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Effects of third-generation aromatase inhibitors on bone

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ARTICLE INFO

Article history:
Received 23 June 2005
Received in revised form
29 September 2005
Accepted 13 October 2005
Available online 22 March 2006

Keywords:
Anastrozole
Letrozole
Exemestane
Bone
Bone mineral density
Fracture
Breast cancer

ABSTRACT

Low oestradiol levels in women are associated with decreased bone mineral density (BMD) and increased fracture risk. The third-generation aromatase inhibitors (AIs; anastrozole, letrozole, and exemestane) are used in the treatment of early and advanced breast cancer and act by substantially reducing oestrogen synthesis in postmenopausal women. However, due to their mechanism of action, there is concern regarding the long-term effects of these agents on bone, particularly when used in the adjuvant setting. In this paper, the currently available data on the effects of the third-generation AIs on markers of bone turnover, BMD, and fracture risk are reviewed, with the emphasis on results in the adjuvant treatment of early breast cancer. These data suggest that both the steroidal (exemestane) and non-steroidal (anastrozole and letrozole) AIs appear to affect bone turnover. Conclusions regarding any clinically relevant differences between these agents are difficult to make, and further data are awaited from long-term adjuvant use of these three agents in ongoing clinical studies. Postmenopausal women are at increased risk of osteoporosis and fracture, and the increasing use of AIs 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.

1. Introduction

Oestrogens play a critical role in the development and growth of most breast cancers. Oestrogens stimulate normal breast epithelium and breast cancer cell proliferation,[1–3] with oestrogen deprivation—achieved by blocking or reducing endogenous levels of oestrogen—forming the basis of endocrine treatments for breast cancer. Until recently, the selective oestrogen receptor modulator tamoxifen had been the mainstay of early breast cancer treatment, although the partial oestrogen agonist activity of this agent has caused concern, as long-term treatment significantly increases the risk of endometrial cancer and thromboembolic events.[4] Oestrogens also play a critical role in maintaining normal bone mass,[5] therefore long-term oestrogen deprivation may be associated with the development of osteoporosis and increased susceptibility to fractures. The partial agonist effects of tamoxifen are associated with a protective effect on bone, which may be a benefit to postmenopausal women receiving adjuvant treatment with tamoxifen for breast cancer.[6,7] However, tamoxifen treatment is associated with a significant loss of bone mineral density (BMD) in premenopausal women.[8]

Due to their improved efficacy and tolerability profiles, it is likely that the third-generation aromatase inhibitors (AIs) will replace tamoxifen as the preferred treatment for postmenopausal patients with both early and advanced breast cancer. However, because AIs profoundly reduce the already low circulating oestrogen levels in postmenopausal women by a further 80–90%, these agents may also potentially have deleterious effects on bone. There are two types of AIs, steroidal (or 'irreversible', substrate-site binding type I) and non-steroidal (haem-binding, type II), known to be different with respect to enzyme binding site and their effect on the aromatase enzyme. Both the non-steroidal AIs, anastrozole and

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doi:10.1016/j.ejca.2005.10.028

letrozole, and the steroidal AI exemestane, have been approved as second-line treatment for oestrogen receptor-positive metastatic breast cancer after first-line treatment with tamoxifen. Anastrozole and letrozole have been widely approved as first-line endocrine therapy for postmenopausal women with hormone receptor-positive metastatic breast cancer. Anastrozole is now also approved for adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer, and letrozole as extended adjuvant therapy for women who have received 5 years of tamoxifen. The increasing use of these agents in the adjuvant treatment of early breast cancer, which usually entails treatment for >5 years, means that it is important to evaluate the long-term effects of these agents on bone health.

