Breast Cancer RESEARCH

REVIEW

Aromatase inhibitor-associated bone and musculoskeletal effects: new evidence defining etiology and strategies for management

Stéphanie Gaillard and Vered Stearns*

Abstract

Aromatase inhibitors are widely used as adjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer. While the agents are associated with slightly improved survival outcomes when compared to tamoxifen alone, bone and musculoskeletal side effects are substantial and often lead to discontinuation of therapy. Ideally, the symptoms should be prevented or adequately treated. This review will focus on bone and musculoskeletal side effects of aromatase inhibitors, including osteoporosis, fractures, and arthralgias. Recent advances have been made in identifying potential mechanisms underlying these effects. Adequate management of symptoms may enhance patient adherence to therapy, thereby improving breast cancer-related outcomes.

Introduction

In 2010, it is estimated that more than 200,000 women will be newly diagnosed with invasive breast cancer in the United States [1], making it the most commonly diagnosed cancer in women. The majority of women are post-menopausal at the time of diagnosis. Adjuvant endocrine manipulations reduce the risk of breast cancer-related recurrence and death in women with hormone receptor-positive disease. The introduction of aromatase inhibitors (AIs) to the adjuvant treatment of postmenopausal women with hormone receptor-positive breast cancer has significantly changed the management of the disease. These agents are commonly used instead of or in sequence with tamoxifen because of the demonstrated improvement in disease-free survival compared to tamoxifen alone [2]. Since long-term survival rates are high in patients with early-stage breast cancer who receive AIs and treatment may continue for many years, the complications arising from therapy in this patient population can have long-term effects and may greatly impact patient quality of life.

The three third-generation AIs in routine clinical use - anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) - have similar efficacy and toxicity profiles when evaluated in cross-study comparisons. The primary adverse effects include menopausal symptoms, vaginal dryness, sexual dysfunction, and musculoskeletal symptoms, including bone demineralization with risk of osteoporosis and fracture, arthralgias, and myalgias. This review will focus on AI-associated bone and musculoskeletal toxicities, including prevalence, typical symptoms, potential etiologies, and strategies for management of these side effects.

Aromatase inhibitor efficacy and safety

Estrogen is primarily produced in the ovary prior to menopause. After menopause, estrogen production occurs in peripheral tissues (skin, muscle, fat, and benign and malignant breast tissue) through the conversion of androgens to estrogens by the P450 cytochrome enzyme aromatase (CYP19) [3-6]. There are two primary approaches to the hormonal treatment of estrogen receptor (ER)-positive breast cancers: selective ER modulators (for example, tamoxifen) that directly interact with the ER and inhibit its activity in breast tissue; and AIs that reduce post-menopausal production of estrogen [2]. The nonsteroidal AIs anastrozole and letrozole competitively inhibit aromatase, while the steroidal AI exemestane irreversibly inhibits the enzyme; however, both types of inhibitors suppress plasma and tissue estrone concentrations, the dominant estrogen in post-menopausal women, by >93% [7-9]. AIs are ineffective in women with functional ovaries because of their inability to block ovarian production of estrogen [10].

Numerous large randomized controlled trials have evaluated AIs in the treatment of early-stage hormone

*Correspondence: vstearn1@jhmi.edu
Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, 1650 Orleans Street, CRBI, Room 144, Baltimore, MD 21231, USA

Table 1. Incidence of bone fractures and osteoporosis in patients treated with aromatase inhibitors versus tamoxifen or placebo in randomized phase III trials

Study	Treatment arms (years of treatment)	Symptom	Aromatase inhibitor (%)	Tamoxifen/ placebo (%)	*P*-value
ATAC [11,21]	Anastrozole (5) versus Tamoxifen (5)	Fractures Osteopenia or osteoporosis	2.93 11	1.9 7	<0.0001 <0.0001
ABCSG8/ ARNO95 [16]	Tamoxifen (2-3) → Anastrozole (3) versus Tamoxifen (5)	Fractures	2	1	0.015
ABCSG6a [17]	Tamoxifen (5) → Anastrozole (3) versus Tamoxifen (5) → Placebo (3)	Fractures	0.8	1.1	NA
BIG 1-98 [13]	Letrozole (5) versus Tamoxifen (5)	Fractures	8.6	5.8	<0.001
IES [14]	Tamoxifen (2-3) → Exemestane (2-3) versus Tamoxifen (5)	Fracture[a] Osteoporosis	4.3 7.3	3.1 5.5	0.03 0.01
MA.17 [15]	Tamoxifen (5) → Letrozole (5) versus Tamoxifen (5) → Placebo (5)	Fracture Osteoporosis	5.3 8.1	4.6 6	0.25 0.003

[a]Fracture risk increased with exemestane versus tamoxifen (7 versus 4.9, respectively; *P*-value 0.003) after completion of therapy. ABCSG, Austrian Breast and Colorectal Cancer Study Group; ARNO, Arimidex-Nolvadex; ATAC, Arimidex, Tamoxifen, Alone or in Combination; BIG, Breast International Group; IES, International Exemestane Study; NA, not available.

receptor-positive breast cancer. The studies have consistently demonstrated improved disease-free survival when used in multiple settings: upfront in place of tamoxifen, following 2 to 3 years of tamoxifen (sequential strategy), or after completion of 5 years of tamoxifen therapy (extended strategy) [11-19]. However, there has been no overall survival advantage when compared to tamoxifen.

Results of these clinical trials have also demonstrated a favorable safety profile for the AIs compared to tamoxifen. In the long-term safety analysis of the Anastrozole, Tamoxifen Alone or in Combination (ATAC) trial, significantly fewer treatment-related adverse events were observed resulting in fewer withdrawals due to drug-related adverse events in the anastrozole group compared to tamoxifen alone. In comparison to tamoxifen, anastrozole was associated with fewer thromboembolic events, cerebrovascular events, and diagnoses of endometrial cancer [11]. However, reports of osteopenia, osteoporosis, and fracture rates were increased in the anastrozole group as were rates of dyspareunia and decreased libido secondary to vaginal dryness, increased lipidemia, and worsening joint symptoms. Similar results were seen in the major trials of each of the third generation AIs [11-18,20].

Bone demineralization and aromatase inhibitors

Numerous reports have demonstrated that aromatase suppression leads to clinically significant bone demineralization resulting in increased rates of osteopenia, osteoporosis, and fractures (Table 1). In the ATAC study, higher fracture rates were reported in the anastrozole arm when compared to tamoxifen (2.93% versus 1.9%, respectively, $P < 0.0001$, after a median follow-up of 100 months) [21]. However, after treatment was completed, fracture rates were equivalent. The fracture rate in anastrozole-treated women appeared to plateau after 24 months, with no progressive increase in fracture risk, although the fracture risk remained significant [22]. In the Breast International Group (BIG) 1-98 trial, which directly compared 5 years of adjuvant tamoxifen with 5 years of letrozole, the fracture rate was significantly higher in the letrozole group (8.6% versus 5.8%, $P < 0.001$) at 60 months follow-up [13]. The Intergroup Exemestane Study is a sequential dosing study designed to compare 5 years of tamoxifen with 2 to 3 years of tamoxifen followed by 2 to 3 years of exemestane [23]. After a median follow-up of 55.7 months, fracture rates and new diagnoses of osteoporosis were increased in patients receiving exemestane versus tamoxifen alone (4.3% versus 3.1%, respectively, for fractures, $P = 0.03$; and 7.3% versus 5.5%, respectively, for osteoporosis, $P = 0.01$) [14]. In each of these studies, the AI was compared to tamoxifen, which is thought to have a weak estrogenic effect on bone tissue, reducing bone resorption and maintaining bone mineral density [24,25]. The difference in fracture rates becomes less apparent when compared to placebo. In the National Cancer Institute of

Canada Clinical Trials Group MA.17 study in which 5 years of letrozole were compared to placebo in women who completed 5 years of tamoxifen, there was no difference in the incidence of clinical fractures in the letrozole group compared with the placebo group (5.3% versus 4.6%, $P = 0.25$); however, more women receiving letrozole reported new diagnosis of osteoporosis in the 2 years following initiation of therapy (8.1% versus 6%, $P = 0.003$) [15]. Overall, fracture and osteoporosis rates were increased regardless of which AI or dosing strategy was used.

