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PERSPECTIVES

Aromatase Inhibitors and Bone Health

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Abstract

The third-generation aromatase inhibitors (anastrozole, letrozole, and exemestane) are increasingly used in the treatment of early and advanced breast cancer and act by substantially reducing estrogen synthesis in postmenopausal women. Low estradiol levels in women are associated with decreased bone mineral density (BMD) and increased fracture risk. Current data suggest that both the steroidal (exemestane) and non-steroidal (anastrozole and letrozole) aromatase inhibitors increase bone turnover. Conclusions regarding any clinically relevant differences between these agents are difficult to make, and further data are awaited from use of these three agents as long-term adjuvants in ongoing clinical studies and head-to-head studies. Postmenopausal women are at increased risk of osteoporosis and fracture, and the increasing use of aromatase inhibitors in the adjuvant treatment of postmenopausal breast cancer patients will require appropriate consideration of fracture risk, with the use of anti-osteoporotic therapies, if necessary. *BoneKEy-Osteovision*. 2006 June;3(6):5-13.

Introduction

Estrogens stimulate normal breast epithelium and breast cancer cell proliferation, thus enhancing the growth of most breast cancers (1;2). Estrogen deprivation – achieved by blocking or reducing endogenous levels of estrogen - forms the basis of endocrine treatments for breast cancer. Until recently, the selective estrogen receptor modulator tamoxifen had been the mainstay of early breast cancer treatment, with the assumption that its partial estrogen agonist activity had a protective effect on bone (3;4). Due to their improved efficacy and tolerability profiles, it is likely that third-generation aromatase inhibitors (AIs) will replace tamoxifen as the preferred treatment for postmenopausal patients with both early and advanced breast cancer (5). However, because AIs profoundly reduce the already low circulating estrogen levels in postmenopausal women by a further 80 to 90%, these agents may also have deleterious effects on bone.

There are two types of AIs, steroidal (or 'irreversible', substrate-site binding type I) and non-steroidal (heme-binding, type II), known to differ with respect to their enzyme binding sites and effects on the aromatase enzyme. Both the non-steroidal AIs, anastrozole and letrozole, and the steroidal AI exemestane, have been approved as second-line treatments for estrogen receptor-positive metastatic breast cancer after first-line treatment with tamoxifen. However, the recent approval of these agents for use in adjuvant treatment of early breast cancer, which usually entails treatment for up to 2-5 years, makes it important to evaluate the long-term effects of these agents on bone health, particularly in this setting.

Effects of the Third-Generation AIs on Bone

Preclinical Studies

Some preclinical data suggest that differences might exist between exemestane and the non-steroidal AIs. Rather than increasing bone turnover in ovariectomized rats, exemestane and its 17-hydro metabolite appeared to prevent loss of BMD and to reduce markers of bone turnover (6;7). This effect was attributed to a possible androgenic effect of exemestane, due to structural similarities with androstenedione and to stimulation of androgen receptors. However, the utilized dose was very high (40 times greater than the human clinical dose), and the ovariectomized rat model may not be appropriate for examining the potential effects of such drugs on bone in humans. For example, rats have no peripheral tissue aromatase activity and ovariectomy usually results in complete estrogen deficiency, though peripheral estrogen production may be enhanced in some rat models via a positive feedback loop. In the setting of complete estrogen deficiency in the rat, letrozole has no impact on bone turnover or bone mineral density, whereas exemestane decreases bone turnover and improves bone density, suggesting that androgenic effects of the steroidal inhibitor can be observed in this setting (8). It is unclear whether this effect has any clinical relevance in postmenopausal women where all aromatase inhibitors will likely increase bone turnover by reducing estrogen levels.

	Anastrozole (n=29)	Letrozole (n=29)	Exemestane (n=32)
Bone ALP (formation)			
Estimated % change*	+1.9	+2.9	+6.6
95% CI	(-4.3, 8.6)	(-2.9, 9.1)	(0.8, 12.7)
PINP (formation)			
Estimated % change*	+13.6	+11.4	+23.5
95% CI	(3.0, 25.3)	(1.8, 21.8)	(13.3, 34.6)
CTX (resorption)			
Estimated % change*	+16.6	+27.7	+23.1
95% CI	(2.9, 32.2)	(13.9, 43.2)	(10.3, 37.4)
PTH			
Estimated % change*	-7.6	-10.7	-20.5**
95% CI	(-18.0, 4.0)	(-19.9, -0.4)	(-28.4, -11.8)

*Estimated % change from baseline (computed from back transformed LS mean from ANCOVA)
*p-value versus anastrozole = 0.04

Table 1: Bone biomarker changes at 24 weeks in a comparative study of the three commercially available AIs in healthy postmenopausal women (13).