Bone, as living tissue, forms through a modelling process when mineralised tissue is deposited at specific sites. Subsequently, the skeleton undergoes continuous remodelling throughout life. Remodelling comprises a series of interactions between mesenchymal osteoblasts and haematopoietic osteoclasts. Mature osteoclasts resorb old bone whereas osteoblasts synthesise new bone, and bone mass is maintained when the volume of bone resorbed equals the amount of new bone formed.[9] Oestrogens are known to inhibit the activity of osteoclasts and have been linked, at least in high concentrations, to an increased number of osteoblasts and osteoblast-related collagen formation. In the normal bone microenvironment (Fig. 1A) pre-osteoblasts (pre-B cells) produce receptor activator of nuclear factor κβ ligand (RANKL), which binds to a receptor on osteoclasts increasing osteoclastogenesis and activating osteoclast precursors into mature osteoclasts, which then initiate bone resorption. The extent of osteoclastic resorption to some extent depends on the rate of apoptosis in osteoclasts. RANKL has been shown to be a potent negative regulator of osteoclast apoptosis[10,11] by providing survival signalling through several pathways. However, the underlying mechanism by which apoptosis is regulated by RANKL, in both osteoclast precursors and osteoclasts, remains largely unknown and requires further study. Osteoprotegerin (produced by osteoblasts in response to oestrogen) is present in the circulation and acts as a decoy receptor for RANKL, thus serving as an inhibitory factor to shutdown osteoclast function, helping to maintain the balance between bone resorption and formation.[12]

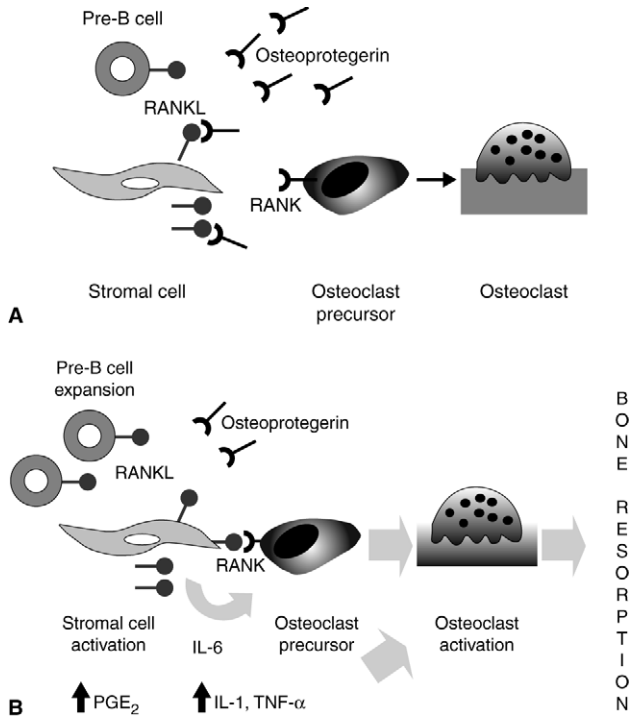
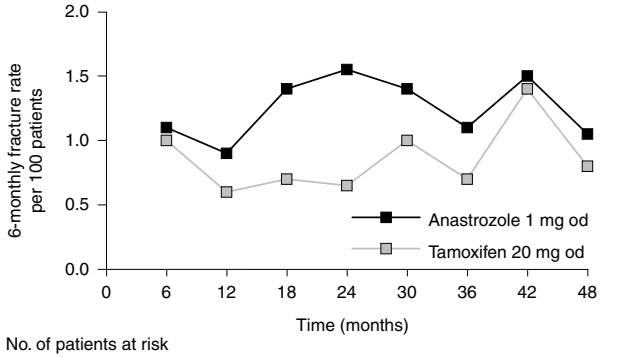


Fig. 1 – Cellular and cytokine activities in (A) the normal bone microenvironment and (B) the oestrogen-deprived microenvironment. RANK, receptor activator of nuclear factor-κβ; RANKL, RANK ligand; IL, interleukin; PGE_2, prostaglandin E2, TNFα, tumour necrosis factor α.

Oestrogen deprivation (Fig. 1B), such as that associated with AI treatment, leads to an expansion of pre-B cells, increased production of RANKL by stromal cells and increased activity of RANK, thus leading to increased levels of osteoclastic precursors and osteoclastogenesis. This, along with the reduction in circulating levels of osteoprotegerin, results in an increase in the number of mature osteoclasts and increased bone breakdown. This process is further augmented by interleukin-6 (IL-6) production, which occurs in response to oestrogen deprivation and may also occur as a consequence of the increased IL-1, prostaglandin E2 (PGE2), and tumour necrosis factor alpha (TNFα) levels observed in the presence of bone metastases in advanced breast cancer. Oestrogen deficiency may also have additional effects on bone by directly modulating the production, storage, or activity of bone growth factors (e.g., transforming growth factor-β [TGF-β]).[13] This reduces the ability of bone to respond to osteoclastic activity, and gives rise to an imbalance between bone resorption and formation thus exacerbating bone loss.

