Aromatase inhibitor-induced arthralgia: a review

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Though aromatase inhibitors (AIs) are an essential part of estrogen receptor-positive (ER+) breast cancer therapy, many patients discontinue the medicine before their adjuvant therapy is completed because of the arthralgia which often accompanies the medicine. Up to half of women on AI therapy experience joint pain, and up to 20% will become non-compliant with the medicine because of the joint pain. Yet, very little is known about what causes AI-induced arthralgia (AIA), and there is no established, effective treatment for this difficult problem. It compromises survivors’ quality of life and leads to non-compliance. This paper will discuss AIA in depth, including potential etiologies, clinical significance, risk factors, and possible management solutions. Of note, this article presents one of the first proposed algorithms which clearly lays out a treatment plan for AIA, incorporating a variety of interventions which have been proven by the available literature.

Key words: aromatase inhibitors, arthralgia, breast cancer, survivorship

introduction

The emerging field of breast cancer survivorship is becoming increasingly relevant as therapies for breast cancer continually improve and survival rates surge. In the United States, there are estimated to be over 2.97 million breast cancer survivors, and this number is expected to climb to 3.79 million by January 2022 [1]. According to SEER data, the 5-year relative survival for breast cancer patients, compared with the rest of the population, is 89%. Furthermore, even those with metastatic disease have a 23% 5-year survival on average [2]. Clearly, our breast cancer patients are living longer than they were previously, and a special set of needs arises for them in relation to the side-effects of therapy.

In this review, I will focus on the arthralgia related to aromatase inhibitor (AI) therapy, as this is an extremely common problem among breast cancer patients which negatively impacts day-to-day well-being. Because AI therapy is often continued for up to 5 years, arthralgia may be a very plaguing problem for women, sometimes resulting in non-compliance with AI therapy. This is a significant public health issue because we know that AIs are the most effective hormonal therapy available for post-menopausal women; AIs offer improved disease-free survival and decreased rates of contralateral breast cancer when compared with adjuvant tamoxifen [3–5].

definition

In order to discuss the issue of AI-induced arthralgia (AIA), it is first important to clearly define the term. In fact, the current ambiguity surrounding the syndrome has presented a problem in the literature. In the absence of a clear definition of the problem, various clinical trials have reported a wide range of AIA incidence, likely because they are each defining AIA differently. Also, some physicians may not recognize more subtle manifestations of this side-effect because no objective diagnostic criteria exist. Generally, AIA presents with symmetrical joint pains, most commonly affecting the wrists, hands, and knees [6]. Carpal tunnel syndrome and trigger finger may be common complaints as well. Retrospective data from both the aromidex, tamoxifen, alone or in combination (ATAC) trial and the Intergroup Exemestane Study (IES) showed significantly higher rates of carpal tunnel syndrome with AI use when compared with tamoxifen [7, 8]. Other symptoms may include morning stiffness, myalgia, and decreased grip strength. The median time to onset of symptoms is 1.6 months, though it can range from a couple of weeks to more than 10 months. Symptoms tend to peak at ~6 months [9].

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For the purpose of increased clarity and ease of future study, I propose the following definition for AIA in which patients must meet all of the following major criteria, and at least three minor criteria (See Table 1):

**incidence**

As mentioned earlier, the incidence of AIA is not entirely clear due to lack of a consistent definition. Furthermore, the large trials which are often quoted to provide incidence of AIA were not created to primarily examine AIA. The ATAC trial recorded a 35% incidence of arthralgia on anastrazole [3]. However, the IES reported only 5% incidence of arthralgia while on exemestane [5]. The remaining large trials report incidence rates of AIA which fall in between these two, and they are detailed in Figure 1.

This clear disparity among trials is likely not due to different side-effect profiles of each AI. Rather, studies comparing the three AIs (exemestane, anastrazole, and letrozole) have shown no significant difference in the incidence of AIA between these agents [10, 11].

One study, which was designed to look specifically at the prevalence of AIA, examined 200 women on adjuvant AI therapy and asked them to rate their joint pain on a scale of 0–10 periodically. They discovered that an alarming 47% of women developed AI-related joint pain, with half of them having new onset joint pain, and the other half with worsening of pre-existing joint pain. There was no significant difference in the incidence of AIA between the three different AIs [6], and another trial has shown similar incidence rates [9]. Thus, the true incidence of AIA is likely closer to 50%.