Effects on Bone Turnover in Human Subjects

While there are some discrepancies in the effects of the various AIs on bone turnover markers, it is reasonable to conclude that all three currently available agents are associated with increased bone turnover. The discrepancies may relate to the relatively short duration (≤6 months) and relatively small numbers of subjects in the studies. Thus in a 12-week study examining the effects of anastrozole (1 mg po qd), letrozole (2.5 mg po qd), and exemestane (25 mg po qd) in healthy volunteers, exemestane significantly increased both markers of bone formation (P1NP; P = 0.01) and resorption (CTx; P = 0.02) compared to the other AIs or placebo (9).

These results were confirmed in a recently published follow-up to this study with data examined over 24 weeks of treatment exposure. Anastrozole and letrozole appeared to have neutral effects on biochemical markers of bone resorption and formation, while exemestane increased PINP and serum CTx (10). Increases in bone resorption markers have also been reported with letrozole. In a 3-month pilot prevention study of 32 patients with benign breast disease or ductal/lobular carcinoma *in situ* (DCIS/LCIS), letrozole treatment was associated with a significant increase (25%; P = 0.02) in the bone resorption marker CTx (11). Data on markers of bone formation were not reported. In a further 6-month, double-blind, placebo-controlled study in 42 healthy volunteers (12), letrozole significantly increased urinary pyridinoline and deoxypyridinoline excretion by approximately 14% (P < 0.05), without an expected compensatory increase in the bone formation markers BAP or osteocalcin.

	Anastrozole (14;15)	**Exemestane** (16)
Bone resorption markers, increase (%)		
SCTx	–	35.1 (2.0)
UNTx	12.9 (1.0)	13.7 (2.0)
Bone formation markers, increase (%)		
BAP	21.5 (1.0)	51.7 (2.0)
Osteocalcin	–	23.9 (2.0)
PINP	–	44.1 (2.0)

sCTx, serum type I collagen C telopeptide; uNTx, urinary type I collagen N-telopeptide; BAP, bone-specific alkaline phosphatase; PINP, serum procollagen type I aminoterminal propeptide

Table 2: Effects of anastrozole and exemestane on markers of bone turnover in clinical studies of patients with early breast cancer. Currently, there are no bone marker data available for letrozole in these settings. Numbers in parentheses indicate the duration of treatment in years.

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More recently, all three AIs were compared in an open, randomized, multicenter pharmacodynamic study (13). 102 healthy postmenopausal volunteers were randomized to receive anastrozole (1 mg/day), letrozole (2.5 mg/day), or exemestane (25 mg/day) daily for 24 weeks. In the 90 participants evaluable at 24 weeks, increased markers of bone resorption and formation were observed with all three agents, while no statistically significant differences were observed between the AIs (Table 1). Serum PTH decreased in all three treatment groups, consistent with a net efflux of calcium from bone and a significantly greater decrease in PTH with exemestane (p=0.04 vs. anastrozole).

These studies suggest that the steroidal and non-steroidal AIs appear to have similar effects on bone biochemical measurements, and thus on bone turnover, in human subjects. Similar effects have been observed in available studies of anastrozole and exemestane in early breast cancer (Table 2) (14-16). Given these effects, the use of aromatase inhibitors in breast cancer may be expected to increase fracture rates.

Effects on BMD and Fracture Rates

The effects of the third-generation AIs on BMD in patients with early breast cancer are summarized in Figure 1 (17-19). It is important to stress that these data were combined from multiple studies and no head-to-head studies are available.