At menopause, oestrogen levels fall dramatically and the rate of bone turnover increases. As the regulatory effects of oestrogens on bone cells decline, bone resorption begins to exceed bone formation, leading to a net loss of bone and weaker bone micro-architecture.[7] This reduction in oestrogen level is associated with a reduction in BMD, and a 2- to 4-fold increase in the rate of bone loss is observed at menopause,[14] which in turn leads to an increased risk of bone fractures.[15] In fact, the risk of fractures has been shown to double for every 10% reduction in bone mass,[16] and almost one in every two women over 50 years of age will experience an osteoporosis-related fracture in their remaining lifetime.[17]

The World Health Organization (WHO) has defined osteoporosis as a BMD measurement 2.5 standard deviations (SD) or more below the young adult mean value (often expressed as a *T*-score $\leqslant -2.5$).[18] Osteoporosis commonly leads to fractures of the spine, wrist, or hip, which can cause disability or even fatality. Fractures of the hip are associated with the greatest morbidity, mortality and economic cost. Osteoporosis can significantly reduce the patient's quality of life and is proving to be a major contributor to healthcare costs.[15] Moreover, the yearly incidence of spine and hip fractures in women aged between 50 and 79 years increases with age[19,20] (Fig. 2).[21] Many other factors including family history, height, weight, general health, nutrition, and smoking also influence fracture risk.[22] As the incidence of breast cancer also increases following menopause, evaluation of the



No. of patients at risk

Months	0	6	12	18	24	30	36	42	48
Anastrozole	3092	2862	2721	2563	2410	2190	1700	1002	401
Tamoxifen	3093	2858	2692	2524	2382	2185	1690	1008	418

Fig. 2 – Six-monthly fracture rates with anastrozole and tamoxifen treatment in the ATAC trial.[21] Reproduced by permission.

potential for endocrine breast cancer treatments to add to existing risk factors for the development of osteoporosis is critical.

There are a variety of methods available for evaluating bone loss and to help identify women at risk of osteoporosis and fracture. Single-energy X-ray absorptiometry (SXA) allows quantitative assessment of BMD at peripheral sites of the skeleton, whereas dual-energy absorptiometry (DXA) provides measurements at the spine and hip.[9] In contrast to these regional measurements, biochemical markers of bone turnover in the blood or urine provide additional information on the bone remodelling process in the whole skeleton. Bone-specific alkaline phosphatase (BAP), osteocalcin, and procollagen peptides (e.g., serum procollagen type I aminoterminal propeptide [P1NP]) can be used to assess bone formation.[23] Serum and urinary excretion levels of pyridinoline cross-links (e.g., urinary free deoxypyridinoline [DPD] or serum pyridinoline [PYD]) and cross-linked peptides derived from bone collagen degradation (e.g., urinary type I collagen N-telopeptides [NTx] and urinary and serum type I collagen C-telopeptides [CTx]) can provide sensitive markers of bone resorption, with high specificity. Assays for DPD and PYD, however, are older and less specific for bone resorption. Because of the physiological link between bone resorption and formation,[24] increases in markers of bone resorption are typically accompanied by increases in markers of bone formation. While such changes may be useful for the examination of mechanisms of increases or decreases in fracture risk in various disease states or during therapy, the role of biochemical markers in predicting fracture risk is inferior to that of DXA. Fracture rate incidence remains the most clinically relevant and reliable endpoint when evaluating the effect of any treatment on bone, but if such data are not available, direct measurement of BMD (using DXA), may be the next most reliable marker.

Government and private organisations, many of which recommend BMD screening in women at risk for osteoporosis, have developed screening recommendations in postmenopausal women. According to the National Osteoporosis Foundation,[25] 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. Although most of these women would have normal BMD, the screening might identify patients who are at increased risk and may subsequently want to consider treatment.