**significance**

AIs have taken on a very important role in breast cancer therapy, as several trials have established their superiority over tamoxifen in improving disease-free survival [3, 4, 5]. However, the arthralgia associated with AIs can be so troubling that it actually leads to a significant rate of non-compliance. One trial, which was engineered specifically to further characterize AIA, followed 100 women on adjuvant AI therapy with a median follow-up of 12 months. They found that 13% of women discontinued treatment due to arthralgia [9]. Another study discovered a 22% rate of discontinuation because of AIA [12]. In longer follow-up, the rates of non-adherence are even higher. By reviewing pharmacy records of 12,000 patients, one researcher quantitated the rate of non-adherence to adjuvant anastrazole therapy. With non-adherence defined as taking <80% of the prescribed AI dose, compliance progressively worsened over 3 years. Only 50%–68% of women were adherent to their AI medication at 3 years [13]. Other studies have shown similar trends; see Figure 2 [13–16]. Though reasons for non-adherence were not ascertained in these studies, it is clear that a lack of compliance with AI therapy is a significant problem among breast cancer survivors. Because arthralgia is such a common, troubling side-effect, AIA likely plays a significant role in the high rate of AI drop-out. Other potential reasons for non-compliance may include fears about bone loss, vaginal dryness, and hot flashes.

Furthermore, AIA carries further significance beyond quality of life and compliance issues for breast cancer survivors; it may also be tied to recurrence risk. Retrospective analysis of the ATAC data shows that women who developed arthralgia within 3 months of starting endocrine therapy actually had a lower risk of breast cancer recurrence. Women taking anastrazole who experienced AIA had a HR of 0.65 (95% CI 0.50–0.85,

<table>
<thead>
<tr>
<th>Table 1. Definition of aromatase inhibitor-induced arthralgia (AIA)</th>
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<tr>
<td><strong>Major criteria</strong></td>
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<tr>
<td>• Currently taking AI therapy</td>
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<tr>
<td>• Joint pain which has developed or worsened since starting AI therapy</td>
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<tr>
<td>• Joint pain improves or resolves within 2 weeks of stopping AI therapy</td>
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<td>• Joint pain returns upon resuming AI</td>
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<td><strong>Minor criteria</strong></td>
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<tr>
<td>• Symmetrical joint pains</td>
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<tr>
<td>• Pain in hands and/or wrists</td>
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<td>• Carpal tunnel syndrome</td>
</tr>
<tr>
<td>• Decreased grip strength</td>
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<tr>
<td>• Morning stiffness</td>
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<tr>
<td>• Improvement in joint discomfort with use or exercise</td>
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Figure 1. Arthralgia incidence among large adjuvant trials, comparing ATAC [3], ITA [49], IES [5], BIG 1-98 [4], MA-17 [50], MAP.3 [51].
with arthralgia on endocrine therapy [8]. This may have been
due to the use of the non-steroidal AI (anastrozole) in ATAC,
when compared with the steroidal AI (exemestane) in IES.
Also, data were examined for musculoskeletal symptoms at 3
months in the ATAC analysis, and at 6 months in the IES
analysis. Finally, the data in each trial were analyzed differently
and controlled for varying factors. Notably, the IES data
initially did appear to show a significantly lower recurrence
rate for women with arthralgia; however, this difference
disappeared on adjusted analysis. The IES analysis was
adjusted for geographical location of the patients, while ATAC
was not. For reasons that are not totally clear, women in
central and eastern Europe had lower rates of arthralgia than
women in the United States and UK [8]. Clearly, these data
need to be validated in future studies, as there are now
conflicting trials, and it is not clear whether the presence of
AIA truly correlates with the improved breast cancer outcome.

etiology

Many theories have been postulated regarding the cause of
AIA, though very little is known in regards to its etiology. AIA
commonly believed to be caused by estrogen depletion,
though this has never been proven, and the pathway is not
understood. However, a correlation between low estrogen and
joint pain has been recognized since at least 1925 when a
syndrome of ‘arthritis of the menopause’ was first described
[20]. Peri-menopausal women have been shown to have higher
rates of arthralgia than pre-menopausal women, though it is
difficult to ascertain the importance of this because other
competing causes for arthralgia also develop during this age,
such as osteoarthritis [21]. In one Chinese study of 2125
women, 41% of peri-menopausal women described joint
aching and stiffness, compared with only 25% of pre-
menopausal women and 29% of post-menopausal women [22],
suggesting that perhaps the relatively sudden decline in the
estrogen level promotes arthralgia more strongly than simply a
low estrogen state, as is seen in post-menopausal women.
Furthermore, estrogen replacement therapy may improve
arthralgia and joint health, as shown in the Women’s Health
Initiative (WHI). Censoring arthroplasties due to hip fracture,
the WHI found that post-menopausal women on estrogen
replacement therapy had significantly less arthroplasty than the
women on placebo [23].

