Aromatase Inhibitor–Associated Musculoskeletal Symptoms: Etiology and Strategies for Management

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By N. Lynn Henry, MD, PhD [1], Jon T. Giles, MD [2], and Vered Stearns, MD [3]

In the United States, approximately 180,000 women are diagnosed with breast cancer annually.

In the United States, approximately 180,000 women are diagnosed with breast cancer annually.[1] The incidence of breast cancer increases with advancing age; approximately 75% of patients are postmenopausal at diagnosis.[2] Hormone receptors (HR) are overexpressed on 80% of breast cancer tumors in postmenopausal women.[3] Therefore, more than 100,000 postmenopausal women who are diagnosed with breast cancer each year in the United States are potential candidates for antiendocrine breast cancer therapy with an aromatase inhibitor (AI), either in the front-line setting or after 2 to 5 years of tamoxifen therapy.

Survival of patients with early-stage HR-positive breast cancer has significantly improved during the past few decades, in part because of the introduction of adjuvant endocrine therapy with agents such as tamoxifen.[4,5] More recently, large randomized clinical trials of the three third-generation AIs in routine clinical use—anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin)—have demonstrated improvements in disease-free and overall survival with the use of AI therapy upfront or in sequence with tamoxifen in postmenopausal women with early-stage HR-positive breast cancer.[6]

In cross-study comparisons, the three AIs appear to have both similar efficacy (Table 1) and similar toxicity profiles. The primary toxicities include decreases in bone mineral density, increases in risk of fracture, and musculoskeletal symptoms. This review will focus on AI-associated musculoskeletal toxicity, including typical symptoms, potential etiologies, and strategies for management of the side effects.

Aromatase Inhibitor Efficacy and Safety

The aromatase (CYP19) enzyme catalyzes the final step in the conversion of androgens to estrogens.[6] The nonsteroidal AIs anastrozole and letrozole competitively inhibit aromatase, whereas the steroidal AI exemestane irreversibly inhibits the enzyme. This inhibition of aromatase in postmenopausal women leads to reductions of serum estradiol concentrations significantly below postmenopausal levels, which decreases the likelihood of breast cancer recurrence in women with HR-positive tumors. AIs are ineffective in women with functional ovaries because of their inability to block ovarian production of estrogen.[7]
intent-to-treat analysis, and only two studies have demonstrated an overall survival advantage in selected subgroups (Table 1).

Overall, results of these clinical trials have demonstrated a favorable safety profile for the AIs compared to tamoxifen.[16] The serious toxicities caused by tamoxifen, notably thromboembolic disease and endometrial cancer, were not increased by AI therapy. However, the AIs were noted to cause a loss of bone mineral density, with a concomitant increased risk of fractures. Across the large randomized controlled studies, between 20% and 36% of AI-treated patients also developed arthralgias, which was statistically significantly higher than the incidence in either tamoxifen- or placebo-treated patients (Table 2).[11,14,17,18] However, the clinical impact of these AI-associated musculoskeletal symptoms (AIMSS) was not fully appreciated since few subjects in the large clinical trials were reported to discontinue therapy as a direct result of this toxicity.

**AI-Associated Arthralgias**

As the clinical importance of AIMSS has become more evident, a number of reports have characterized the variety of symptoms and syndromes that develop in AI-treated patients.

**ATAC Trial**

A comprehensive analysis of musculoskeletal data from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial revealed that 36.5% of women without preexisting joint symptoms developed arthralgias when treated with anastrozole, compared to 30.9% of women treated with tamoxifen (P < .001).[19] The majority of symptoms that developed were mild or moderate, and there was no difference in the incidence of severe arthralgias between the two treatment groups. Patients were more likely to develop pain during the first few years of treatment, although the risk persisted throughout the 5-year duration of the trial. Further description of the symptoms that developed (ie, location and character of symptoms, diagnostic evaluation by a trained musculoskeletal assessor) was not reported in this analysis.

**Columbia University Study**

Researchers at Columbia University reported the results of a cross-sectional study of 200 women on adjuvant AI therapy.[20] In their cohort, 47% reported AI-related joint pain and 44% reported joint stiffness. The arthralgias were equally divided between new onset of pain and exacerbation of preexisting symptoms, whereas the majority of joint stiffness was new since initiation of AI therapy. The most common sites of pain and stiffness reported by subjects in this study were the hands, knees, and back. Two-thirds of patients self-rated their pain as moderate or severe, which was greater than what was reported in the ATAC trial.

