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Aromatase Inhibitor-Associated Bone Loss

Clinical Considerations

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Abstract

Aromatase inhibitors (AIs) are standard treatments for postmenopausal women with estrogen responsive breast cancers. The mechanism of AIs, inhibition of the aromatase enzyme that causes decreases in endogenous estrogens, is responsible for bone loss and increased fractures. Screening and prevention of AI-induced bone loss closely follows the standard recommendations for postmenopausal osteoporosis. Lifestyle changes such as increasing physical activity and weight-bearing exercise, stopping smoking, and taking adequate amounts of daily calcium and vitamin D promote bone and overall health. Bisphosphonates are specific inhibitors of osteoclasts and reduce bone loss in women treated with AIs. The optimal dose administration schedule and duration of bisphosphonate treatment for AI-induced bone loss remains undefined.

The use of aromatase inhibitors (AIs) in the treatment of breast cancer has expanded with randomized trials showing that AIs are superior to tamoxifen in the metastatic and adjuvant treatment settings in postmenopausal women. The current American Society of Clinical Oncology (ASCO) and International guidelines recommend either initial treatment with AIs or switching to AIs 2–3 years after tamoxifen in postmenopausal women with early stage breast cancer.[1,2] AIs inhibit the cytochrome P450 (CYP) 19 isoenzyme[3] responsible for the peripheral conversion of androgens to estrogens.[4] Estrogens maintain bone mass and treatment with AIs result in bone loss as a result of estrogen deficiency.[5] As more women are exposed to AIs, it is critical to understand their adverse effects on bone, monitoring for bone loss, and treatments that mitigate bone loss.

1. Mechanisms of Bone Loss and Estrogen Deficiency

Estrogens comprise a group of steroid hormones that function as the primary female sex hormones.[6] In premenopausal women the primary source of estrogen is the ovaries, whereas in postmenopausal women it is via aromatase that converts adrenal androgens to estrogens. Estradiol is the main estrogen and levels of 40–60 pg/mL are considered the minimum levels required to prevent bone loss; postmenopausal women lose bone when the estradiol levels fall below 30 pg/mL.[6-8]

Estrogens play a critical role in maintaining normal bone mass. Breast cancer treatments such as surgical oophorectomy,[9] gonadotropin-releasing hormone (GnRH) agonists,[10] chemotherapy-induced ovarian failure[11,12] and AIs all decrease endogenous estrogens and cause bone loss. The more sudden and severe the estrogen deprivation occurs, the greater the magnitude of bone loss. For example, bone loss in the lumbar spine over 1 year is about 3- to 4-fold higher in premenopausal women who develop chemotherapy-induced ovarian failure or who receive GnRH agonists than in postmenopausal women receiving AIs, which is about 2-fold higher than healthy women who are newly postmenopausal.[11,13-15] In contrast, hormone replacement therapy[16,17] and the selective estrogen receptor modulators tamoxifen and raloxifene preserve postmenopausal bone mass.[17,18] To understand the importance of estrogen deficiency in bone loss, it is useful to review the process that occurs in healthy bone.

Healthy bone strength and structural integrity is governed by a number of interrelated factors including the microarchitecture, geometry, mineralization, collagen matrix and bone remodelling.[19,20] Bone remodelling is a dynamic balance between bone resorption and new bone formation.[21] This balance occurs in discrete areas called remodelling units and is mediated by two cell types: (i) the osteoclasts that resorb bone; and (ii) the osteoblasts that make new bone. When resorption exceeds the formation of new bone, there is bone loss. Osteoclast and osteoblast function is governed by several regulators, including: (i) central control of bone mass via the sympathetic nervous system;[22] (ii) systemic factors such as estrogens and other hormones; and (iii) locally produced autocrine and paracrine factors within the microenvironment of the remodelling unit.[23] Prime examples of such factors are receptor-activator for nuclear factor-κB (RANK) ligand (RANKL), RANK receptor and osteoprotegrin (OPG).[24]