Bone mineral density as a marker of AI-induced bone fragility

In a substudy of the ATAC trial, there was a significant reduction in lumbar spine and hip bone mineral density (BMD; 2.2% and 1.3%, respectively) in patients receiving anastrozole over the first year of treatment; while BMD significantly increased in women treated with tamoxifen over the same time period (1.0% and 0.5% increase in lumbar spine and hip, respectively) [26]. Over the 5 years of the study, the median decrease in lumbar spine BMD was -6.08% in the anastrozole-treated group compared with an increase of +2.77% in the tamoxifen-treated group [27]. Similar results were seen in the total hip measurements (-7.24% and +0.74% in the anastrozole and tamoxifen groups, respectively). After 2 years, patients in the MA.17 bone subprotocol receiving letrozole had a significant decrease in total hip (-3.6% versus -0.71%, $P = 0.044$) and lumbar spine BMD (-5.35 versus -0.7%, $P = 0.008$) compared with placebo [28]. Whether BMD can be used as a surrogate for fragility fracture risk is controversial [29].

Proposed mechanism of bone loss

Bone metabolism is a balance between osteoblastic and osteoclastic activity. Estrogen deficiency has been identified as the key factor in mediating age-related bone loss [30]. There is a clear association between post-menopausal estrogen deficiency and the development of osteoporosis. ERs and aromatase are both expressed in bone, and estrogen has been shown to regulate bone remodeling by stimulating the expression of anti-resorptive factors such as osteoprotegerin. This results in the attenuation of receptor activator of NF-kappa-B (RANK) and RANK ligand (RANKL) signaling, leading to inhibition of osteoclastogenesis and attenuated bone turnover [31,32]. Indeed, estrogen deficiency is associated with increased expression of measurable markers of bone resorption and bone formation [33].

Molecular markers of bone turnover in AI-treated patients

Markers of bone remodeling were evaluated in several studies and the results support AI-associated increase in bone remodeling. In the ATAC bone substudy, at one year patients receiving anastrozole had a significant increase in markers of bone resorption, including C-telopeptide (CTX; +26%) and N-telopeptide (NTX; +15%) along with an increase in markers of bone formation, including bone alkaline phosphatase (ALP; +20%) and procollagen type-I N-propeptide (PINP; +18%) [26]. In contrast, patients receiving tamoxifen had a decrease in both resorption and formation markers (CTX -56%, NTX -52%, ALP -16%, PINP -72%). In the MA.17 bone substudy, an increase in the bone resorption markers NTX and CTX were observed in patients treated with letrozole at 24 months (+57% and +17%, respectively, compared to +16% and -12%, respectively, in patients treated with tamoxifen) [28]. In a double-blind placebo-controlled study comparing bone turnover markers following 2 years of exemestane to placebo in women with early breast cancer, exemestane was associated with a significant increase in the markers compared to placebo (ALP +52% and +25%, respectively, and CTX +35% and -5%, respectively) [34].

Together, the data demonstrate that all AIs have potentially deleterious effects on measures of bone health with a decrease in BMD and increase in bone-remodeling. However, the overall incidence of fractures during 5 years of AI therapy is quite low. In the Anastrozole versus Letrozole, an Investigation of Quality Of Life and Tolerability (ALIQUOT) study, both anastrozole and letrozole were associated with similar effects on bone metabolism and turnover in postmenopausal women with ER-positive breast cancer [35]. In this study, discontinuing tamoxifen therapy and initiating an AI was associated with an increased rate of turnover compared to starting an AI in a patient who had never received tamoxifen. At the same time, the administration of tamoxifen after AI therapy is associated with a decrease in markers of bone resorption.

Risk factors

In the bone substudy of the BIG1-98 trial, several risk factors for the development of fractures were identified, including increased age, prior fractures, diagnosis of osteoporosis at baseline, and previous hormone therapy [36]. Similarly, another study identified eight risk factors among women with breast cancer: AI therapy, T-score <-1.5, age >65 years, low body mass index (<20 kg/m^2), family history of hip fracture, personal history of fragility fracture after age 50 years, oral corticosteroid use >6 months, and smoking [37]. Bone mineral loss was also increased in women who received letrozole in the 4 years since menopause compared to women who were more than 4 years since their menopause (median percent change -11.32 in women <4 years from last menstrual period and -5.41 in women >4 years since last menstrual

period) [27]. Each of these factors may be an important consideration in assessing the most appropriate adjuvant therapy with the least toxicity for an individual woman.

Guidelines for management of AI-associated bone loss

Given the risk of developing skeletal-related events in otherwise healthy women with early-stage breast cancer treated with AIs, there has been a significant interest in determining the best preventative measures and treatment strategies. Recent guidelines have been published with recommendations for the management of AI-induced bone loss [2,37,38]. As in all postmenopausal women, adequate dietary vitamin D and calcium intake are important for maintaining BMD [39]. Resistance and aerobic exercise also slows BMD loss in women with early breast cancer receiving cytotoxic chemotherapy [40]; however, the effects on AI-associated BMD are unknown. Reduction of other risk factors, such as cessation of smoking and minimization of other drugs associated with decreasing BMD (for example, corticosteroids), are also likely to have a positive impact on bone health. Dual energy X-ray absorptiometry (DEXA) scan to assess BMD is recommended at the initiation of therapy and at least every 2 years while receiving an AI [37].

The American Society of Clinical Oncology (ASCO) guidelines on the management of bone health issues in women with breast cancer recommend initiation of bisphosphonate therapy if osteoporosis is present on DEXA scan (T-score <2.5) [41]. The UK guidelines recommend more aggressive treatment of bone mineral loss. Bisphosphonate therapy is recommended in all elderly (>75 years of age) women with one or more risk factors for osteoporotic fracture irrespective of BMD [38]. Bisphosphonate therapy should be considered for any post-menopausal woman whose T-score falls below -2 or if the rate of bone loss in a woman with pre-existing osteopenia exceeds 4% per year. In premenopausal women receiving ovarian suppression and an AI, the threshold for intervention is a T-score <-1 (because of very rapid bone loss averaging 17% over 3 years) [42].

Which bisphosphonate to use in the treatment of AI-associated bone loss has not been determined. Studies have demonstrated that intravenous zoledronic acid, oral ibandronate, and oral risedronate increase bone mineral density in AI-treated patients [42-47]. Another unanswered question is whether bisphosphonates should be initiated at the start of AI therapy rather than delaying until osteoporosis develops. The Zometa-Femara Adjuvant Synergy (Z-FAST and ZO-FAST) trials were designed to evaluate an immediate versus delayed strategy of bone protection with zoledronic acid [43,44]. Immediate therapy was more effective in preserving BMD at 12 months than delaying bisphosphonate therapy until the lumbar spine or total hip T-score was below -2.0 or when a non-traumatic fracture occurred. Neither study was powered to show a difference in the number of fractures. In the ARIBON trial (Arimidex-Bondronate), all patients received anastrozole but osteopenic patients were randomized at the start of therapy to receive either oral ibandronate or placebo. Patients receiving ibandronate gained rather than lost BMD (lumbar spine: +2.98% compared to -3.22% in patients receiving placebo) [45]. Similar results were found in the Study of Anastrozole with the Bisphosphonate Risedronate (SABRE) [46] and Arimidex Bone Mass Index and Oral Bisphosphonates (ARBI) [47] trials, showing the BMD loss can effectively be reduced or even completely mitigated by the addition of a bisphosphonate. However, whether the increase in bone mineral density and decrease in bone turnover translates into reduced fracture risk is under debate. Recent meta-analyses of the bisphosphonates in AI patients have called their use into question, particularly for prevention of BMD loss. While bisphosphonates were associated with improved BMD, there was no effect on fracture risk [48,49].

