combination therapy was associated with an impressive increase in spinal bone mineral density. Parathyroid hormone monotherapy was even better, however. In laboratory animals, there is a direct relationship between parathyroid hormone–induced increases in bone mineral density and resistance to fracture. Considerable evidence also demonstrates a direct relationship between increases in bone mineral density and decreases in the risk of fracture in humans.[1] Thus, until clinical trials compare the effects of parathyroid hormone alone and those of parathyroid hormone plus alendronate on the risk of fracture, it seems reasonable to treat patients with the regimen that provides greater increases in bone density, particularly because parathyroid hormone monotherapy is less expensive than combination therapy and exposes patients to a lower risk of side effects.

Dr. Fuller is concerned that only base-line levels of 25-hydroxyvitamin D are reported, and that the results might have been altered if the subjects subsequently had vitamin D deficiency. Although we did not report these data, we did measure serum 25-hydroxyvitamin D levels every six months. The mean (±SD) levels ranged from a low of 23±8 ng per milliliter to a high of 25±9 ng per milliliter in the men treated with alendronate alone, from 18±5 to 27±10 ng per milliliter in the men treated with parathyroid hormone alone, and from 21±7 to 28±12 ng per milliliter in the men treated with both. These levels did not differ significantly among the groups.

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D-Dimer in Venous Thromboembolism

TO THE EDITOR: Wells and colleagues (Sept. 25 issue)[1] report on the use of D-dimer testing in patients with suspected deep-vein thrombosis. Patients with a low pretest probability of deep-vein thrombosis and a negative result on the D-dimer test did not undergo confirmatory testing. This is problematic. Current recommendations for the evaluation of new diagnostic tests suggest an independent, blinded comparison with a reference standard and application of that standard independently of the test being evaluated.[2] The gold standard for deep-vein thrombosis is either duplex ultrasonography or venography, neither of which was performed in this study group. The "gold standard" for these patients was the absence of a clinical event at three months. A false negative result would be identified if a patient had a symptomatic recurrence. It is unclear whether there would be a significant number of such recurrences in just three months. These limitations make it likely that the study overestimates the sensitivity and clinical utility of D-dimer testing. In addition, other studies have suggested that the SimpliRED assay has only 77 percent sensitivity for detecting pulmonary embolism.[3] Confirmation of the utility of D-dimer testing awaits trials that uniformly apply diagnostic standards.

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