RANKL, a member of the tumour necrosis factor family, is produced by osteoblasts and binds to the RANK receptor on osteoclasts. Ligand binding stimulates haematopoietic precursors to differentiate into multinucleated osteoclasts and activates osteoclasts to increase bone resorption.[25] Similarly, OPG is secreted from osteoblasts, binds RANKL and decreases osteoclast-mediated bone resorption. Simply stated, RANKL drives resorption, OPG puts the brakes on, and the ratio between these two factors governs normal remodelling, osteoporosis and other metabolic bone diseases, and tumour-related osteoclast activation.[23,26-28]

The ratio of RANKL to OPG is influenced by estrogens as well as other hormones, cytokines and growth factors.[24,29] Estrogens stimulate osteoblasts to increase OPG, RANKL and other autocrine osteoblast growth factors such as insulin growth factor-1, transforming growth factor-β (TGF-β), type-1 procollagen and bone morphogenic protein 2. Estrogens also increase inhibitors of osteoclast differentiation and activation, such as TGF-β, and inhibit expression of interleukin-6, which is a potent stimulator of osteoclasts.[21] Conversely, estrogen deficiency states such as those caused by breast cancer treatment have opposite effects, resulting in increased osteoclast differentiation and activation leading to increased bone resorption and bone loss.

2. Aromatase Inhibitors (AIs) Cause Estrogen Deficiency

Aromatase is the final step in the conversion of the androgen precursors to estrogens. In postmenopausal women, AIs cause relatively rapid decreases in circulating estrogen levels, leading to bone loss.[30,31] The AIs are divided into steroidal inac-

Table I. Fractures in the major randomized aromatase inhibitor (AI) trials

Trial	No. of patients	F/U (mo)	Treatment	Clinical fracture rate (%) [p-value]
AI vs TAM				
ATAC[49]	9366	100	ANA vs TAM	11.0 vs 7.7 [p < 0.001]
BIG 1-98[47]	4922	51	LET vs TAM	8.6 vs 5.8 [p < 0.01]
AI after 2–3 years of TAM				
IES[48]	4724	58	EXE vs TAM	7.0 vs 5.0 [p = 0.003]
ABCSG8/ARNO[51]	3224	28	ANA vs TAM	2.0 vs 1.0 [p = 0.015]
AI after 5 years of TAM				
MA-17[50]	5187	30	LET vs placebo	5.3 vs 4.6 [p = 0.25]

ANA = anastrozole; **EXE** = exemestane; **F/U** = follow-up; **LET** = letrozole; **TAM** = tamoxifen.

tivators (type I) and non-steroidal inhibitors (type II). Exemestane is a steroidal analogue of androstenedione and binds irreversibly to aromatase.[32,33] Type II inhibitors, such as letrozole or anastrazole, bind reversibly to the heme group of the enzyme by way of a basic nitrogen atom. At clinical doses, these third generation AIs are successful in inhibiting greater than 97% of aromatase activity *in vivo*.[30,34,35] The half-life of these compounds varies from 27 hours for exemestane[33] to 48 hours for letrozole and anastrazole.[36,37] *In vivo* animal studies suggest that exemestane may be more bone sparing than letrozole,[38] possibly attributed to the androgenic structure;[39] however, this remains to be validated in the MA-27 trial[40] that randomizes postmenopausal women to either exemestane or anastrazole and includes endpoints such as bone mineral density (BMD) and fractures.

3. AIs Increase Fracture Risk

There are several recent reviews of AIs and their effects on bone.[41-46] Table I describes the fracture rate in the major AI trials.[47-51] With exception of the MA-17 trial,[50] all other adjuvant AI trials demonstrate a statistically significant increase in the rate of overall fractures. The ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial, directly comparing anastrazole with tamoxifen, is the largest randomized trial with the longest follow-up.[49] The annual incidence of fractures was higher in women receiving anastrazole compared with tamoxifen throughout the 5 years of treatment; however, beginning in the 6th year, the fracture rate decreased in the anastrazole treatment arm such that in the years 7–9, the fracture rates with both treatments were similar. This suggests that AI-related fracture rates will decrease upon cessation of the drug.