**COBRA Study**

A randomized prospective study of women with early-stage breast cancer initiating adjuvant therapy with either exemestane or letrozole is currently being conducted by the Consortium on Breast Cancer Pharmacogenomics (COBRA).[21] Musculoskeletal symptoms are prospectively assessed using both the modified Health Assessment Questionnaire (HAQ) [22] to assess patient functional status and a pain visual analog scale (VAS). Patients who meet predefined objective criteria for development of musculoskeletal symptoms since initiation of AI therapy based on increase in pain or decrease in functional status are referred for a standardized evaluation by a rheumatologist, including history, physical examination, and laboratory assessment. The COBRA investigators recently reported data from the first 97 eligible patients who had been enrolled in the study for at least 6 months.[21] A total of 45.4% patients met criteria for referral,
which was similar to the prevalence reported in the Columbia study described above.[20] Median time to onset of symptoms was 1.6 months, ranging from a few days to more than 10 months. Thirteen patients, representing nearly one-third of those who reported significant musculoskeletal symptoms, discontinued therapy because of musculoskeletal toxicity, and median time to discontinuation was 6.2 months.

The majority of symptoms occurred in the upper and lower extremities, especially in the hands and wrists, shoulders, knees, feet, and ankles. Of the 36 patients evaluated by rheumatologists, the majority were diagnosed with tendinitis, especially rotator cuff tendinitis, osteoarthritis, and bursitis. In addition, more than 20% of evaluated patients were diagnosed clinically with carpal tunnel syndrome. Other studies have also shown an increased incidence of carpal tunnel syndrome with AI therapy, including the ATAC (anastrozole 3% vs tamoxifen 1%)[16] and International Exemestane Study (exemestane 2.8% vs tamoxifen 0.4%)[18] randomized clinical trials.

**Smaller Studies**

Both the Columbia University and COBRA patient cohorts are representative of breast cancer patients treated in the general community, and the reported incidence of symptoms is consistent with reports by clinicians in both the academic and community oncology settings.[23] Other smaller case series and case reports have also described pathology occurring in small joints and tendons. Small observational studies have described wrist, hand, and finger toxicity, especially carpal tunnel syndrome, trigger finger, and digital stiffness.[24,25]

One patient was reported to develop disabling wrist and Achilles’ tendinopathy following initiation of anastrozole therapy.[26] A total of 12 patients with severe wrist and hand symptoms, most of whom were treated with letrozole, were evaluated using magnetic resonance imaging (MRI). Tendon sheath enhancement and thickening was noted in all patients. Approximately 50% of the evaluated patients subsequently discontinued therapy because of the toxicity.[24] A follow-up small prospective study demonstrated a correlation between development of tenosynovial changes on MRI and decreased grip strength. However, the association between the objective changes on MRI and the development of symptoms remains unclear.[27]

Other small studies have evaluated potential etiologies underlying the development of symptoms, including a possible link between AI therapy and autoimmunity. A small prospective study reported on 24 patients, most of whom were treated with anastrozole, who developed AI-associated pain rated at least 5 on a 10-point VAS and who were referred to rheumatology.[28] Median time to onset of pain in this patient cohort was 2.5 months. Nineteen patients were found to have inflammatory pain of multiple joints. Nine of the nineteen 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 Sjgren’s syndrome.

Other reports have also suggested a possible underlying autoimmune mechanism, including new onset rheumatoid arthritis in one patient.[29] However, another small prospective study of 40 women initiating therapy with letrozole found no evidence of development of antinuclear antibodies or Sjgren’s syndrome within 3 to 6 months of treatment initiation, although laboratory evaluation was only performed in the 8 patients who developed arthralgias.[30]

**Summary**

In summary, AIMSS are common, and can lead to premature discontinuation of AI therapy in a minority of patients. Symptoms occur fairly quickly after treatment initiation, but time to onset of toxicity can vary substantially between patients. A number of specific symptoms have been noted in some patients, including carpal tunnel syndrome, tenosynovitis and tendonopathies, and polyarthralgias of the hands and fingers. Other patients tend to present with monoarthralgias or oligoarthralgias, bursitis, or exacerbations of pain from osteoarthritis. Sensory neuropathy has also been described with AI therapy, and may be related to carpal tunnel syndrome. No clear association between AI therapy and development of autoimmune disease has been demonstrated, although a number of reports have suggested that there may be an association in a minority of patients.

**Factors Predictive of Developing Toxicity**

One key question which remains outstanding is how to identify the patients most likely to develop clinically significant toxicity. The ability to predict which patients will develop moderate to severe AIMSS would be helpful both for designing trials of interventions to prevent or treat symptoms, and...
to guide endocrine treatment decisions.