Nonetheless, the question remains: how does low estrogen
cause joint pain? Several theories exist. Estrogen has naturally
anti-nociceptive properties, which may be an evolutionary
adaptation to help women better tolerate pain during
childbirth, when estrogen levels are naturally increased. This is
believed to be mediated by opioid-containing neurons in the
spinal cord which express estrogen receptors [24]. Also, animal
studies have shown that mice with surgically removed ovaries
have accelerated cartilage turnover, presumably from their low-
estrogen state [25]. Perhaps, this higher rate of cartilage
turnover contributes to bone pain from lack of cushioning in
the joints.

Both circumstantial and scientific evidence support a
cytokine-mediated mechanism of AI-induced arthralgia.
Inflammatory cytokines are tied to estrogen levels in the body.

\[ P = 0.001 \] when compared with those women with no
arthralgia [17]. The graph, shown in Figure 3, demonstrates a
clear difference in recurrence in both the anastrazole and the
tamoxifen groups, based on the presence or absence of AIA.

Similarly, retrospective analysis of the TEAM trial showed
improvements in overall survival and disease-free survival in
patients who had either arthralgia or hot flashes while on
endocrine therapy [18]. BIG1-98 analysis showed increased
disease-free survival in those women who had arthralgia or
myalgia on endocrine treatment [19].

The mechanism behind this interesting correlation, however,
remains unclear. It is unknown whether the women with
arthralgia simply have more effective estrogen depletion on
endocrine therapy, and this, in turn, leads to a lower risk of
recurrence. Or, perhaps the arthralgia is mediated by a totally
different mechanism, which may also have antitumor
properties. Eventually unlocking the reason behind this
connection between arthralgia and lower recurrence rate could
very well lead to a potential new target to decrease breast
cancer recurrence.

However, it should be noted that the recent retrospective
analysis of the Intergroup Exemestane Study (IES) showed no
such improvement in disease-free survival for those patients

Figure 2. Compliance with AI therapy over time.

Figure 3. Decreased recurrence with arthralgia while on anastrozole or
tamoxifen [17].
For example, in the rheumatology literature, it is well documented that higher levels of estrogen suppress inflammatory cytokine production, and lower estrogen levels increase their production [26]. This may explain why women who are beginning menopause have higher levels of inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α). These inflammatory cytokines may contribute to the post-menopausal woman’s syndrome of arthralgia which is very similar to AIA [27]. Additionally, research has shown that synovial cells express aromatase, and when it catalyzes the conversion from androstenedione to estrone and estradiol, IL-6 expression is reduced in the joint [28]. Thus, AIs may cause a relative increase in IL-6 production, which is known to act as both a pro- and anti-inflammatory cytokine. It is also known to be one of the key mediators of increased bone loss in post-menopausal women [29].

Weight and physical activity also connect inflammatory cytokines with AIA. Obese patients have higher levels of inflammatory cytokines, particularly IL-17 [30], and they have a higher risk of developing AIA [6]. Conversely, exercise, which releases anti-inflammatory cytokines [31], has been anecdotally linked to improvement in AIA. Finally, this increase in inflammatory cytokines (namely TNF-α, IL-1, and IL-6) upregulates RANK ligand expression on osteoblasts, hastening their conversion to osteoclasts and thus causing bone breakdown, resulting in joint discomfort [32].

There is also radiologic evidence to support the inflammatory nature of AIA. Morales et al. conducted a study with 12 patients on adjuvant AI therapy in which they carried out ultrasound and magnetic resonance imaging (MRI) on the wrists and hands. Five patients had ultrasound examination, which showed fluid in the tendon sheath surrounding the digital flexor tendons in all five patients. All 12 patients had MRIs, and these showed fluid in the various tendon sheaths of the digital flexor and extensor muscles as well as intra-articular fluid in the metacarpal joints. Enhancement and thickening of the tendon sheaths were seen in all 12 patients as well [33].