The IES (Intergroup Exemestane Study), combined ABCSG-8/ARNO (Austrian Breast and Colorectal Study Group/German ARIMIDEX-Nolvadex) and the MA-17 trial are all 'switch' trials, where trial participants received between 2 to 5 years of tamoxifen prior to being randomized to an AI or continuing to receive tamoxifen. There are several important points regarding the interpretation of the fracture rates described in the switch trials. As tamoxifen mitigates bone loss in postmenopausal women,[18] it may have contributed to decreasing the fracture rates in the AI treatment arm. In addition, in these trials calcium and vitamin D supplementation was not specifically recommended, or, if recommended, compliance was not assessed. Although the effects of calcium and vitamin D on reducing fractures is conflicting, a randomized, placebo-controlled trial from the Women's Health Initiative[52] and a randomized, placebo-controlled meta-analysis of vitamin D with or without calcium[53] suggests that calcium and vitamin D improved hip BMD and reduced hip fractures at high doses of vitamin D (700–800 IU/day). Despite the uncertainty about fractures, guidelines for cancer treatment-induced bone loss include supplemental calcium and vitamin D.[54-56]

4. AI Effects on Bone Mineral Density and Fracture Risk

In several of the AI trials, BMD and bone turnover markers were evaluated in subsets of women (table II). The percentage change from baseline of lumbar spine and hip BMD was statistically significantly higher in women receiving AIs versus tamoxifen or placebo.[13,39,57-59] Markers of bone resorption, including serum and urine n-telopeptides and serum C-terminal cross-linked telopeptide type 1 collagen, were statistically significantly increased with AI treatment. Depending the specific AI, there was a more variable effect on the markers of bone formation osteocalcin, bone-specific alkaline phosphatase and procollagen type-I N-propeptide.[57,58,60]

It is important to remember that all women with breast cancer will lose bone as a result of normal aging,[61] menopausal-mediated bone loss[62-64] and treatment-related bone loss. However, not all of these women will develop osteoporosis, a reduction in bone mass leading to fractures.[65-67] The development of osteoporosis can be thought of as an equation.[23] On one side of the equation is the peak bone mass usually attained by ages 20–29 years;[68] the other side is the ongoing loss of bone due to aging and menopause. Genetic determinants of osteoporosis, such as family history, race and low body mass index, affect this equation, as well as exposures or conditions that are potentially modifiable, such as current cigarette smoking, alcohol intake greater than two drinks per day and chronic corticosteroid therapy.[67,69] The peak bone mass minus the ongoing losses that result from aging, the estrogen deficiency of menopause and AI-induced estrogen deficiency define who will develop osteoporosis.

The clinically relevant question is how much do AIs increase the risk of osteoporosis and fractures? Fracture risk is predicted by the T-score and other risk factors such as maternal history of hip fracture.[66,67,70,71] The T-score is defined as the number of standard deviations an individual's BMD falls below the normal distribution of healthy women aged 20–29 years.[68] Normal is considered a T-score greater than −1, osteopenia score is between −1 and −2.5, osteoporosis score is less than or equal to −2.5 and severe osteoporosis is a score of less than or equal to −2.5 with one or more fractures.

The effect of AIs to cause osteopenia or osteoporosis is described in table III. The delayed zoledronic acid treatment arm in Z-FAST (Zometa-Femara Adjuvant Synergy Trial) is a useful example, where letrozole treatment resulted in only 8% and 15% of women requiring zoledronic acid for a T-score less than −2 at 12 and 36 months, respectively.[72,73] Table III shows that in women with normal T-scores in the lumbar spine at baseline, 63–77% still had normal scores after 12 or 24 months of AI treatment and none of them became osteoporotic. Similarly, of the women who were osteopenic at baseline, 67–75% of these patients were osteopenic at subsequent follow-up with only 10–21% becoming osteoporotic. This suggests that the rate and magnitude of AI-induced bone loss is

Table II. Bone mineral density (BMD) in randomized aromatase inhibitor (AI) trials