In addition to bisphosphonates, other treatment options are emerging. Denosumab, a RANKL targeted antibody that prevents bone resorption, was shown to increase BMD in AI-treated patients [50]. Combination therapy of AIs with inhibitors of Src, a non-receptor tyrosine kinase with roles in growth, metastasis, and bone metabolism, have shown promise in restoring sensitivity to endocrine-resistant cells [51]. The effects of this combination, and in particular evaluation of the effect on markers of bone resorption, are under evaluation in phase II clinical trials.

Aromatase inhibitor-induced arthralgias

Musculoskeletal symptoms have arisen as important adverse effects of AIs. In the major phase III clinical trials that compared AI to tamoxifen, the reported incidence of musculoskeletal symptoms ranged from 5 to 36% [11-18,20] (Table 2). However, case series have reported an even higher incidence of emergence of new or worsening joint symptoms in up to 61% of AI-treated women [52-55]. By contrast, tamoxifen has not been associated with increased joint symptoms [56,57]. While AI-induced arthralgias were reported as mild to moderate in severity and did not result in significant discontinuation of medication in the large trials [58,59], in more recent analyses, severe AI-induced arthralgias resulted in therapy interruption in up to 20% of patients [52,55,60]. Therefore, AI-associated arthralgia may account for reduced medication compliance, leading to decreased efficacy and an increase in recurrence rates. Despite the frequent reporting of AI-induced arthralgias, the etiology of this adverse effect remains unknown.

The most commonly reported symptoms include morning stiffness and pain of the hands, knees, hips,

Table 2. Incidence of musculoskeletal symptoms in patients treated with aromatase inhibitors versus tamoxifen or placebo in randomized phase III trials

Study	Treatment arms (years of treatment)	Symptom	Aromatase inhibitor (%)	Tamoxifen/ placebo (%)	*P*-value
ATAC [11,12]	Anastrozole (5) versus Tamoxifen (5)	Arthralgia Carpal tunnel syndrome	35.6 3	29.4 1	<0.0001 <0.0001
ABCSG8/ ARNO95 [16]	Tamoxifen (2-3) → Anastrozole (3) versus Tamoxifen (5)	Bone pain	19	16	0.0546
ABCSG6a [17]	Tamoxifen (5) → Anastrozole (3) versus Tamoxifen (5) → Placebo (3)	Bone pain including joint pain	24.5	18.3	0.009
ITA [20]	Tamoxifen (2-3) → Anastrozole (2-3) versus Tamoxifen (5)	MSK disorders and bone fractures	9.9	6.7	0.2
BIG 1-98 [13]	Letrozole (5) versus Tamoxifen (5)	Arthralgia Myalgia	20.0 7.1	13.5 6.1	<0.001 0.19
IES [14]	Tamoxifen (2-3) → Exemestane (2-3) versus Tamoxifen (5)	Arthritis Arthralgia Carpal tunnel syndrome MSK pain Cramps Joint stiffness	14.1 18.6 2.8 21 2.3 1.9	12.0 11.8 0.3 16.1 4.2 1	0.03 <0.0001 <0.0001 <0.0001 0.0002 0.009
NSABP B33 [18]	Tamoxifen (5) → Exemestane (5) versus Tamoxifen (5) → Placebo (5)	Arthralgia	1	0.5	NA
MA17 [15]	Tamoxifen (5) → Letrozole (5) versus Tamoxifen (5) → Placebo (5)	Arthritis Arthralgia Myalgia Bone pain	6 25 15 5	5 21 12 6	0.07 <0.001 0.004 0.67

ABCSG, Austrian Breast and Colorectal Cancer Study Group; ARNO, Arimidex-Nolvadex; ATAC, Arimidex, Tamoxifen, Alone or in Combination; BIG, Breast International Group; DFS, disease-free survival; IES, International Exemestane Study; ITA, Italian Trial of Anastrozole; MSK, musculoskeletal; NA, not available; NSABP, National Surgical Adjuvant Breast and Bowel Project.

lower back, and shoulders [54,60], impairing ability to perform activities of daily living as well as work-related tasks [53,61]. In a cross-sectional analysis of post-menopausal women treated with adjuvant AI therapy at a university-based oncology clinic, the most common sites of joint pain were wrist/hand (60.4%), knee (59.7%), back (54%), ankle/foot (51.8%), and hip (42.5%) [62]. Digital stiffness, trigger finger, and carpal tunnel syndrome have been frequently reported clinical symptoms [11,55,61,63]. Surgery for carpal tunnel syndrome was found to be up to seven times more frequent in patients receiving an AI than those receiving tamoxifen [11,64]. In initial studies exemestane was associated with dramatically increased risk of carpal tunnel syndrome compared to tamoxifen (2.8% versus 0.3%, respectively). In a 100-month follow-up of the ATAC trial, symptoms were typically reported within the first few months of therapy, to be of mild to moderate intensity, and of short duration [65]. There was increased reporting of carpal tunnel symptoms, although the incidence remained low (2.6%) and generally did not require surgical intervention. In a prospective evaluation of 92 postmenopausal patients with early stage breast cancer taking adjuvant AIs, 32% of patients reported new or worsening arthralgia most commonly affecting the knees (70%), wrists (70%), and small joints of the hands (63%) [66]. Most patients reported mild to moderate symptoms that were easily managed with analgesics and very few patients discontinued therapy due to emergence of symptoms. In contrast, in a small prospective study of 25 patients, 15 patients developed AI-induced arthralgia within the first 12 months of treatment and 13 patients discontinued therapy as a result of the musculoskeletal symptoms [67].

Etiology of aromatase inhibitor-induced arthralgias

Estrogen deprivation

Post-menopausal status and estrogen deficiency are associated with the development of joint pain and joint

symptoms and frequently improve with hormone supplementation [68]. Estrogen deprivation has been hypothesized as the major cause of AI-induced arthralgias. Indeed, development of arthralgia has also been seen in patients treated with the gonadotropin-releasing agonist leuprolide, which results in menopausal range estrogen concentrations [69]. Approximately 25% of women developed arthralgia within 3 weeks of initiation of leuprolide. Alternatively, estrogen-based therapy is associated with reduced incidence of radiologic knee osteoarthritis and decreased incidence of joint pain/swelling [70-72]. However, this effect has not been seen in all studies of estrogen therapy [73]. Whether the effect is secondary to systemic or localized estrogen deficiency is unclear. ERs have been identified in cartilage and estrogen deficiency in ovariectomized rats accelerated cartilage turnover and increased cartilage surface erosion while administration of estrogen suppressed cartilage degradation significantly [74-78]. Surgically ovariectomized primates similarly develop osteoarthritic changes that can be prevented by estrogen therapy [79]. Estrogen is associated with chondroprotective effects by decreasing collagen degradation [80,81]. In addition, aromatase is expressed in synovial cells and chrondrocytes of articular cartilage with evidence of local conversion of androstenedione to estrone and estradiol [82,83]. Therefore, both systemic and local AI-induced estrogenic deficiency may impair cartilage maintenance.

Anti-nociceptive effects

Estrogen has also been associated with anti-nociceptive effects and it has been postulated that estrogen deficiency results in increased sensation of pain [84]. This hypothesis mainly stems from the observation that pain thresholds are affected by various hormonal states (increased pain thresholds during pregnancy) [85]. This estrogen-dependent effect is mediated through the spinal cord kappa-opioid analgesic system. The absence of estrogens thus would be expected to result in a reduction in analgesic effect [86]. ERs and aromatase are expressed in the central nervous system and local estrogen production may modulate pain and sensory perception [87]. In contrast, several studies have reported that pain thresholds are actually decreased when estrogen levels are high [88,89]. Given the radiologic findings associated with AI-induced arthralgia (see below), this effect is not likely solely related to pain perception.