2. Effects of the third-generation AIs on bone

As endocrine agents with similar mechanisms of action may have different toxicity profiles,[26] it is possible that the different third-generation AIs may have variable effects on bone. Such effects are difficult to study in women with advanced breast cancer, as skeletal effects may be confounded by the presence of bone metastases and the concurrent use of other therapies. It is likely, therefore, that any negative impact on bone is best determined from observations and data from preclinical and volunteer studies as well as from clinical trials in early breast cancer. Furthermore, as AIs are increasingly used as treatments for early breast cancer, any negative impact on bone may be most clinically relevant for this patient group, as they receive longer durations of treatment in the setting of a high likelihood of long-term survival, but increased risk of future osteoporotic fracture.

2.1. *Preclinical and healthy volunteer studies*

Some preclinical data suggested that differences might exist between exemestane and the non-steroidal AIs. Rather than increasing bone turnover in ovariectomised rats, exemestane and its 17-hydro metabolite appeared to prevent loss of BMD and to reduce markers of bone turnover (PYD and osteocalcin).[27,28] This effect was attributed to a possible androgenic effect of exemestane, but the utilised dose was very high (40-times greater than the human clinical dose), and the rat model appears to be inappropriate for examining the potential effects of such drugs on bone. For example, AIs suppress only ovarian oestrogen production in rats[29,30] and in some rat models, ovariectomy can actually enhance peripheral oestrogen production via a positive feedback loop that attempts to restore oestrogen production.[31,32] Primates may form better models for the postmenopausal state, as AIs have been shown to inhibit both ovarian and peripheral aromatase activity in these systems.[29,30]

The effects of exemestane and letrozole on markers of bone turnover have been investigated in a 12-week, placebo-controlled study in healthy volunteers. Here, no significant effects on markers of bone formation (BAP) or resorption (CTx) were observed with either agent compared with placebo.[33] However, in a further 12-week study examining the effects of anastrozole (1 mg by mouth every day [p.o. q.d]), letrozole (2.5 mg p.o. q.d.), and exemestane (25 mg p.o. q.d.) in healthy volunteers, exemestane significantly increased both markers of bone formation (P1NP; $P = 0.01$) and resorption (CTx; $P = 0.02$) in comparison with the other AIs or placebo.[34] 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 P1NP and serum CTx.[35] Overall, this relatively small study suggests that non-steroidal AIs might have less impact on markers of bone turnover. It is unclear whether the increased bone turnover during exemestane treatment may result in an increased or decreased fracture risk, though in most clinical studies of osteoporosis, increased bone turnover is associated with higher fracture rates.

The effects of letrozole (2.5 mg/day) on bone markers have also been investigated in two small studies: a 3-month pilot prevention study in 32 patients with benign breast disease or ductal/lobular carcinoma in situ (DCIS/LCIS)[36] and a 6-month, double-blind, placebo-controlled study in 42 healthy volunteers.[37] In the 3-month study, letrozole treatment was associated with a significant increase (25%; $P = 0.02$) in the bone resorption marker CTx.[36] Data on markers of bone formation were not reported. In the 6-month study, letrozole significantly increased urinary markers of bone resorption; PYD increased by 13.3% ($P < 0.05$) and DPD increased by 14.2% ($P < 0.05$),[37] without an expected compensatory increase in the bone formation markers BAP or osteocalcin. The clinical significance of the latter observation is unknown but if confirmed, it would suggest that the three third-generation AIs may have different effects on bone turnover.

3. Clinical studies in patients with advanced or early breast cancer

3.1. *Effects on markers of bone turnover*

The effects of the third-generation AIs on markers of bone turnover in patients with advanced or early breast cancer are summarised in Table 1.[38–43] It should be noted, however, that these data are from multiple studies and it is difficult to assess the differences between agents in the absence of head-to-head comparisons.

3.1.1. *Anastrozole*

The effects of anastrozole on markers of bone turnover have been investigated in two clinical studies: one in the advanced breast cancer setting[38] and one in patients with early disease.[39] In postmenopausal patients ($n = 34$) with advanced breast cancer, 12 weeks of treatment with anastrozole 1 mg/day resulted in significant increases in the bone formation markers BAP ($P = 0.039$) and osteocalcin ($P = 0.016$), and in the bone resorption markers CTx ($P = 0.0021$) and NTx ($P = 0.0013$). However, the presence of bone metastases significantly correlated with increased CTx and NTx; in patients without bone disease BAP, osteocalcin and CTx remained unchanged, but increased levels of NTx were observed in two patients who subsequently developed bone metastases.[38] This may suggest that in the advanced breast cancer setting, observed increases in bone marker levels may be more related to the presence of bone metastases than anastrozole treatment per se.