Trial	No. of patients	F/U (mo)	Treatment	Lumbar spine BMD change (%) [p-value]	Hip BMD change (%)
AI vs placebo					
Lonning et al.[39]	147	24	EXE vs placebo	−2.2 vs −1.8 [p = 0.57]	−2.7 vs −1.5 [p = 0.02]
AI vs TAM					
ATAC[13]	167	24	ANA vs TAM	−4.1 vs +2.2 [p < 0.001]	−3.9 vs +1.2 [p < 0.001]
TEAM[59]	183	12	EXE vs TAM	−0.21 vs −0.06 [p = 0.25]	−2.7 vs 0.0 [p = 0.01]
AI after 2–3 years of TAM					
IES[57]	206	24	EXE vs TAM	−4.0† vs −1.1†	−2.5† vs −1.0†
AI after 5 years of TAM					
MA-17[58]	226	24	LET vs placebo	−5.4 vs −0.7 [p = 0.008]	−3.6 vs −0.7 [p = 0.044]

ANA = anastrozole; **EXE** = exemestane; **F/U** = follow-up; **LET** = letrozole; **TAM** = tamoxifen; † indicates absolute decrease in BMD.

Table III. Effect of aromatase inhibitors on T-scores

T-score[a]	Baseline BMD [n] (%)			12[72] or 24[39,57] mo BMD [n] (%)			
	normal	osteopenic	osteoporosis	normal	osteopenic	osteoporosis	missing
Z-FAST[72][b]							
normal	198 (100)			152 (77)[c]	25 (13)[c]	0[c]	21 (10)[c]
osteopenic		81 (100)		8 (10)[c]	54 (67)[c]	12 (15)[c]	7 (8)[c]
osteoporosis			0			0	
IES[57][d]							
normal	52 (100)			34 (65)[e]	8 (15)[e]	0[e]	10 (20)[e]
osteopenic		49 (100)		0[e]	36 (73)[e]	5 (10)[e]	8 (17)[e]
osteoporosis			0			0	
Lonning et al.[39][d]							
normal	27 (100)			17 (63)[e]	10 (37)[e]	0[e]	0[e]
osteopenic		28 (100)		1 (4)[e]	21 (75)[e]	6 (21)[e]	0[e]
osteoporosis			7 (100)	0[e]	1 (14)[e]	6 (86)[e]	0[e]

a T-scores in the lumbar spine.

b Treatment with letrozole in the delayed treatment arm.

c 12 mo BMD.

d Treatment with exemestane.

e 24 mo BMD.

BMD = bone mineral density.

low relative to the rates chemotherapy-induced ovarian failure or oophorectomy.

5. Monitoring and Prevention of AI-Induced Bone Loss

The ASCO guidelines[55] for monitoring BMD using dual energy x-ray absorptiometry (DXA) were developed largely from guidelines for screening, monitoring, prevention and treatment of osteoporosis in postmenopausal women.[54,66,67,74] Table IV describes indications for monitoring of BMD with DXA scanning. These guidelines are currently being updated and the recommendations for annual DXA scans and threshold for treatment based on T-scores may change.

How well are we doing with respect to bone health? A recent survey of physicians in the UK regarding practice patterns in treatment-induced bone loss in women with breast cancer revealed that a majority of physicians were not monitoring BMD in women receiving AIs, nor had confidence in their interpretation of DXA scans and knowing when to recommend treatment with bisphosphonates.[75] This survey suggests that more work is needed to educate physicians about these issues.