A number of the studies described above have addressed this issue (Table 3). In the ATAC trial, the following characteristics were found to be associated with increased risk of development of toxicity on both univariate and multivariate analysis: prior chemotherapy, prior hormone replacement therapy, body mass index (BMI) > 30 kg/m$^2$, patient location in North America or the United Kingdom, and overexpression of estrogen receptors on tumor specimens.[19] Many but not all of these factors are associated with increased pretreatment estrogen levels. No patients enrolled in this study received prior tamoxifen therapy.

In the cross-sectional study from Columbia University mentioned above, predictors of increased development of joint pain identified on univariate analysis included BMI < 25 kg/m$^2$ or > 30 kg/m$^2$ and prior taxane therapy.[20] On multivariate analysis, factors associated with decreased risk of developing symptoms included BMI of 25 to 30 kg/m$^2$ (joint pain) and prior tamoxifen therapy (joint stiffness). Prior taxane therapy was associated with increased risk of both joint pain and stiffness. No medication-specific differences were noted, although 64% of patients were taking anastrozole.

A recent study retrospectively evaluated the association between bone mineral density and the use of calcium and bisphosphonate therapy with the development of AIMSS in 316 patients.[31] Patients were treated with an AI for at least 3 months, had bone mineral density assessed during AI therapy, and developed bone fracture or musculoskeletal symptoms, defined as arthralgia, generalized bone pain, or myalgia of at least 5 on a 10 point VAS. The investigators found a statistically significant correlation between the development of musculoskeletal symptoms or bone fracture and bone mineral density (P < .001).

Fewer patients treated with tamoxifen prior to initiation of AI therapy developed arthralgia or bone fracture compared to those treated with upfront AI therapy (P < .001). The authors also found a higher incidence of arthralgias in women treated with the steroidal AI exemestane compared to either nonsteroidal AI. However, in this retrospective study it is unclear when the bone mineral density measurements were performed relative to either AI initiation or development of arthralgias, and therefore is it unknown whether the loss of bone mineral density led directly to the musculoskeletal symptoms.

No predictors of toxicity have been identified thus far in the COBRA trial, possibly due to insufficient power to detect associations.[21] Analysis of samples and data from the prospective COBRA trial following accrual of the remaining patients may yield additional information regarding potential pharmacogenetic and biochemical predictive factors. In addition, planned analyses from both the previously conducted and currently enrolling large randomized AI trials may also help identify factors predictive for development of AIMSS. In summary, a number of factors, including BMI and prior chemotherapy, have been identified as potential predictors of developing AIMSS, although none is clinically useful for decision-making regarding AI therapy in an individual patient.

**Etiology of AIMSS**

Despite the increased awareness of the clinical importance of AIMSS, the mechanism underlying development of these symptoms remains unknown. Given the variability of presenting symptoms, it is likely that there are multiple different etiologies that can lead to development of AIMSS in
individual patients. A number of potential hypotheses have been proposed, including an autoimmune phenomenon, a direct off-target effect of the AI or a drug metabolite, and circulating or localized estrogen deprivation. Identification of the mechanisms that lead to the development of musculoskeletal side effects may enable identification of more directed treatment approaches for management of the symptoms.

**Autoimmune Phenomenon**

As noted above, some small studies and case reports have suggested that AI therapy can lead to an induction of autoimmune disease, such as rheumatoid arthritis or Sjögren's disease.[28,29] Comprehensive rheumatologic evaluation of 36 patients in the COBRA study did not demonstrate development of autoimmune disease in any patients, although a few subjects had mild laboratory abnormalities including elevated antinuclear antibodies, rheumatoid factor, and sedimentation rate.[21] At present, however, no convincing data suggest that AI therapy leads to development of autoimmune disease in a substantial number of patients, or that an autoimmune mechanism is responsible for the development of arthralgias.

The palmar fasciitis with polyarthritis syndrome has some similarities to AIMSS, including development of flexor tendinosis and carpal tunnel syndrome.[32,33] The palmar fasciitis with polyarthritis syndrome was originally noted in women with metastatic ovarian cancer, but has subsequently been noted in association with other malignancies as well as nonmalignant conditions. Since this syndrome typically occurs in women, one hypothesis is that development of this syndrome is related to the female hormonal milieu, but its etiology remains unknown.

**Direct Off-Target Effect**

Another potential mechanism of development of AIMSS may be a direct off-target effect of either the AI medication itself or one of its metabolites. This hypothesis seems less likely since both the steroidal and nonsteroidal AIs appear to lead to similar side effects, although this observation could be due to interindividual variation in drug metabolism. In addition, similar symptoms have been previously reported in a cohort of premenopausal women treated with gonadotropin-releasing hormone antagonist medications but not with AI medications, which provides further evidence that the mechanism may not be drug-specific.[34] As additional information about the metabolism of the AIs becomes available, other studies can be performed to further explore this hypothesis.