One small pilot study examined the use of immunotherapy for the treatment of AIA. Sixteen women were treated with thymosin α1, a protein secreted by the thymus which stimulates T cells. They found that the women had significantly lower levels of serum interferon-γ (IFN-γ) after 4 weeks of treatment, and they also had significantly less joint pain per subjective questionnaires [34], intimating that there may be some connection between elevated levels of inflammatory cytokines such as IFN-γ and the presence of arthralgia.

risk factors and associations

Many factors have been shown to be associated with higher risk of developing AIA, though the underlying mechanism is still not understood. Obesity has been consistently linked to higher incidence of AIA. According to a retrospective analysis of ATAC data, obese women with a BMI of >30 have higher incidence of AIA than normal-weight women with a BMI of <25 and overweight women with BMI 25–30 [35]. Analysis of the IES trial shows similar results, with weight ≥80 kg as a significant risk factor for the development of AIA [8]. However, one study which was specifically conducted to look at the prevalence of AIA found that 57% of women with a BMI of <25 had arthralgia, and 54% of obese women with a BMI of >30 had arthralgia. Both of these rates were significantly higher than that of overweight women with BMI 25–30, who had only a 34% incidence of joint pain [6]. It is not clear why overweight women may be relatively protected from AIA. It is possible that the increased adipose tissue in overweight women results in higher levels of estrogen because adipose cells contain aromatase which produces estrogen. However, this effect may be negated in the obese women because of stress on the joints from increased body weight.

Other factors that have been associated with higher incidence of AIA include prior hormone replacement therapy [8, 35] and previous chemotherapy before beginning an AI [35]. However, another study which asked the same questions found that whether or not the patient received chemotherapy was not significant in the development of AIA, but a history of having specifically received a taxane was associated with a higher rate of AIA, with 62% of such women developing this problem when compared with 37% who had never received chemotherapy [6]. The retrospective IES analysis showed that women with a history of baseline arthralgia or osteoarthritis at the start of AI therapy have a higher chance of developing AIA as well [8]. Interestingly, women in the United States and UK had higher rates of arthralgia than those women in central and Eastern Europe [8]. While this may have been due to reporting biases, it should be noted that some genetic polymorphisms have been shown to be correlated with a higher rate of AIA [36], and this may play a role in different rates of arthralgia between various ethnicities and geographic locations.

management

Though quite common, the management of AIA has largely been a mystery in clinical practice because there are almost no prospective, randomized, controlled trials to investigate AIA management. However, it is clearly important to educate the patient before beginning AI therapy that joint pains are a very common side-effect. If the patient is expecting this problem, she may be more likely to tolerate the problem and report it to her doctor. Also, before starting the medication, the physician may educate the patient on simple interventions which may help with arthralgia such as exercise. Once AIA develops, most of the remedies suggested by clinicians are primarily anecdotal. The single intervention which has proven benefit in a prospective, randomized, controlled clinical trial is acupuncture. In a small study, 43 women with AIA were randomly assigned to receive either true acupuncture or sham acupuncture twice weekly for 6 weeks. They found that, per questionnaires, women reported significantly less pain, lower pain severity, and less pain-related interference in the true acupuncture arm [37]. Though these findings need to be validated in a larger trial and possibly incorporate more objective measures of improvement, this is nonetheless an extremely interesting study, and the only randomized, blinded, controlled study to show benefit for any intervention in women with AIA.
Another trial, the ATOLL study, proved that women who do not tolerate one AI because of arthralgia may be able to tolerate another AI instead. The investigators studied 179 women who had discontinued adjuvant anastrazole due to musculoskeletal symptoms. After a 1-month washout period, the women were started on letrozole. They found that only 28.5% of these women discontinued letrozole at 6 months, indicating that they were better able to tolerate letrozole than anastrazole. Though women reported improved quality of life and less joint pains on letrozole than on anastrazole, 74% of women still had significant arthralgia after 6 months of letrozole therapy. Only 15% did not report any joint discomfort after 6 months of letrozole therapy [38]. Although arthralgia is not eradicated by switching AIs, this is a relatively simple measure which may offer some relief to patients and allow them to continue adjuvant AI therapy. At this point, we do not have any evidence to clearly state whether women who could not tolerate a steroidal AI would be more likely to tolerate a non-steroidal AI.

Similarly, switching patients to tamoxifen may also provide significant benefit, as tamoxifen has been shown to have lower rates of arthralgia than AIs. In the ATAC study, 36% of women on anastrazole reported arthralgia, while only 29% of women on tamoxifen reported this problem, for an odds ratio of 1.32 [3]. Similarly, in the BIG 1-98 study, 35% of women on letrozole monotherapy had arthralgia or myalgia, compared with only 30% on tamoxifen monotherapy, which was a statistically significant difference. However, before a patient is switched to tamoxifen, she should ideally complete at least 2 years of AI therapy, as this has been found to achieve similar results as 5 years of AI monotherapy [4]. Also, in order to justify switching a patient to tamoxifen, the arthralgia from AI therapy should significantly affect a woman’s quality of life or medication compliance, as tamoxifen is known to have higher rates of stroke and deep venous thromboembolism when compared with AI therapy [3]. Of course, side-effects of each course of therapy must be carefully weighed and thoroughly discussed with the patient.