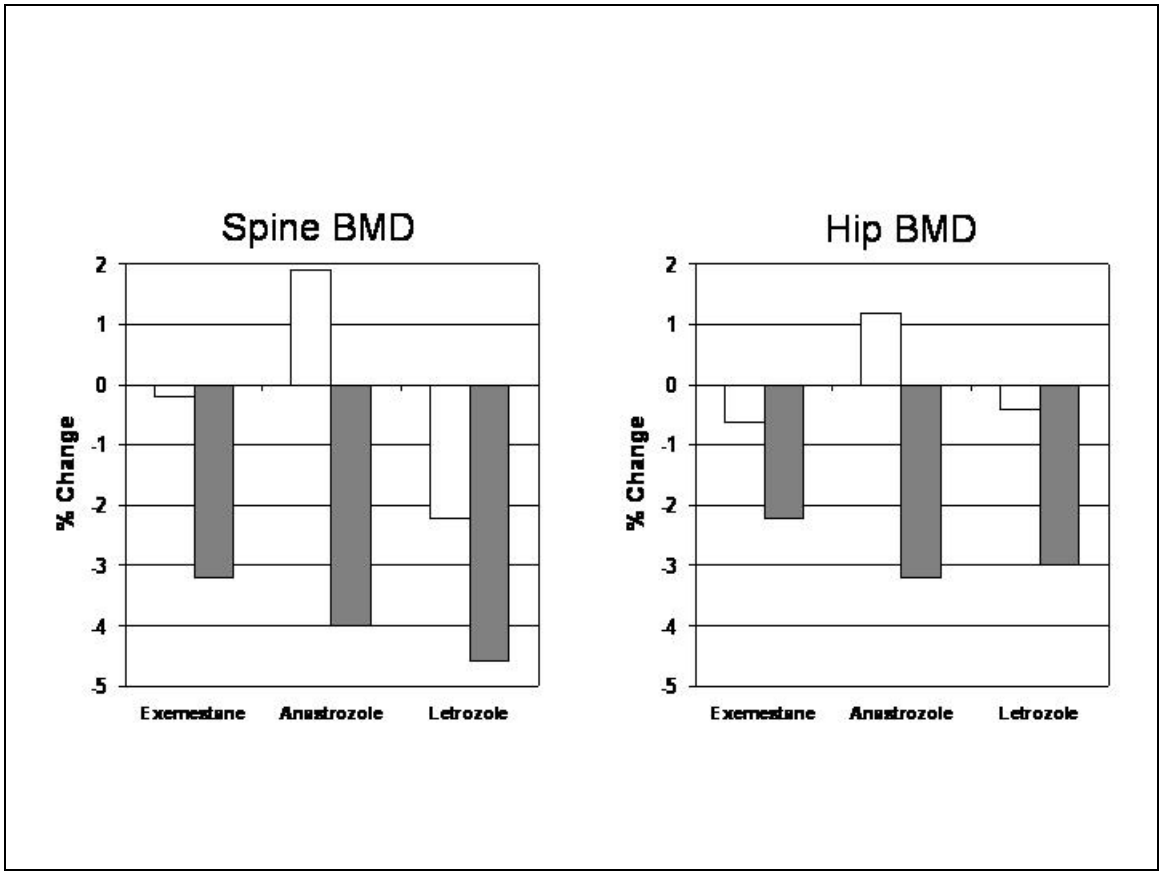

Figure 1: Effects of anastrozole, letrozole and exemestane on bone mineral density in clinical studies in patients with early breast cancer. Changes in the exemestane study (18) are over the first year, while 2-year data are shown for anastrozole (17) and letrozole (19). Note: These data are from multiple studies and it is difficult to assess the differences between agents in the absence of head-to-head comparisons.

It is also critical to appreciate that as the comparator these studies have usually used tamoxifen, which is known to exert a protective effect on the skeleton. Thus, several studies have demonstrated maintained or increased bone mineral density at the spine and hip in postmenopausal women with breast cancer receiving tamoxifen, but a significant effect on fracture risk has not been documented in this population. Tamoxifen has been shown to reduce the incidence of spine, hip and distal radial fractures by 32% in a large primary prevention breast cancer study after an average of 7 years follow-up (20). More recently, tamoxifen was associated with a similar incidence of fractures at these skeletal sites as the SERM, raloxifene, in a head-to-head breast cancer prevention study (1.06% vs. 0.99%) (http://www.cancer.gov/newscenter/pressreleases/STARresultsQandA). The inability of raloxifene to reduce peripheral fracture risk in more osteoporotic individuals means that the ability of tamoxifen to reduce fracture risk in women with breast cancer and accelerated bone loss due to systemic therapy remains somewhat uncertain. Nonetheless, the effect of AIs on bone loss and fracture rates may appear somewhat greater due to the administration of tamoxifen in the comparator arm. Likewise, in sequential or cross-over studies where AIs are administered after tamoxifen, the withdrawal of tamoxifen may contribute to bone loss and fracture rates.