**Estrogen Deprivation**

The mechanism that seems most probable based on currently available data is estrogen deprivation, although it is unclear whether the effect is systemic or localized. Perimenopausal exacerbations of multiple musculoskeletal disorders, including osteoarthritis and carpal tunnel syndrome, have been observed.[35,36] AI therapy results in significant decreases in serum estrogen concentrations below postmenopausal levels, although the absolute levels are difficult to measure with currently available estradiol assays.[37] Therefore, it remains unknown whether there is an association between development of arthralgias and either absolute serum estradiol concentration or rate of decrease of estrogen level upon initiation of AI therapy.

Aromatase is known to be expressed in osteoblasts, synovial cells, and chondrocytes of articular cartilage.[38,39] It is possible that local inhibition of estrogen production in bone leads directly to arthralgias. For example, some have suggested that estrogen depletion in bone could cause microfractures, leading to pain. This mechanism seems improbable in patients who develop pain within days to weeks of initiation of AI therapy, as it seems unlikely that microfractures could develop and become symptomatic that quickly.

Tendon sheath enhancement and swelling occurs in women treated with AIs.[24] These changes could potentially develop in the setting of decreased estrogen concentrations within the joints, although the reason for the development of these changes in the setting of AI therapy remains unclear. Proinflammatory cytokines, including interleukin (IL)-1, tumor necrosis factor–alpha, and IL-6 are known to increase at the time of menopause, and remain elevated for the first few years of the postmenopausal period.[40]

Estrogen deficiency also increases the responsiveness of some cells to these inflammatory markers, via upregulation of receptors, cofactors, and other mechanisms. Therefore, severe estrogen depletion by AI therapy could potentially lead to an increase in local inflammation, thereby leading to signs such as tendon sheath edema noted in some patients. However, a systemic effect of estrogen depletion on inflammation has not been demonstrated in AI-treated patients, since the majority have not been shown to have elevated serum concentrations of inflammatory markers, including C-reactive protein and sedimentation rate.[21]

Aromatase and estrogen receptors are also known to be expressed in the brain and spinal cord. Therefore, neurohormonal changes due to local estrogen depletion in the central nervous system
(CNS) may lead to alterations in pain sensitivity. One prominent antinociceptive pathway in the CNS is the opioid pathway. Endogenous opioids are decreased in women who have undergone oophorectomy, and can be increased by the administration of estrogen.[41] Other studies have reported increased pain sensitivity in women with lower estrogen levels.[42,43] Functional imaging studies have also demonstrated differential involvement of different pathways in the brain depending on estrogen levels.[44,45] Therefore, estrogen deprivation could potentially decrease pain thresholds, which could lead to an increase in pain perception in women treated with AIs.

**Summary of Potential Mechanisms**
Given the variety of musculoskeletal syndromes that arise in patients treated with AIs, a single unifying mechanism may not be responsible for the development of all symptoms. In addition, few mechanistic studies have been reported to date. Therefore, multiple potential hypotheses are still being evaluated as potential etiologies underlying the development of AIMSS. At present, the preponderance of evidence is weighted toward circulating and/or local estrogen depletion playing a large role in the etiology of these symptoms, although other mechanisms may cause the symptoms in a subset of patients. Further elucidation of the underlying mechanism through carefully designed studies will lead to more targeted management approaches.

**Management of AIMSS**
Because of the paucity of mechanistic studies, most approaches for the treatment of AIMSS are
empiric (Table 4). Multiple reports have described treatment with analgesics, including nonsteroidal anti-inflammatory drugs, acetaminophen, and opioids, although only a subset of affected patients obtain relief from this approach.[20,21,28,46] In a small study, almost 50% of patients with inflammatory pain obtained partial or complete amelioration of symptoms with prednisone.[28] Although given the substantial short- and long-term toxicities from steroids, this option is not practical. Other patients have used dietary supplements, such as glucosamine and chondroitin, omega fish oils, and the Chinese medicine Keishi-ka-nijutsuto, with variable results.[20,25] Because of the detrimental effect of AI therapy on bone mineral density, current clinical practice includes recommending calcium and standard-dose vitamin D supplementation for AI-treated patients. The role of assessing vitamin D levels remains unclear, however. Minimal data are currently available to support use of high-dose vitamin D supplementation for management of these symptoms,[47] although a prospective randomized clinical trial of this therapy vs placebo is currently accruing subjects with vitamin D deficiency and AIMSS.[48] Despite these conservative therapies, however, a proportion of patients still discontinue therapy because of intolerable symptoms.[21,24]