Vitamin D may also prove to play an important role in the management of AIA. It is known that proximal muscle strength improves as vitamin D levels increase, suggesting that it plays a role in musculoskeletal health [39]. Also, patients with non-specific musculoskeletal pain and arthralgia who are not taking AIs have significant rates of vitamin D deficiency when compared with matched controls [40]. Vitamin D is closely tied to estrogen because estrogen increases the activity of 1-α hydroxylase, the enzyme responsible for conversion of 25OHD to the biologically active 1,25-dihydroxyvitamin D form. Estrogen also increases the activation of the vitamin D receptor. Thus, it seems logical that the drop in estrogen levels caused by AIs may cause a decrease in vitamin D, and thus, a vitamin D deficient-like arthralgia syndrome. In a prospective study, 60 women who were beginning adjuvant AI therapy had baseline vitamin D (25OHD) levels measured. All women were started on standard supplementation with 1200 mg/day of calcium and 600 IU/day of vitamin D. At 4 weeks, the women who were vitamin D deficient by their baseline measurement started increased D3 supplementation with 50 000 IU per week for 12 weeks. At the conclusion of 16 weeks of letrozole, 52% of women with 25OHD levels >66 ng/ml reported no disability from joint pain, whereas only 19% of those with levels <66 ng/ml had no disabling joint pain [39]. While not conclusive evidence, this trial does show promising results that vitamin D may play an important role in AIA. Currently, there is a large, multi-center national trial going on to test this hypothesis.

Though nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are frequently used in clinical practice to treat AIA, there is no robust clinical trial evidence to support this approach. However, many clinicians have anecdotal stories of success treating AIA with NSAIDs. Of course, it must be kept in mind that while NSAIDs may offer some relief, they also come with a slew of side-effects including gastrointestinal, renal, and cardiovascular effects. While selective NSAIDs (COX-2 inhibitors) are especially appealing, in that they are also known to downregulate aromatase [41], they also cause several potentially dangerous

![Figure 4](image-url)
side-effects including heart attack and stroke. Thus, selective COX-2 inhibitors are not recommended for routine treatment of AIA.

Because AIA is generally worse in obese women, weight loss is an excellent intervention for obese women with AIA. Though there has not been a clinical trial to test this hypothesis, it is well known that overweight people have more arthritis than normal weight people, and many women report the use of exercise to effectively control their AIA symptoms [6]. Furthermore, data also show that weight loss and regular exercise are effective in lowering a woman’s risk of recurrent breast cancer [42]. Though the exact mechanism is not known, studies have shown that anti-inflammatory cytokines released during exercise may inhibit cancer growth [43].

There are some very preliminary data to state that yoga may be an effective intervention in treating AIA [44], though this clearly needs verification in further trials. In one small, non-randomized trial of 27 patients, a short course of low-dose prednisolone did show promise as a potentially effective treatment for AIA. Patients with AIA were given 5 mg of prednisolone daily for 1 week, and 67% of patients reported immediate relief in joint pain, with 63% still reporting improvement at 1 month [45]. Retrospective data suggest that diuretics and bisphosphonates may play a role in reducing discomfort from AIA [46, 47]. In a single-arm trial, 29 women with AIA received duloxetine for 8 weeks, and 72% experienced at least a 30% reduction in the average pain level [48].

In the absence of adequate clinical data for this common problem among breast cancer survivors, I propose the following management algorithm (Figure 4), based on the best available evidence:

**future directions**

For the purpose of clearer study, I recommend amending the National Cancer Institute Common Terminology Criteria for Adverse Events to include a clear definition of AIA, similar to the one which I have posited above. If in future clinical trials, AIA is clearly defined and measured using a universal standard, this would lead to better understanding of the incidence, risk factors, and potential treatments for AIA.

Many questions remain to be answered regarding AIA, including the etiology of AIA, as well as its effect on women’s medication compliance, recurrence risk, and quality of life. As this issue becomes more standardized, future clinical trials will hopefully address these very important issues.

**conclusion**

AIA has clearly been an important, though understudied, problem among breast cancer survivors. Up to half of women on AI therapy may have significant joint pain which will sometimes lead to discontinuation of the medicine. Nonetheless, we still do not understand the etiology of AIA, nor is there a proven therapy which helps women with this troublesome side-effect. Thus, much work remains to be done in the field to improve our care of breast cancer survivors. Future studies will likely focus on the cause of and potential treatments for AIA; this will hopefully tie in with new insights into the role which AIA plays in breast cancer recurrence.