With the above provisos in mind, each of the three commercially available AIs has been associated with an increased incidence of fracture (Figure 2).

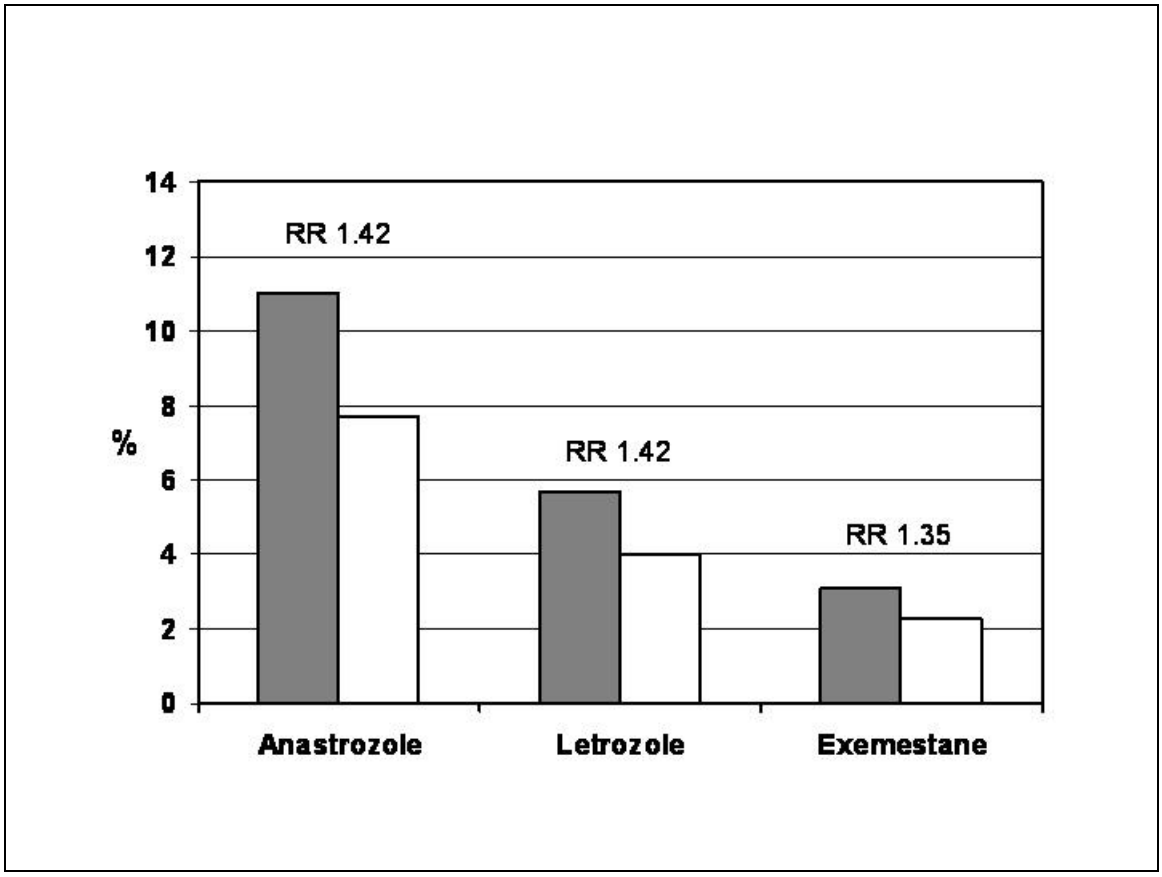

Figure 2: Effects of anastrozole (21), letrozole (24) and exemestane (25) on fractures in clinical studies of patients with early breast cancer where the comparator group was receiving tamoxifen. The relative risks (RR) are similar. Note: These data are from multiple studies and it is difficult to assess the differences between agents in the absence of head-to-head comparisons.