In the retrospective study described above evaluating the association between bone mineral density and the use of calcium and bisphosphonate therapy with the development of AIMSS or bone fracture, fewer patients who were taking calcium and bisphosphonate therapy developed musculoskeletal symptoms or osteoporosis (P < .001).[31] Based on these results, the authors concluded that treatment with calcium and bisphosphonate therapy reduced the likelihood of development of musculoskeletal symptoms and osteoporosis. However, no prospective randomized trial has yet been reported demonstrating that the addition of bisphosphonate therapy to a patient’s medication regimen can either prevent or treat AIMSS. Anecdotal reports and small prospective studies have also described benefits from other treatment modalities, such as exercise. A pilot study of 21 patients treated with acupuncture for AIMSS demonstrated that acupuncture led to improvements in pain severity, function, and physical well-being, and led to decreased analgesic usage in the majority of patients who were taking pain medications at baseline.[49] Although these pilot results are promising, future randomized studies of acupuncture and other pharmacologic and nonpharmacologic treatment options are required to confirm that treatment is superior to placebo, since some patients experience spontaneous resolution of their symptoms.

**Recommendations**

Given the lack of data regarding management options for AIMSS, how should oncologists manage these patients? Initial pharmacologic therapy is generally with analgesics, although some patients opt for nonpharmacologic therapy such as exercise or acupuncture. If a patient is experiencing severe symptoms, or has moderate symptoms unresponsive to conservative measures, it may be worthwhile to refer her for formal rheumatologic evaluation.

If symptoms continue to have a significant impact on a patient’s quality of life despite these measures, then it is reasonable to discontinue AI therapy for a few weeks. If symptoms lesson considerably with treatment discontinuation, then one can consider switching the patient to a different aromatase inhibitor (eg, exemestane if the patient was originally on anastrozole), or changing to tamoxifen if clinically appropriate.[50] Regardless of the treatment approach, however, it is important to follow patients closely for progression or resolution of symptoms in order to optimize adherence to endocrine therapy.

**Future Directions**

Musculoskeletal symptoms are increasingly recognized as a clinically important AI-associated toxicity, and are likely to affect up to 40,000 patients in the United States each year. However, physicians are unable to predict which patients are likely to develop symptoms, and also have difficulty managing this toxicity effectively in the majority of patients. Both small pilot studies designed to explore the mechanisms underlying the development of toxicity, and larger prospective trials of symptom management interventions, are needed.

It is possible that the symptoms arise in the context of other toxicities associated with estrogen depletion, such as hot flashes, sleep disturbances, depression, or cognitive changes. Therefore, mechanistic studies should simultaneously evaluate the constellation of symptoms being experienced by patients, since management approaches may be most effective when directed toward the patient as a whole, rather than just focusing on pain symptoms in isolation.

Pharmacologic agents, such as antidepressants and anticonvulsants, have previously been shown to improve hot flashes and sleep quality, and a subset is effective in chronic pain disorders including fibromyalgia and diabetic peripheral neuropathic pain.[51-54] Nonpharmacologic interventions, such
as exercise, yoga, and acupuncture, may also have promise for management of this symptom complex.

Not all patients develop toxicity. Some patients may have underlying pathology, such as osteoarthritis or tendinopathy, which predisposes them to the development of AIMSS. In others, pharmacogenetics may play a role. Germline variation in a number of different pathways could account for differences in symptom development. For example, single nucleotide polymorphisms in the aromatase gene, or in genes involved in AI drug metabolism, estrogen signaling, or central pain pathways, could influence development of toxicity. Other candidate genes may be identified as more is learned about the underlying mechanisms of the development of AIMSS.

Given the large number of women diagnosed annually with early-stage HR-positive breast cancer each year and treated with AI therapy, and the high proportion of patients who experience these symptoms, musculoskeletal toxicity will affect tens of thousands of women per year. These symptoms, if not addressed effectively by patients and physicians, are likely to lead to poor adherence to AI therapy in a subset of patients.[55] It is therefore important to have a greater understanding of the development of this toxicity, so that interventions can be identified that lead to better tolerance of the medication, which should lead to improved breast cancer outcomes.

This article is reviewed here: Improving Tolerance of AIs: Predicting Risk and Uncovering Mechanisms of Musculoskeletal Toxicity Aromatase Inhibitors and Arthralgia: A Growing Pain?

**References:**

4. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year

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