Table 1 – Effects of anastrozole and exemestane on markers of bone turnover in clinical studies in patients with advanced (ABC) or early (EBC) breast cancer

	Anastrozole		Exemestane	
	ABC[38]	EBC[39,40]	ABC[41,43]	EBC[42]
Bone resorption markers, increase (%)				
SCTx	8.0[a] (0.23)	–	18.9[b] (0.15)	35.1 (2.0)
UNTx	27.0[a] (0.23)	12.9 (1.0)	–	13.7 (2.0)
Bone formation markers, increase (%)				
BAP	5.7 (0.23)	21.5 (1.0)	20.9[b] (0.15)	51.7 (2.0)
Osteocalcin	14.0 (0.23)	–	9.2 (0.15)	23.9 (2.0)
P1NP	–	–	–	44.1 (2.0)

Currently, there are no bone marker data available for letrozole in these settings. Numbers in parentheses indicate the duration of treatment in years.
sCTx, serum type I collagen C-telopeptide; uNTx, urinary type I collagen N-telopeptide; BAP, bone-specific alkaline phosphatase; P1NP, serum procollagen type I aminoterminal propeptide.
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.
a Significantly correlated with the presence of bone metastases; in patients without bone metastases BAP, osteocalcin and CTx remained unchanged.
b Greater increases were seen in patients with bone metastases than in those without.

The 'Arimidex', tamoxifen, alone or in combination (ATAC) trial, conducted in 9366 postmenopausal patients with early breast cancer[44,45] included a bone sub-protocol ($n = 308$) where the effect of the different treatments on the bone turnover markers NTx and BAP were examined[39,40] as well as the effects on BMD[46] and fracture rates.[21,47] After 1 year of treatment, anastrozole 1 mg/day was associated with an increase in the bone turnover markers NTx and BAP whereas tamoxifen 20 mg/day was associated with a decrease in these markers, in line with its known bone-protective effect due to its partial oestrogen agonist activity.[39,40] Fracture rates were also reported in this study, and these data are summarised later in this review.

3.1.2. *Letrozole*

There are currently no published data on the effects of letrozole on markers of bone turnover in patients with advanced or early breast cancer.

3.1.3. *Exemestane*

The effects of exemestane on markers of bone turnover have been investigated in a sub-protocol ($n = 53$) of a randomised, double-blind, phase III study comparing exemestane with megestrol acetate in the second-line treatment of patients with advanced breast cancer.[43] After 8 weeks of treatment, exemestane significantly increased levels of both the bone resorption marker CTx and the marker of bone formation BAP ($P < 0.01$) compared with baseline values.[43] Similarly, in a smaller study including 13 postmenopausal patients with advanced breast cancer and disease progression on one non-steroidal AI, 8 weeks of exemestane treatment resulted in significant increases in BAP, osteocalcin, and CTx.[41] More

recently, treatment with exemestane over 2 years in women with early breast cancer has been shown to increase both bone resorption and formation.[42] For example, serum markers of bone formation increased by 23.9–51.7% at 2 years, while serum and urine markers of bone resorption increased by 13.7–35.1%.

3.2. *Effects on BMD and fracture rates*

The effects of the third-generation AIs on BMD and fractures in patients with advanced or early breast cancer are summarised in Table 2.[21,44,46,48–52] It is important to stress that these data are gained from multiple studies, and so it is difficult to draw any firm conclusions from indirect comparisons of the three AIs.

3.2.1. *Anastrozole*

Fracture data are available for anastrozole both in first-line advanced and adjuvant settings. In a combined analysis of two phase III trials including 1021 patients with advanced breast cancer, similar incidences of fractures were observed in the anastrozole and tamoxifen groups at a median follow-up of 18.2 months (2.2% vs. 2.9%, respectively).[48]

The ATAC bone sub-protocol examined the effect of treatment with anastrozole, tamoxifen, or the combination on BMD in 308 postmenopausal women with early breast cancer.[46] Compared with baseline, lumbar spine BMD decreased by 4% during 2 years treatment with anastrozole, whereas a 1.9% increase was observed in the tamoxifen group, probably due to the known bone-protective properties of this agent. Similar but smaller changes were observed for total hip BMD.[46]