At a median of 33 months follow-up in the ATAC study (Anastrozole, Tamoxifen, Alone or in Combination), the overall incidence of fractures was lower in the tamoxifen arm compared with the anastrozole arm (3.7% *vs.* 5.9%; P < 0.0001). The incidence of hip fractures was low (0.4% in both arms) reflecting the relatively young age of the study participants (mean age 64 years). The increase in fracture risk remained throughout exposure to treatment but the relative risk versus tamoxifen did not appear to worsen with continued treatment (14). In the latest tolerability update from ATAC (median duration of treatment: 60 months) the overall fracture rates were 11.0% and 7.7% in the anastrozole and tamoxifen groups, respectively (P < 0.0001) (21).

Letrozole has been compared to placebo in women with breast cancer who had completed the usual five years of tamoxifen therapy (MA-17 study) (22). The study was stopped after a median follow up of just 2.4 years due to a significant improvement in breast cancer outcomes in the letrozole users. However, within this time frame, more diagnoses of osteoporosis were made in the letrozole group compared to the placebo group, at 5.8% and 4.5% respectively (p = 0.07) suggesting that, like anastrozole, letrozole increases bone loss. The increased fracture risk was not significant, but a trend was observed at the time of study discontinuation (3.6% vs. 2.9%, p = 0.24). Updated safety data revealed that the increased incidence of osteoporosis is now statistically significant in the letrozole group compared with placebo (8% vs. 6%, respectively; P = 0.003); however, fracture rates remained similar in the two groups (5.3% vs. 4.6%, respectively; P = 0.25) (23). More recently, a study of letrozole vs. tamoxifen (BIG 1-98) in women with primary breast cancer found that the increased fracture risk with letrozole was statistically significant (5.7% vs 4.0%, p < 0.001) (24).

Exemestane has been studied in patients who had received 2-3 years of tamoxifen therapy (25). At this time point, women were randomized to complete 5 years of tamoxifen therapy or to switch to exemestane for the remainder of the 5 years (the IES study). Fractures were reported more frequently in the exemestane group than in the tamoxifen group, although the difference was not statistically significant (3.1% vs. 2.3%, P= 0.08) (25). More exemestane-treated patients had newly diagnosed osteoporosis (7.4% vs. 5.7%; P = 0.05) than patients who continued on tamoxifen. These data suggest that despite its steroidal structure and putative androgenic activity, exemestane does not appear to have a protective effect on bone in patients with breast cancer.

Despite the higher incidence of fractures in the AI arm of these studies, the overall risk:benefit ratio favors the use of AIs, a benefit that may become even more marked if the effects on distant disease-free survival translate into improved overall survival.

Summary

Because of their mode of action, the AIs as a group have the potential to have deleterious effects on the skeletal health of postmenopausal women receiving treatment for early breast cancer. Results to date suggest that in clinical studies all three third-generation AIs affect bone turnover, BMD, and fracture risk. There is a critical need, however, for comparative data from prospective, randomized trials that directly assess the clinical impact of the AIs on bone. One such trial (MA-27), a head-to-head comparison of anastrozole and exemestane, will shortly complete recruitment. Guidelines for the identification of high risk women in whom BMD assessments are indicated have been produced in many countries. For example, according to the National Osteoporosis Foundation (26), BMD measurement should be performed in all women aged 65 years and older regardless of risk factors, in younger postmenopausal women with one or more risk factors (other than being white, postmenopausal and female), and in postmenopausal women who present with fractures. If these general guidelines were applied to women with breast cancer, it would be appropriate for patients <45 years old who became postmenopausal because of their therapy, and patients who receive

adjuvant aromatase inhibitors, to be considered for early BMD assessment. The current American Society of Clinical Oncology guidelines (27) also recommend BMD assessment for all women commencing AI therapy. Although most of these women would have normal BMD, the screening might identify patients who are at increased risk and who may subsequently want to consider treatment.

In more limited health care systems, BMD measurements may be restricted to those women with other risk factors of osteoporosis. Several risk factors for osteoporotic fracture have been identified in postmenopausal women, including advancing age, prior fracture, family history of fracture, low body mass index, premature menopause, and smoking. This case-finding approach has been advocated by the Royal College of Physicians in the UK (28). It is likely that these risk factors could also be used to identify those postmenopausal women receiving AI therapy who may require BMD investigation.

Further follow-up of the ongoing adjuvant studies will confirm the long-term effects of AIs on bone. Until such long-term data become available, patients receiving these agents who are known to be osteoporotic or are thought to be at increased risk of fractures should be reviewed and managed according to local practice.

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