Most estrogen and/or progesterone receptor-positive postmenopausal women with breast cancer will receive AIs because they reduce the risk of recurrence and contralateral breast cancers. There are two points that deserve special emphasis: (i) as AIs cause bone loss, the identification of the healthcare professional (i.e. primary care doctor, gynaecologist, oncologist, endocrinologist or rheumatologist) who is going to take responsibility for bone health, including monitoring and treatment if indicated, is a necessity; and (ii) encouraging women to adopt lifestyle changes that promote not only bone health but also overall health. These include increasing physi-

Table IV. American Society of Clinical Oncology guidelines for monitoring with dual energy x-ray absorptiometry scans in women with breast cancer

Monitoring indicated for:
Women aged over 65 years
Women aged 60–64 years with the one or more of the following: family history of osteoporosis low bodyweight <70 kg prior non-traumatic fracture other risk factors such as sedentary and smoking
Postmenopausal women receiving aromatase inhibitors
Premenopausal women who develop treatment-related premature menopause

cal activity including weight-bearing exercise,[76] reducing or stopping smoking, and recommending calcium and vitamin D supplementation.[77,78]

6. Bisphosphonates and Other Treatments to Prevent AI-Induced Bone Loss

Bisphosphonates are specific inhibitors of osteoclast-mediated bone resorption.[79] Table V describes the use of bisphosphonates in women receiving AIs. The two largest randomized trials were the Z- and ZO-FAST trials, conducted in the US and Europe, respectively.[72,73,80,81] The two trials were similar in design, with postmenopausal women receiving letrozole randomized to either intravenous zoledronic acid 4 mg every 6 months (upfront treatment) for 5 years or delayed zoledronic acid (where zoledronic acid was initiated only when the T-score was less than −2). With 36 months of follow-up in the Z-FAST trial, AI-induced bone loss was completely eliminated with upfront treatment. The mean percentage increase in lumbar spine and total hip BMD was 3.7% and 1.7%, whereas the mean decrease in the delayed zoledronic acid arm was 3% and 3.5%, respectively.[73] The absolute differences were 6.7% ($p < 0.0001$) in the lumbar spine and 5.2% ($p < 0.0001$) in the hip. With shorter follow-up, the results of the ZO-FAST trial were similar.[80] Only 15% of the patients in the delayed zoledronic acid arm had a decreased T-score of less than −2 and thus received zoledronic acid. Currently, zoledronic acid every 6 months is not approved for preventing bone loss in women treated with AIs.

In the SABRE (Study of Anastrazole with the Bisphosphonate Risedronte) trial, postmenopausal women receiving anastrazole were stratified by their baseline T-scores into low risk (T-score of greater than or equal to −1), moderate-risk (T-score of less than −1 to −2) and high risk (T-score of less than −2). The women with moderate risk were randomized in a double-blind fashion to receive oral risedronate 35 mg/week or placebo, whereas women at low risk received anastrazole alone and women at high risk received anastrazole and risedronate.[82] The women at high and moderate risk who were receiving risedronate had numerically increased BMD; the women at moderate risk who were treated with placebo and the women at low risk who were treated with anastrozole alone had decreased BMD. The majority of these changes were not statistically significant because of the small samples sizes in each strata and relatively short follow-up.

The two trials in table V describe different approaches. The upfront zoledronic acid in the Z- and ZO-FAST treated all women, irrespective of the baseline T-score. After 3 years, only 15% of the delayed zoledronic acid group met criteria for receiving zoledronic acid. This suggests that upfront zoledronic acid will result in over treatment of many women. The SABRE trial utilizes risk stratification with treatment, which is based on the T-scores. This is a more clinically relevant approach and represents a model for subsequent trials.

The schedule for AI-induced bone loss was zoledronic acid every 6 months for 5 years in the Z- and ZO-FAST trials.[72,80] In the women who were randomized to receive 'upfront' zoledronic acid, the

Table V. Use of bisphosphonates in women treated with aromatase inhibitors

Trial	No. of pts	F/U (mo)	Treatment	Absolute difference in Δ BMD between pts receiving ZA and D-ZA[a] (%) [p-value]		Fractures (%)
				lumbar spine	hip	
Z-FAST[72,73]	602	12	LET + ZA/D-ZA	4.4 [p < 0.0001]	3.3 [p < 0.0001]	1.0 vs 0.7
		36		6.7 [p < 0.001]	5.2 [p < 0.001]	5.6 vs 6.3
ZO-FAST[80]	1065	12	LET + ZA/D-ZA	5.7 [p < 0.0001]	3.6 [p < 0.0001]	NA
SABRE[82]	276	12	ANA + RIS/placebo	2.1	1.4	NA

a ZA only given if T-score falls below −2.