Tenosynovial changes and joint effusions

Several studies have recently identified characteristic radiologic changes associated with AI-induced arthralgia. In a small study that evaluated 12 patients with severe AI-associated arthralgia, ultrasound evaluations revealed fluid in the tendon sheath surrounding the digital flexor tendons and MRI showed increased intra-articular fluid as well as enhancement and thickening of the tendon sheath in all 12 patients [61]. In a larger prospective trial, patients who developed AI-related arthralgia were evaluated with musculoskeletal sonography and electromyography [66]. Patients with AI-induced arthralgia had higher rates of joint effusions and more electromyography findings consistent with carpal tunnel syndrome. Interestingly, a retrospective analysis of women treated with adjuvant AI therapy showed that women who were on chronic diuretic treatment for heart disease or hypertension were less likely to have symptoms of arthralgia, muscular or skeletal stiffness (6.97% versus 15.85%, $P = 0.01$), suggesting that fluid retention within joints may play a role in AI-induced arthralgia [90].

Autoimmunity

Another possible etiology involved a potential link between AI therapy and autoimmunity. In one study, 24 women who developed disabling joint pain were referred for rheumatological consultation, radiological evaluation, and immunologic investigations [91]. Nineteen of the 24 patients were found to have inflammatory pain of multiple joints. Nine of the 19 had elevated antinuclear antibodies, four had increased rheumatoid factor serum concentrations, and two had laboratory abnormalities consistent with a systemic inflammatory syndrome. Ten patients had symptoms consistent with sicca syndrome, and one met diagnostic criteria for Sjogren's syndrome. In support of a possible autoimmune mechanism, there appears to be an association between estrogen deficiency and increased secretion of proinflammatory cytokines [92]. Estrogens have also been shown to have significant anti-inflammatory properties by repressing the transcription of proinflammatory genes through the ER [93]. In a prospective randomized study designated Exemestane and Letrozole Pharmacogenetics (ELPh), patients who developed worsening joint symptoms were referred for rheumatologic evaluation [55]. Only a small fraction of the participants had elevated concentrations of inflammatory or rheumatologic markers (5 to 18%). They were most likely to be diagnosed with a moderate intensity, non-inflammatory regional musculoskeletal disorder, including tendonitis/tenosynovitis (37%), osteoarthritis (29%), and carpal tunnel syndrome (21%). In a small cohort of the ELPh study, evaluation of concentrations of circulating inflammatory markers in patients with AI-induced arthralgia showed no significant change in the tested markers relative to pre-treatment concentrations or compared to women who did not report symptoms [94]. Although a small preliminary study, it supports other reports that AI-induced arthralgia is probably not associated with a systemic inflammatory response.

Predictive factors mediating risk of developing AI-induced arthralgia

Several studies have evaluated the risk factors associated with AI-induced arthralgia. Overweight patients and those who had previously been treated with tamoxifen were at lower risk for AI-induced arthralgia, while patients who had previously been treated with taxanes were four times more likely to develop the symptoms [54]. In a separate study, interval since menopause was the only significant risk factor (possibly linked to cytokine activity or to a more precipitous drop in estrogen levels), with women who had their last menstrual period within 5 years of starting therapy more likely to develop joint symptoms compared to those whose last menstrual period was 10 years prior to starting therapy (73% versus 35%, adjusted odds radio, 3.39; 95% confidence interval, 1.21 to 9.44; $P = 0.02$) [62]. The majority of patients (75%) developed symptoms within 3 months of starting therapy. In a prospective evaluation of musculoskeletal symptoms that develop in women treated with AI, the median time to onset of symptoms was 1.6 months and 13% of patients discontinued AI therapy after a median of 6.1 months secondary to musculoskeletal toxicity [55]. Type of surgery, radiation therapy, chemotherapy, or tamoxifen use did not predict the development of symptoms, although the report focused on the first 100 participants only.

A retrospective analysis of the ATAC trial identified several risk factors for the development of arthralgia: previous hormone therapy, hormone receptor positivity, previous chemotherapy, obesity, and treatment with anastrozole. Only women without baseline joint symptoms at the outset of the trail were included in the analysis; thus, the study does not evaluate risk factors associated with worsening joint symptoms in patients with baseline arthralgia [58]. This study reports that women with joint symptoms at the outset reported fewer symptoms during treatment, which is in contrast to other studies.

In a retrospective analysis from the ATAC trial, treatment-induced vasomotor or joint symptoms were associated with improved efficacy of the treatment, suggesting that adequate management of the symptoms is particularly important in maintaining medication compliance [95]. Women who experienced joint symptoms (with or without vasomotor symptoms) after 3 months of endocrine therapy (anastrozole or tamoxifen) had a significantly reduced risk of developing recurrent disease than those without joint symptoms (adjusted hazard ratio 0.60 (0.50 to 0.72) $P < 0.0001$). While other preliminary investigation failed to show an association between AI-related symptoms and outcomes [96], until prospective data are available, it is important to develop better symptomatic management of these symptoms and to improve adherence in women receiving endocrine treatment.

Table 3. Treatment strategies for aromatase inhibitor-associated musculoskeletal symptoms

Analgesics
Acetaminophen
NSAIDS
COX2-specific agents
Opioids
Other prescription medications
Bisphosphonates
Diuretics
Antidepressants
Anti-convulsants
Dietary supplements
Calcium/vitamin D
Omega fish oil
Glucosamine/chondroitin
Non-pharmacologic approaches
Acupuncture
Exercise
Yoga
Massage
Other
Drug holiday
Switching hormone therapy (to another AI or tamoxifen)

AI, aromatase inhibitor; COX, cyclo-oxygenase; NSAID, non-steroidal anti-inflammatory drug.

Management

No large study has focused on the optimal management of AI-induced arthralgia (Table 3). The majority of patients in the ATAC retrospective analysis had received some kind of treatment for their joint symptoms that consisted typically of non-steroidal anti-inflammatory drugs and/or other analgesics [58]. Other reports have also described successful treatment of a subset of patients with analgesics, including non-steroidal anti-inflammatory drugs, acetaminophen, and opioids [54,55,91,97]. Low dose corticosteroids were reported to be effective in one study, but the toxicity profile and long-term side effects of corticosteroids make them an unappealing choice for treatment of AI-induced arthralgia [91].

Dietary supplementation with vitamins, glucosamine and chondroitin, omega fish oils, and Chinese herbal remedies have shown variable efficacy [54,63]. A small study evaluated the effect of vitamin D and calcium supplementation started at the outset of AI therapy [98]. Although it was not a randomized placebo-controlled study, the authors showed that maintaining vitamin D levels >66 ng/ml resulted in lower rates of joint disability. Similarly, in a prospective cohort study [99], vitamin D

levels ≥40 ng/ml were associated with lower risk for development of joint pain, although the authors found that despite supplementation many women on the study did not achieve adequate vitamin D levels. A larger prospective randomized placebo-controlled trial to evaluate vitamin D supplementation in AI-induced arthralgia is ongoing (NCT00263185). Bisphosphonates were identified in a retrospective study as an inverse risk factor for developing AI musculoskeletal symptoms [100]; however, this has not been evaluated in a prospective randomized placebo-controlled trial. Diuretics were recently reported to reduce arthralgia symptoms in a retrospective study consistent with the finding of joint effusion and fluid in the tendon sheaths [90]. Duloxetine, a serotonin and norepinephrine reuptake inhibitor, was shown to significantly reduce AI-associated pain in a single-arm, open-label phase II study and improved functional status [101]. Other antidepressants and anticonvulsants are often used in the treatment of chronic pain disorders; however, their use has not been evaluated in AI-induced arthralgia.