These results suggest that it may be appropriate to consider concomitant treatment with an anti-resorptive agent such as a bisphosphonate, at least in women deemed to be at high risk of osteoporosis. For example, in a study of anastrozole in combination with the luteinising hormone-releasing hormone analogue goserelin as a treatment for premenopausal patients with breast cancer, concomitant treatment with zoledronic acid counteracted the loss of BMD seen in patients treated with goserelin plus anastrozole or goserelin plus tamoxifen.[53]

The incidence of bone fractures, a more clinically relevant endpoint than BMD, was evaluated in the main ATAC trial ($n = 9366$). At a median of 33.3 months' follow-up (median duration of treatment: 31 months), 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 number of hip fractures was small and the incidence was the same in the anastrozole and tamoxifen groups (0.4% vs. 0.4%), possibly reflecting the relatively young age of the study participants (mean age 64 years).[44] Compared with the 33-month results, at a median follow-up of 47 months (median duration of treatment: 37 months), there was little change in the overall incidence of fractures (4.4% vs. 7.1%, in the tamoxifen and anastrozole groups, respectively; $P < 0.001$); the tamoxifen arm still showed a significantly lower incidence versus anastrozole.[45] An analysis of fracture rates over time (between 6 and 48 months of treatment) showed that the fracture rate with anastrozole was stable from 18 to 24 months of treatment and the relative risk versus tamoxifen did not appear to worsen with continued treatment (Fig. 2).[21] No new safety concerns has emerged in the latest (final) tolerability update from ATAC (median duration of treatment: 60 months), with overall fracture rates being 11.0% and 7.7% in the anastrozole and tamoxifen groups, respectively ($P < 0.0001$).[54] The strength of the association of anastrozole with increased fracture risk in the ATAC trial may be questioned as there was no

Table 2 – Effects of anastrozole, letrozole and exemestane on bone mineral density and the incidence of osteoporosis and fractures in clinical studies in patients with advanced (ABC) or early (EBC) breast cancer

	Anastrozole		Letrozole		Exemestane	
	ABC[48]	EBC[21,44,46,51]	ABC[52]	EBC[50]	ABC	EBC[49]
BMD, loss (%)						
Lumbar spine	–	4.0 (2.0)	–	–	–	2.17 (1.0)[d]
Total hip	–	3.2 (2.0)	–	–	–	–
Clavicle	–	–	7.1[b] (0.5)[a]	–	–	–
Rib	–	–	14.8[b] (0.5)[a]	–	–	–
Femoral neck	–	–	–	–	–	2.72 (1.0)[d]
Osteoporosis (%)	–	–	–	5.8 (1.9)[a] 8.0 (2.0)[a,c]	–	7.4 (2.5)
Overall fractures (%)	2.2 (1.5)[a]	5.9 (2.6) 7.1 (3.1)[c]	–	3.6 (1.9)[a] 5.3 (2.0)[a,c]	–	3.1 (2.5)
Hip	–	0.5 (3.1)	–	–	–	–
Spine	–	0.9 (3.1)	–	–	–	–
Wrist/colles	–	1.5 (3.1)	–	–	–	–

Numbers in parentheses indicate the median duration of treatment in years.

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.

a Median duration of treatment not available, median follow-up presented.

b Percent change calculated from the change in linear spongious/cortical width ratio.

c Longer-term follow-up.

d Annual loss in BMD, measured over 2 years.

placebo group and the difference between the anastrozole and tamoxifen groups could be explained on the basis of a reduced fracture risk in tamoxifen-treated women. Furthermore, despite the higher incidence of fractures in the anastrozole arm, the overall risk:benefit ratio remains in favour of the AI,[39] a benefit that may become even more marked if the effects on distant disease-free survival translate into improved overall survival.[54,55]

3.2.2. *Letrozole*

There are very limited published data on the effects of letrozole on BMD, but they are suggestive of a similar effect to anastrozole. For example, the effect of a median duration of 15 months of letrozole as either first- or second-line treatment on bone mass has been evaluated in 57 postmenopausal patients with advanced breast cancer.[52] While BMD was not assessed at the most clinically relevant sites (spine and hip), bone mass as measured using radiometrical digital analysis was found to decrease significantly in the clavicle ($P = 0.006$) and rib ($P = 0.01$) during letrozole treatment compared with baseline measurements.[52]