ANA = anastrazole; **BMD** = bone mineral density; **D-ZA** = delayed zoledronic acid; **F/U** = follow-up; **LET** = letrozole; **NA** = not applicable; **pts** = patients; **RIS** = risedronate; **ZA** = zoledronic acid.

only toxicities that were increased relative to the 'delayed' zoledronic acid, in which only 15% of women received zoledronic acid, were bone pain (11–12% vs 4–7%) and fevers (15% vs < 1%) temporally associated with the zoledronic acid infusions. No moderate or severe renal dysfunction was observed.

Osteonecrosis of the jaw is an emerging problem that seems to depend on the administration frequency (monthly) and duration (in excess of 3 years) of treatment in individuals receiving zoledronic acid or other intravenous bisphosphonates for palliation of skeletal metastases.[83-85] While there is some uncertainty as to whether having a major dental procedure during bisphosphonate treatment is causal or merely associated with the development of subsequent osteonecrosis,[86] in most studies, dental surgery has emerged as a potential predisposing factor. This has led to the recommendation to have dental screening and, if necessary, dental extractions, periodontal surgery and dental implants, prior to starting treatment with intravenous bisphosphonates.[87,88] There is less known about oral bisphosphonates and jaw osteonecrosis, but cases have been reported.[89] In the Z- and ZO-FAST trials[72,73,80] and the ABCSG-12 trial,[10] after 3 years of follow-up, there were no confirmed cases of jaw osteonecrosis in women who were receiving zoledronic acid every 6 months.

If indicated by T-scores or other risk factors,[55] women receiving AIs should receive one of the approved oral bisphosphonates, including alendronate, risedronate or ibandronate.[67,79,90] Common toxicities of oral bisphosphonates include mylagias, arthralgias, constipation, diarrhoea, dyspepsia, nausea and vomiting. Recently, an intravenous dose of zoledronic acid 5 mg given annually has been approved on the basis of a large, randomized, placebo-controlled trial that demonstrated statistically significant reductions in vertebral and hip fractures in postmenopausal women with osteoporosis.[91] There was no significant renal toxicity and two cases of possible osteonecrosis were observed (one in the zoledronic acid arm and one in the placebo arm). Although there are no published randomized trials to date of women receiving AIs who have been treated with an annual dose of zoledronic acid, this seems like a reasonable option, especially if there is intolerance of oral bisphosphonates.

Denosumab, a humanized antibody to RANKL, is in ongoing phase III trials in women with postmenopausal osteoporosis, skeletal metastases and cancer treatment-induced bone loss.[92] Recently, the results of a randomized, double-blind, placebo-controlled trial of denosumab in postmenopausal women receiving AIs were presented.[93] At 12 and 24 months of treatment with denosumab, statistically significant increases in the lumbar spine, total hip and femoral neck BMD were seen, with no apparent increase in serious toxicities relative to placebo.

7. Summary and Key Points

Osteoporosis screening, treatment and prevention are part of standard practice and health maintenance for postmenopausal women. The predisposing risk factors for osteoporosis are known and guidelines for monitoring, treatment and lifestyle changes exist.[54,66,67,74] All of the approved AIs for treating postmenopausal women cause bone loss as a result of estrogen deficiency.

Health professionals should be aware of AI-induced bone loss, and within the healthcare team clearly identify who is going to take responsibility for monitoring and treating this problem. Guidelines for when to initiate and the monitoring of treatment with oral bisphosphonates have been published[55] and are being updated. These guidelines generally follow those developed for osteoporosis.

Not all women receiving AIs will require treatment with bisphosphonates. Risk stratification strategies based on baseline T-scores is being employed in clinical trials and has the potential to identify who is more or less likely to benefit from bisphosphonates. The optimal schedule and duration of zoledronic acid therapy has not been defined for AI-induced bone loss. In women with early-stage breast cancer who are receiving AIs and zoledronic acid every 6 months, the incidence osteonecrosis is zero in the first 3 years.

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