Acupuncture has been shown to be a feasible and effective treatment modality for AI-associated arthralgia [102]. In a randomized, single-blinded sham-controlled acupuncture trial, women treated with true acupuncture reported a two-point improvement in pain score compared to women treated with sham acupuncture (80% versus 22%) [103]. Both these studies suggest non-pharmaceutical approaches may be beneficial for women with AI-induced arthralgia and enhance adherence. Other non-pharmaceutical approaches, such as exercise, yoga, and massage, may also be beneficial but have not been evaluated.

The effect of switching aromatase inhibitors on musculoskeletal symptoms was recently evaluated in the Articular Tolerance of Letrozole (ATOLL) study, a 6-month, prospective, non-randomized, multicenter trial [104]. Patients who discontinued anastrozole because of musculoskeletal symptoms were started on letrozole and assessed for recurrence of symptoms, severity, and discontinuation of therapy. At the end of 6 months after switching from anastrozole to letrozole, 71.5% of patients continued therapy with letrozole while 28.5% discontinued therapy secondary to severe joint pain. Although the joint symptoms were more tolerable and did not result in as many discontinuations, the majority of patients continued to have joint symptoms despite switching therapy. However, this study suggests that patients who are intolerant to one AI may benefit from switching to another AI to continue to receive the benefits of the hormonal adjuvant therapy. Whether switching classes of AI (from steroidal to non-steroidal or vice versa) will be associated with improvement of symptoms has not been reported. Other reasonable alternatives include a drug holiday and/or switching to tamoxifen if clinically appropriate.

This article is part of a review series on *Controversies in AI therapy*, edited by Lewis Chodosh. Other articles in the series can be found online at http://breast-cancer-research.com/series/AI_controversies.

Conclusion

AIs are widely used in the treatment of early-stage breast cancer. While results from the definitive phase III randomized clinical trials comparing AI use to tamoxifen initially suggested that AI may result in a reduced toxicity profile compared to tamoxifen, patient-reported outcomes in prospective studies demonstrate that the musculoskeletal side effects of these agents are substantial, increasing treatment-related morbidity and resulting in treatment discontinuation. Given the significantly increased risk of osteoporosis and fractures associated with AIs, a thorough assessment of risk factors prior to the start of therapy is indicated with consideration to initiating preventative measures (calcium, vitamin D, bisphosphonates as indicated) at the outset of treatment.

In our practice, we encourage all women on AIs to participate in weight bearing exercise and take calcium and vitamin D supplements, and generally follow the United States Preventative Task Force guidelines for initiation of bisphosphonate therapy if osteoporosis is present on DEXA scan [105]. No guidelines are available for the treatment of AI-associated arthralgia. We approach treating these patients on a case-by-case basis, reserving discontinuation of therapy or switching to tamoxifen for refractory cases [2]. In our experience, there is a wide variability in response to non-steroidal anti-inflammatory drugs, but newer approaches, including non-pharmacologic treatments, hold promise for improving the tolerability of AIs.

Musculoskeletal symptoms in women treated with AIs represent a significant burden whose etiology is still unexplained. There is a need to identify the mechanisms underlying the development of toxicity with a focus on determining predictive factors and prospective assessment of interventional approaches. Effective management and symptomatic treatment of these symptoms is imperative to enhance adherence to therapy, improve outcomes, and decrease breast cancer recurrences.

Abbreviations

AI, aromatase inhibitor; ALP, alkaline phosphatase; ATAC, Anastrozole, Tamoxifen Alone or in Combination; BIG, Breast International Group; BMD, bone mineral density; CTX, C-telopeptide; DEXA, dual energy X-ray absorptiometry; ELPh, Exemestane and Letrozole Pharmacogenetics; ER, estrogen receptor; NTX, N-telopeptide; PINP, procollagen type-I N-propeptide; RANKL, receptor activator of NF-kappa-B ligand.

Competing interests
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References