A placebo-controlled, post-adjuvant study (MA-17) has evaluated the efficacy and safety of extended adjuvant therapy with letrozole versus no further therapy following completion of 5 years of tamoxifen treatment in patients with early breast cancer.[50] At a median follow-up of 1.9 years for safety (when 4299 patients had been enrolled), there were numerically more cases of newly diagnosed osteoporosis in the letrozole group compared with placebo (5.8% vs. 4.5%; $P = 0.07$), although this difference was not quite statistically significant. More patients in the letrozole group also reported fractures (3.6% vs. 2.9%; $P = 0.24$), but again this difference was not statistically significant at this short follow-up.[50] 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; $P = 0.25$).[56,57] Given the differences in comparator treatments (i.e tamoxifen or placebo) and the potential effects of 5 years of pre-treatment with tamoxifen in the letrozole trial, it is difficult to compare these results with those observed in the ATAC trial. Both studies suggest, however, that AIs are associated with an increased risk of osteoporosis and fracture in postmenopausal women undergoing adjuvant treatment of breast cancer. The same letrozole study (MA-17) also included a sub-study evaluating the effects of letrozole on BMD, but these results have not yet been reported. Unfortunately, as this study was terminated early following positive disease-free survival results in the first interim analysis, some questions will remain regarding the long-term effects of letrozole on bone. A new cross-over study comparing the efficacy and safety of letrozole and tamoxifen (BIG 1-98) as initial 5-year adjuvant therapy for postmenopausal women with early breast cancer should provide further data on the effects of letrozole on bone.

3.2.3. *Exemestane*

The available data suggest that, despite any apparent differences in effects on bone turnover, exemestane has a similar effect on BMD and fracture risk to that of anastrozole. In a study of 147 postmenopausal women with early breast cancer, an annual loss in spine BMD of 2.17% was observed in women receiving exemestane 25 mg daily, compared with 1.84% in the placebo group. Over the same period, femoral neck BMD decreased by 2.72% in the exemestane group compared with a 1.48% decrease in the placebo group ($P = 0.023$).[58] With regard to fractures, an interim analysis has recently been reported for a randomised trial (BIG 97-02) evaluating the efficacy and safety of switching to exemestane following 2–3 years of tamoxifen adjuvant therapy in postmenopausal women with early breast cancer.[49] In this study, at a median of 2.5 years' follow-up for efficacy (median follow-up for safety not reported), more exemestane-treated patients had newly diagnosed osteoporosis (7.4% vs. 5.7%; $P = 0.05$), and there was a trend towards more fractures in this group (3.1% vs. 2.3%; $P = 0.08$) compared with patients continuing on tamoxifen.[49] These interim data confirm 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.

4. Summary

Due to their mode of action, AIs as a group have the potential to have deleterious effects on the skeletal health of postmenopausal women receiving treatment for early breast cancer. It has been suggested that the three third-generation AIs may have differential effects on bone, particularly in terms of differences in the effects of steroidal AIs such as exemestane in comparison with non-steroidal AIs such as anastrozole or letrozole. Such differences, however, are not apparent based on data from clinical trials in breast cancer patients.[42,43,49,58] Results to date suggest that in clinical studies all three third-generation AIs affect bone turnover, BMD, and fracture risk. The availability of 5-year safety data from the ATAC trial has further quantified the impact of anastrozole on bone, though a potential protective effect of tamoxifen has to be borne in mind. Definitive and comparable fracture data for letrozole and exemestane are unlikely to be available for several years, but are awaited with interest.

Drawing conclusions regarding any clinically relevant differences between these agents is difficult as the dataset is incomplete and less mature for letrozole and exemestane compared with anastrozole. It is not unreasonable to conclude at this stage, however, that both the steroidal and non-steroidal AIs appear to have some adverse effects on bone turnover and fracture risk. There is a critical need, however, for comparative data that directly assesses the impact of the three AIs on bone, perhaps measured by markers of bone turnover and/or BMD in prospective, randomised trials.

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,[25] 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[59] also recommend BMD assessments in 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 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.[60] It is likely that these risk factors could also be used to identify those postmenopausal women receiving AI therapy who may require BMD investigations.

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.

Conflict of interest statement

None declared.

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