1. Jemal A, Siegel R, Xu J, Ward E: **Cancer Statistics, 2010.** *CA Cancer J Clin* 2010, **60:**277-300.
2. Burstein HJ, Prestrud AA, Seidenfeld J, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Malin J, Mamounas EP, Rowden D, Solky AJ, Sowers MR, Stearns V, Winer EP, Somerfield MR, Griggs JJ: **American society of clinical oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer.** *J Clin Oncol* 2010, **28:**3784-3796.
3. Simpson ER, Davis SR: **Minireview: aromatase and the regulation of estrogen biosynthesis - some new perspectives.** *Endocrinology* 2001, **142:**4589-4594.
4. Nelson LR, Bulun SE: **Estrogen production and action.** *J Am Acad Dermatol* 2001, **45(3 Suppl):**S116-124.
5. Miller WR, Hawkins RA, Forrest AP: **Significance of aromatase activity in human breast cancer.** *Cancer Res* 1982, **42(8 Suppl):**3365s-3368s.
6. Chen S, Ye J, Kijima I, Kinoshita Y, Zhou D: **Positive and negative transcriptional regulation of aromatase expression in human breast cancer tissue.** *J Steroid Biochem Mol Biol* 2005, **95:**17-23.
7. Geisler J, King N, Anker G, Ornati G, Di Salle E, Lonning PE, Dowsett M: ***In vivo* inhibition of aromatization by exemestane, a novel irreversible aromatase inhibitor, in postmenopausal breast cancer patients.** *Clin Cancer Res* 1998, **4:**2089-2093.
8. Geisler J, Detre S, Berntsen H, Ottestad L, Lindtjorn B, Dowsett M, Einstein Lonning P: **Influence of neoadjuvant anastrozole (Arimidex) on intratumoral estrogen levels and proliferation markers in patients with locally advanced breast cancer.** *Clin Cancer Res* 2001, **7:**1230-1236.
9. Geisler J, Haynes B, Anker G, Dowsett M, Lonning PE: **Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study.** *J Clin Oncol* 2002, **20:**751-757.
10. Dowsett M, Haynes BP: **Hormonal effects of aromatase inhibitors: focus on premenopausal effects and interaction with tamoxifen.** *J Steroid Biochem Mol Biol* 2003, **86:**255-263.
11. Arimidex, Tamoxifen, Alone or in Combination Trialists' Group, Buzdar A, Howell A, Cuzick J, Wale C, Distler W, Hoctin-Boes G, Houghton J, Locker GY, Nabholtz JM: **Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial.** *Lancet Oncol* 2006, **7:**633-643.
12. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, Hoctin-Boes G, Houghton J, Locker GY, Tobias JS, ATAC Trialists' Group: **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005, **365:**60-62.
13. Coates AS, Keshaviah A, Thurlimann B, Mouridsen H, Mauriac L, Forbes JF, Paridaens R, Castiglione-Gertsch M, Gelber RD, Colleoni M, Lang I, Del Mastro L, Smith I, Chirgwin J, Nogaret JM, Pienkowski T, Wardley A, Jakobsen EH, Price KN, Goldhirsch A: **Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98.** *J Clin Oncol* 2007, **25:**486-492.
14. Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, Jones SE, Jassem J, Van de Velde CJ, Delozier T, Alvarez I, Del Mastro L, Ortmann O, Diedrich K, Coates AS, Bajetta E, Holmberg SB, Dodwell D, Mickiewicz E, Andersen J, Lonning PE, Cocconi G, Forbes J, Castiglione M, Stuart N, Stewart A, Fallowfield LJ, Bertelli G, Hall E, Bogle RG, Carpentieri M, Colajori E, Subar M, Ireland E, Bliss JM, Intergroup Exemestane Study: **Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial.** *Lancet* 2007, **369:**559-570.
15. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Tu D, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Cameron DA, Palmer MJ, Pater JL: **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005, **97:**1262-1271.
16. Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, Hilfrich J, Kwasny W, Menzel C, Samonigg H, Seifert M, Gademann G, Kaufmann M, Wolfgang J, ABCSG and the GABG: **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005, **366:**455-462.
17. Jakesz R, Greil R, Gnant M, Schmid M, Kwasny W, Kubista E, Mlineritsch B, Tausch C, Stierer M, Hofbauer F, Renner K, Dadak C, Rucklinger E, Samonigg H, Austrian Breast and Colorectal Cancer Study Group: **Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a.** *J Natl Cancer Inst* 2007, **99:**1845-1853.
18. Mamounas EP, Jeong JH, Wickerham DL, Smith RE, Ganz PA, Land SR, Eisen A, Fehrenbacher L, Farrar WB, Atkins JN, Pajon ER, Vogel VG, Kroener JF, Hutchins LF, Robidoux A, Hoehn JL, Ingle JN, Geyer CE Jr, Costantino JP, Wolmark N: **Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial.** *J Clin Oncol* 2008, **26:**1965-1971.
19. Boccardo F, Rubagotti A, Puntoni M, Guglielmini P, Amoroso D, Fini A, Paladini G, Mesiti M, Romeo D, Rinaldini M, Scali S, Porpiglia M, Benedetto C, Restuccia N, Buzzi F, Franchi R, Massidda B, Distante V, Amadori D, Sismondi P: **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial.** *J Clin Oncol* 2005, **23:**5138-5147.
20. Boccardo F, Rubagotti A, Guglielmini P, Fini A, Paladini G, Mesiti M, Rinaldini M, Scali S, Porpiglia M, Benedetto C, Restuccia N, Buzzi F, Franchi R, Massidda B, Distante V, Amadori D, Sismondi P: **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial.** *Ann Oncol* 2006, **17 Suppl 7:**vii10-4.
21. Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group, Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M: **Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial.** *Lancet Oncol* 2008, **9:**45-53.
22. Locker GY, Eastell R: **The time course of bone fractures observed in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial [abstract].** *Proc Am Soc Clin Oncol* 2003; **22:**abstract 98.
23. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, Jones SE, Alvarez I, Bertelli G, Ortmann O, Coates AS, Bajetta E, Dodwell D, Coleman RE, Fallowfield LJ, Mickiewicz E, Andersen J, Lonning PE, Cocconi G, Stewart A, Stuart N, Snowdon CF, Carpentieri M, Massimini G, Bliss JM, van de Velde C, Intergroup Exemestane Study: **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004, **350:**1081-1092.
24. Love RR, Barden HS, Mazess RB, Epstein S, Chappell RJ: **Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years.** *Arch Intern Med* 1994, **154:**2585-2588.
25. Assikis VJ, Jordan VC: **Risks and benefits of tamoxifen therapy.** *Oncology* 1997, **11(2 Suppl 1):**21-23.
26. Eastell R, Hannon RA, Cuzick J, Dowsett M, Clack G, Adams JE, ATAC Trialists' group: **Effect of an aromatase inhibitor on bmd and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230).** *J Bone Miner Res* 2006, **21:**1215-1223.
27. Eastell R, Adams JE, Coleman RE, Howell A, Hannon RA, Cuzick J, Mackey JR, Beckmann MW, Clack G: **Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230.** *J Clin Oncol* 2008, **26:**1051-1057.
28. Perez EA, Josse RG, Pritchard KI, Ingle JN, Martino S, Findlay BP, Shenkier TN, Tozer RG, Palmer MJ, Shepherd LE, Liu S, Tu D, Goss PE: **Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17.** *J Clin Oncol* 2006, **24:**3629-3635.
29. Seeman E: **Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy?** *Bone* 2007, **41:**308-317.
30. Riggs BL, Khosla S, Melton LJ,3rd: **Sex steroids and the construction and conservation of the adult skeleton.** *Endocr Rev* 2002, **23:**279-302.
31. Hofbauer LC, Khosla S, Dunstan CR, Lacey DL, Spelsberg TC, Riggs BL: **Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells.** *Endocrinology* 1999, **140:**4367-4370.
32. Frenkel B, Hong A, Baniwal SK, Coetzee GA, Ohlsson C, Khalid O, Gabet Y:

Regulation of adult bone turnover by sex steroids. *J Cell Physiol* 2010, **224:**305-310.
33. Drake MT, McCready LK, Hoey KA, Atkinson EJ, Khosla S: **Effects of suppression of follicle stimulating hormone secretion on bone resorption markers in postmenopausal women.** *J Clin Endocrinol Metab* 2010, **95:**5063-5068.
34. Lonning PE, Geisler J, Krag LE, Erikstein B, Bremnes Y, Hagen AI, Schlichting E, Lien EA, Ofjord ES, Paolini J, Polli A, Massimini G: **Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer.** *J Clin Oncol* 2005, **23:**5126-5137.
35. McCaig FM, Renshaw L, Williams L, Young O, Murray J, Macaskill EJ, McHugh M, Hannon R, Dixon JM: **A study of the effects of the aromatase inhibitors anastrozole and letrozole on bone metabolism in postmenopausal women with estrogen receptor-positive breast cancer.** *Breast Cancer Res Treat* 2010, **119:**643-651.
36. Rabaglio M, Sun Z, Price KN, Castiglione-Gertsch M, Hawle H, Thurlimann B, Mouridsen H, Campone M, Forbes JF, Paridaens RJ, Colleoni M, Pienkowski T, Nogaret JM, Lang I, Smith I, Gelber RD, Goldhirsch A, Coates AS, BIG 1-98 Collaborative and International *Breast Cancer* Study Groups: **Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial.** *Ann Oncol* 2009, **20:**1489-1498.
37. Hadji P, Body JJ, Aapro MS, Brufsky A, Coleman RE, Guise T, Lipton A, Tubiana-Hulin M: **Practical guidance for the management of aromatase inhibitor-associated bone loss.** *Ann Oncol* 2008, **19:**1407-1416.
38. Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, Powles T, Selby P, Coleman RE: **Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group.** *Cancer Treat Rev* 2008, **34 Suppl 1:**S3-18.
39. Nieves JW, Barrett-Connor E, Siris ES, Zion M, Barlas S, Chen YT: **Calcium and vitamin D intake influence bone mass, but not short-term fracture risk, in Caucasian postmenopausal women from the National Osteoporosis Risk Assessment (NORA) study.** *Osteoporos Int* 2008, **19:**673-679.
40. Schwartz AL, Winters-Stone K, Gallucci B: **Exercise effects on bone mineral density in women with breast cancer receiving adjuvant chemotherapy.** *Oncol Nurs Forum* 2007, **34:**627-633.
41. Hillner BE, Ingle JN, Chlebowski RT, Gralow J, Yee GC, Janjan NA, Cauley JA, Blumenstein BA, Albain KS, Lipton A, Brown S, American Society of Clinical Oncology: **American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer.** *J Clin Oncol* 2003, **21:**4042-4057.
42. Gnant MF, Mlineritsch B, Luschin-Ebengreuth G, Grampp S, Kaessmann H, Schmid M, Menzel C, Piswanger-Soelkner JC, Galid A, Mittlboeck M, Hausmaninger H, Jakesz R, Austrian Breast and Colorectal Cancer Study Group: **Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group.** *J Clin Oncol* 2007, **25:**820-828.
43. Bundred NJ, Campbell ID, Davidson N, DeBoer RH, Eidtmann H, Monnier A, Neven P, von Minckwitz G, Miller JC, Schenk NL, Coleman RE: **Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results.** *Cancer* 2008, **112:**1001-1010.
44. Brufsky A, Harker WG, Beck JT, Carroll R, Tan-Chiu E, Seidler C, Hohneker J, Lacerna L, Petrone S, Perez EA: **Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer.** *J Clin Oncol* 2007, **25:**829-836.
45. Lester JE, Dodwell D, Purohit OP, Gutcher SA, Ellis SP, Thorpe R, Horsman JM, Brown JE, Hannon RA, Coleman RE: **Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer.** *Clin Cancer Res* 2008, **14:**6336-6342.
46. Van Poznak C, Hannon RA, Mackey JR, Campone M, Apffelstaedt JP, Clack G, Barlow D, Makris A, Eastell R: **Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial.** *J Clin Oncol* 2010, **28:**967-975.
47. Markopoulos C, Tzoracoleftherakis E, Polychronis A, Venizelos B, Dafni U, Xepapadakis G, Papadiamantis J, Zobolas V, Misitzis J, Kalogerakos K, Sarantopoulou A, Siasos N, Koukouras D, Antonopoulou Z, Lazarou S, Gogas H: **Management of anastrozole-induced bone loss in breast cancer patients with oral risedronate: results from the ARBI prospective clinical trial.** *Breast Cancer Res* 2010, **12:**R24.
48. Amir E, Ocana A, Seruga B, Josse R, Clemons M: **Medical oncology: zoledronic acid for breast cancer therapy-induced bone loss.** *Nat Rev Clin Oncol* 2010, **7:**187-188.
49. Valachis A, Polyzos NP, Georgoulias V, Mavroudis D, Mauri D: **Lack of evidence for fracture prevention in early breast cancer bisphosphonate trials: a meta-analysis.** *Gynecol Oncol* 2010, **117:**139-145.
50. Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Smith J, Fan M, Jun S: **Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer.** *J Clin Oncol* 2008, **26:**4875-4882.
51. Hiscox S, Barrett-Lee P, Borley AC, Nicholson RI: **Combining Src inhibitors and aromatase inhibitors: a novel strategy for overcoming endocrine resistance and bone loss.** *Eur J Cancer* 2010, **46:**2187-2195.
52. Presant CA, Bosserman L, Young T, Vakil M, Horns R, Upadhyaya G, Ebrahimi B, Yeon C, Howard F: **Aromatase inhibitor-associated arthralgia and/ or bone pain: frequency and characterization in non-clinical trial patients.** *Clin Breast Cancer* 2007, **7:**775-778.
53. Moxley G: **Rheumatic disorders and functional disability with aromatase inhibitor therapy.** *Clin Breast Cancer* 2010, **10:**144-147.
54. Crew KD, Greenlee H, Capodice J, Raptis G, Brafman L, Fuentes D, Sierra A, Hershman DL: **Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer.** *J Clin Oncol* 2007, **25:**3877-3883.
55. Henry NL, Giles JT, Ang D, Mohan M, Dadabhoy D, Robarge J, Hayden J, Lemler S, Shahverdi K, Powers P, Li L, Flockhart D, Stearns V, Hayes DF, Storniolo AM, Clauw DJ: **Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors.** *Breast Cancer Res Treat* 2008, **111:**365-372.
56. Cuzick J, Forbes JF, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A, International *Breast Cancer* Intervention Study I Investigators: **Long-term results of tamoxifen prophylaxis for breast cancer – 96-month follow-up of the randomized IBIS-I trial.** *J Natl Cancer Inst* 2007, **99:**272-282.
57. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M: **Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial.** *J Natl Cancer Inst* 2007, **99:**283-290.
58. Sestak I, Cuzick J, Sapunar F, Eastell R, Forbes JF, Bianco AR, Buzdar AU, ATAC Trialists' Group: **Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis.** *Lancet Oncol* 2008, **9:**866-872.
59. Burstein HJ: **Aromatase inhibitor-associated arthralgia syndrome.** *Breast* 2007, **16:**223-234.
60. Donnellan PP, Douglas SL, Cameron DA, Leonard RC: **Aromatase inhibitors and arthralgia.** *J Clin Oncol* 2001, **19:**2767.
61. Morales L, Pans S, Paridaens R, Westhovens R, Timmerman D, Verhaeghe J, Wildiers H, Leunen K, Amant F, Berteloot P, Smeets A, Van Limbergen E, Weltens C, Van den Bogaert W, De Smet L, Vergote I, Christiaens MR, Neven P: **Debilitating musculoskeletal pain and stiffness with letrozole and exemestane: associated tenosynovial changes on magnetic resonance imaging.** *Breast Cancer Res Treat* 2007, **104:**87-91.
62. Mao JJ, Stricker C, Bruner D, Xie S, Bowman MA, Farrar JT, Greene BT, DeMichele A: **Patterns and risk factors associated with aromatase inhibitor-related arthralgia among breast cancer survivors.** *Cancer* 2009, **115:**3631-3639.
63. Ohsako T, Inoue K, Nagamoto N, Yoshida Y, Nakahara O, Sakamoto N: **Joint symptoms: a practical problem of anastrozole.** *Breast Cancer* 2006, **13:**284-288.
64. Coombes RC, Paridaens R, Jassem J, Van de Velde, CJ, Delozier T, Jones SE, Hall E, Kilburn LS, Snowdon CF, Bliss JM: **First mature analysis of the Intergroup Exemestane Study.** *J Clin Oncol* 2006, **24(Suppl 18):**LBA527.
65. Sestak I, Sapunar F, Cuzick J: **Aromatase inhibitor-induced carpal tunnel syndrome: results from the ATAC trial.** *J Clin Oncol* 2009, **27:**4961-4965.
66. Dizdar O, Ozcakar L, Malas FU, Harputluoglu H, Bulut N, Aksoy S, Ozisik Y, Altundag K: **Sonographic and electrodiagnostic evaluations in patients with aromatase inhibitor-related arthralgia.** *J Clin Oncol* 2009, **27:**4955-4960.
67. Henry NL, Jacobson JA, Banerjee M, Hayden J, Smerage JB, Van Poznak C, Storniolo AM, Stearns V, Hayes DF: **A prospective study of aromatase inhibitor-associated musculoskeletal symptoms and abnormalities on serial high-resolution wrist ultrasonography.** *Cancer* 2010, **116:**4360-4367.
68. Magliano M: **Menopausal arthralgia: Fact or fiction.** *Maturitas* 2010, **67:**29-33.
69. Friedman AJ, Juneau-Norcross M, Rein MS: **Adverse effects of leuprolide**

acetate depot treatment. *Fertil Steril* 1993, **59:**448-450.
70. Zhang Y, McAlindon TE, Hannan MT, Chaisson CE, Klein R, Wilson PW, Felson DT: **Estrogen replacement therapy and worsening of radiographic knee osteoarthritis: the Framingham Study.** *Arthritis Rheum* 1998, **41:**1867-1873.
71. Hart DJ, Doyle DV, Spector TD: **Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study.** *Arthritis Rheum* 1999, **42:**17-24.
72. Chlebowski RT, Johnson KC, Kooperberg C, Hubbell A, Lane D, O'Sullivan M, Cummings S, Rohan T, Yasmeen S, Khandekar J: **The Women's Health Initiative randomized trial of calcium plus vitamin D: Effects on breast cancer and arthralgias [abstract].** *J Clin Oncol* 2006; **24:**Abstract LBA6.
73. Nevitt MC, Felson DT, Williams EN, Grady D: **The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: The Heart and Estrogen/Progestin Replacement Study, a randomized, double-blind, placebo-controlled trial.** *Arthritis Rheum* 2001, **44:**811-818.
74. Ushiyama T, Ueyama H, Inoue K, Ohkubo I, Hukuda S: **Expression of genes for estrogen receptors alpha and beta in human articular chondrocytes.** *Osteoarthritis Cartilage* 1999, **7:**560-566.
75. Tsai CL, Liu TK, Chen TJ: **Estrogen and osteoarthritis: a study of synovial estradiol and estradiol receptor binding in human osteoarthritic knees.** *Biochem Biophys Res Commun* 1992, **183:**1287-1291.
76. Claassen H, Hassenpflug J, Schunke M, Sierralta W, Thole H, Kurz B: **Immunohistochemical detection of estrogen receptor alpha in articular chondrocytes from cows, pigs and humans: in situ and in vitro results.** *Ann Anat* 2001, **183:**223-227.
77. Nilsson LO, Boman A, Savendahl L, Grigelioniene G, Ohlsson C, Ritzen EM, Wroblewski J: **Demonstration of estrogen receptor-beta immunoreactivity in human growth plate cartilage.** *J Clin Endocrinol Metab* 1999, **84:**370-373.
78. Hoegh-Andersen P, Tanko LB, Andersen TL, Lundberg CV, Mo JA, Heegaard AM, Delaisse JM, Christgau S: **Ovariectomized rats as a model of postmenopausal osteoarthritis: validation and application.** *Arthritis Res Ther* 2004, **6:**R169-80.
79. Ham KD, Loeser RF, Lindgren BR, Carlson CS: **Effects of long-term estrogen replacement therapy on osteoarthritis severity in cynomolgus monkeys.** *Arthritis Rheum* 2002, **46:**1956-1964.
80. Nielsen RH, Christiansen C, Stolina M, Karsdal MA: **Oestrogen exhibits type II collagen protective effects and attenuates collagen-induced arthritis in rats.** *Clin Exp Immunol* 2008, **152:**21-27.
81. Oestergaard S, Sondergaard BC, Hoegh-Andersen P, Henriksen K, Qvist P, Christiansen C, Tanko LB, Karsdal MA: **Effects of ovariectomy and estrogen therapy on type II collagen degradation and structural integrity of articular cartilage in rats: implications of the time of initiation.** *Arthritis Rheum* 2006, **54:**2441-2451.
82. Le Bail J, Liagre B, Vergne P, Bertin P, Beneytout J, Habrioux G: **Aromatase in synovial cells from postmenopausal women.** *Steroids* 2001, **66:**749-757.
83. Sasano H, Uzuki M, Sawai T, Nagura H, Matsunaga G, Kashimoto O, Harada N: **Aromatase in human bone tissue.** *J Bone Miner Res* 1997, **12:**1416-1423.
84. Felson DT, Cummings SR: **Aromatase inhibitors and the syndrome of arthralgias with estrogen deprivation.** *Arthritis Rheum* 2005, **52:**2594-2598.
85. Gintzler AR: **Endorphin-mediated increases in pain threshold during pregnancy.** *Science* 1980, **210:**193-195.
86. Dawson-Basoa ME, Gintzler AR: **Estrogen and progesterone activate spinal kappa-opiate receptor analgesic mechanisms.** *Pain* 1996, **64:**169-177.
87. Evrard H, Baillien M, Foidart A, Absil P, Harada N, Balthazart J: **Localization and controls of aromatase in the quail spinal cord.** *J Comp Neurol* 2000, **423:**552-564.
88. Riley JL 3rd, Robinson ME, Wise EA, Price DD: **A meta-analytic review of pain perception across the menstrual cycle.** *Pain* 1999, **81:**225-235.
89. LeResche L, Saunders K, Von Korff MR, Barlow W, Dworkin SF: **Use of exogenous hormones and risk of temporomandibular disorder pain.** *Pain* 1997, **69:**153-160.
90. Xepapadakis G, Ntasiou P, Koronarchis D, Koufoudakis D, Panousis D, Grosomanidis D, Venizelos V, Georgiadis S: **New views on treatment of aromatase inhibitors induced arthralgia.** *Breast* 2010, **19:**249-250.
91. Laroche M, Borg S, Lassoued S, De Lafontan B, Roche H: **Joint pain with aromatase inhibitors: abnormal frequency of Sjogren's syndrome.** *J Rheumatol* 2007, **34:**2259-2263.
92. Vural P, Akgul C, Canbaz M: **Effects of hormone replacement therapy on plasma pro-inflammatory and anti-inflammatory cytokines and some bone turnover markers in postmenopausal women.** *Pharmacol Res* 2006, **54:**298-302.
93. Cvoro A, Tatomer D, Tee MK, Zogovic T, Harris HA, Leitman DC: **Selective estrogen receptor-beta agonists repress transcription of proinflammatory genes.** *J Immunol* 2008, **180:**630-636.
94. Henry NL, Pchejetski D, A'Hern R, Nguyen AT, Charles P, Waxman J, Li L, Storniolo AM, Hayes DF, Flockhart DA, Stearns V, Stebbing J: **Inflammatory cytokines and aromatase inhibitor-associated musculoskeletal syndrome: a case-control study.** *Br J Cancer* 2010, **103:**291-296.
95. Cuzick J, Sestak I, Cella D, Fallowfield L, ATAC Trialists' Group: **Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: a retrospective analysis of the ATAC trial.** *Lancet Oncol* 2008, **9:**1143-1148.
96. Stearns V, Chapman J, Ma C, Ellis M, Ingle JN, Pritchard KI, Budd G, Rabaglio M, Sledge G, Le Maitre A, Elliott C, Shepherd LE, Goss PE: **Treatment-emergent symptoms and the risk of breast cancer recurrence in the NCIC CTG MA.27 Adjuvant Aromatase Inhibitor Trial.** *Cancer Res* 2009, **69:**Abstract 14.
97. Garreau JR, Delamelena T, Walts D, Karamlou K, Johnson N: **Side effects of aromatase inhibitors versus tamoxifen: the patients' perspective.** *Am J Surg* 2006, **192:**496-498.
98. Khan QJ, Reddy PS, Kimler BF, Sharma P, Baxa SE, O'Dea AP, Klemp JR, Fabian CJ: **Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer.** *Breast Cancer Res Treat* 2010, **119:**111-118.
99. Prieto-Alhambra D, Javaid MK, Servitja S, Arden NK, Martinez-Garcia M, Diez-Perez A, Albanell J, Tusquets I, Nogues X: **Vitamin D threshold to prevent aromatase inhibitor-induced arthralgia: a prospective cohort study.** *Breast Cancer Res Treat* 2010, **125:**869-878.
100. Muslimani A, Iqbal MN, Spiro TP, Chaudhry AA, Taylor HC, Daw HA: **Aromatase inhibitor (AI) related musculoskeletal (MS) symptoms: Is preventing osteoporosis the key to eliminating these symptoms?** *J Clin Oncol* 2008, **26:**9554.
101. Henry NL, Banerjee M, Blossom D, Wicha M, Van Poznak C, Smerage JB, Schott AF, Griggs JG, Hayes DF: **Duloxetine for treatment of aromatase inhibitor (AI)-associated musculoskeletal syndrome (AIMSS).** In *San Antonio Breast Cancer Symposium; December 8-12, 2010: San Antonio, Texas, USA*. 2010:PD08-06 [http://www.posters2view.com/sabcs10/viewp.php?nu=PD08-06]
102. Mao JJ, Bruner DW, Stricker C, Farrar JT, Xie SX, Bowman MA, Pucci D, Han X, DeMichele A: **Feasibility trial of electroacupuncture for aromatase inhibitor--related arthralgia in breast cancer survivors.** *Integr Cancer Ther* 2009, **8:**123-129.
103. Crew KD, Capodice JL, Greenlee H, Brafman L, Fuentes D, Awad D, Yann Tsai W, Hershman DL: **Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer.** *J Clin Oncol* 2010, **28:**1154-1160.
104. Briot K, Tubiana-Hulin M, Bastit L, Kloos I, Roux C: **Effect of a switch of aromatase inhibitors on musculoskeletal symptoms in postmenopausal women with hormone-receptor-positive breast cancer: the ATOLL (articular tolerance of letrozole) study.** *Breast Cancer Res Treat* 2010, **120:**127-134.
105. US Preventive Services Task Force: **Screening for osteoporosis: U.S. Preventive Services Task Force recommendation statement.** *Ann Intern Med* 2011 [Epub ahead of print].

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