Therapeutic optimization of aromatase inhibitor–associated arthralgia: etiology, onset, resolution, and symptom management in early breast cancer

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Third-generation aromatase inhibitors (AIs) used in the treatment of hormone-responsive breast cancer are associated with arthralgia, which is the most common reason for treatment discontinuation. This review characterizes the observed arthralgia and describes its variable definitions in key clinical trials; its typical onset and duration; symptom management strategies; and symptom resolution. The symptomatic manifestations of AI-associated arthralgia are highly variable, with typical onset occurring 2-6 months after treatment initiation. Aromatase inhibitor-associated arthralgia is most often bilateral and symmetrical, involving hands and wrists. Other common locations include knees, hips, lower back, shoulders, and feet. To improve standardization of care as well as patient quality of life, we propose a diagnostic algorithm for the management of patients who receive AIs and who develop arthralgia or worsening symptoms from preexisting joint pain. We conclude that although arthralgia is often associated with AI therapy, prompt diagnosis and management of musculoskeletal symptoms may ensure continued AI treatment and improve quality of life.

The use of third-generation aromatase inhibitors (AIs) such as anastrozole, letrozole, and exemestane for the treatment of postmenopausal women with hormone-sensitive breast cancer has increased steadily since 2000, and AIs have been incorporated into many clinical practice guidelines as an effective therapeutic option.[1,2] In the adjuvant setting, AIs reduce the risk of recurrence by 20%-29% relative to tamoxifen.[3,4] Increased use of AIs has led to broader awareness of their side-effect profiles, leading clinicians to consider proactive management of some symptoms with the intent to improve adherence to therapy.

Anastrozole and letrozole reversibly block the cytochrome P450 enzyme aromatase, while exemestane irreversibly blocks aromatase, but a review of the major adjuvant studies has shown that the three AIs have similar safety profiles and disease-free survival rates.[5] One of the commonly reported adverse events (AEs) is arthralgia, which occurs in 18%-36% of patients[5-7] and is particularly important for postmenopausal women who have an increased incidence of joint complaints. Indeed, the reported arthralgia incidence in the general population of postmenopausal women is as high as 74%.[8] In a recent survey of 416 breast cancer specialists, 92% graded AI-induced arthralgia as important or very important.[9]

Subsequent data analyses of AI adjuvant studies show that about 2%-20% of patients reporting arthralgia discontinue treatment.[7,10,11] In addition, retrospective analyses of survey data and medical records from either clinical practice or prescription refill databases have shown that adherence to AI regimens significantly decreased after 1 year of treatment (to 82%-88%) and continued to decrease through year 3 (to 62%-79%).[12-14] The reasons for treatment nonadherence were varied, but they included AEs, especially those events that decrease quality of life, such as arthralgia.[5,15] Reduced medication compliance may then lead to de-

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creased efficacy and increased rates of breast cancer recurrence.[7] Although arthralgia-related symptoms may be severe and lead to discontinuation of AI therapy, data from the ATAC (Arimidex, Tamoxifen Alone or in Combination) study suggest that symptoms may improve within 6 months with continuous AI therapy.[8] It is therefore clinically relevant to differentiate between any comorbid arthralgia and the arthralgia/musculoskeletal symptoms (MSS) that are associated with AI therapy.

Despite the uncertainty surrounding the establishment of an accurate incidence of AI-related arthralgia/MSS (partly due to the wide variability of symptoms and terms used to define arthralgia in clinical studies), several studies have attempted to evaluate and identify potential risk factors for developing arthralgia/MSS during AI therapy. A cross-sectional survey of patients who were treated in the community setting identified prior taxane chemotherapies as a risk factor,[16] and a retrospective analysis of ATAC identified prior chemotherapy, prior hormone therapy, positive hormone-receptor status, anastrozole treatment, and obesity as risk factors.[17] In addition, AI-induced arthralgia seems to be related inversely to the length of time since cessation of menstrual function, with incidence significantly lower in patients whose last menstrual period was more than 10 years ago.[18,19] Prompt diagnosis and management of MSS could ensure continued AI treatment and improve quality of life.[15]

This review characterizes arthralgia-related symptoms, discusses the temporal relationship between symptom onset and duration and the possible etiologies of arthralgia-related symptoms in these patients, and presents diagnostic criteria for arthralgia as well as management strategies to ameliorate these symptoms.

Methods

Evidence was collected from a literature review of the PubMed database through December 2011. Search terms were aromatase inhibitors and breast cancer with arthralgia or musculoskeletal; the permutations included anastrozole, letrozole, or exemestane. Additional information was garnered from oncology conference Web sites.

Arthralgia definition and diagnosis

Arthralgia is commonly defined as pain in one or more joints, and is distinguished from arthritis by the absence of joint inflammation related to structural damage, infection, autoimmunity, or metabolic conditions.

Clinical history and physical examination provide the best assessment tools; laboratory and radiographic analyses can provide additional information.[20] The medical history should include a brief assessment for any comorbidities or medication usage that may contribute to the presence of MSS. A focused physical examination should note any extra-articular features such as nodules, tophi, rashes, or joint effusion, as well as the number of affected joints and any pattern of joint symptoms. The joint pain's location (eg, inside or surrounding the joint), time of onset (eg, morning or at rest), and duration (eg, intermittent or constant), as well as any associated symptoms, are important for determining the cause of arthralgia.[21] A baseline clinical assessment of MSS and the proactive treatment of preexisting joint symptoms are important before AI therapy is initiated.

Typically, AI-associated arthralgia is reported as stiffness, achiness, or pain that is symmetrical, is most noticeable in the morning, and may improve with activity.[22] It is most often bilateral, involving hands and wrists. Other common locations include knees, hips, lower back, shoulders, and feet. However, joint pain has also been reported in the feet, pelvis, arms, and back.[22] There may also be soft tissue thickening and/or fluid in the tendon sheaths.[20,22] Clinical evidence of joint changes has been reported in several small studies.[23-26]

Two studies evaluating musculoskeletal pain during AI therapy found fluid in the sheath surrounding the digital flexor tendons, as well as tendon sheath thickening and enhancement (tenosynovial changes); however, in one of these studies, the majority of patients had tenosynovial changes before initiating AI therapy.[24,25] A retrospective study in patients with AI-induced arthralgia identified a trend toward reduced incidence of arthralgia among patients receiving chronic diuretics, further suggesting the value of reducing fluid in the joints.[27] Another study found no association between tenosynovial changes and reports of new MSS;[23] still another study found no correlation between tenosynovitis and AI use, although MSS were more common among patients receiving AIs.[28] Therefore, although there is some evidence of joint changes in patients receiving AIs, it remains unclear whether those changes are associated with AI therapy.

The most recent National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) for assessing arthralgia severity integrates both pain severity and its effect on physical functioning.[29] According to these criteria, arthralgia ranges from grade 1 (mild pain with no limitations on activities of daily living) to grade 3 (severe pain that limits self-care and activities of daily living).

Onset and duration of MSS

The temporal relationship between MSS onset and the initiation of AI therapy is important in identifying possible etiologies. The most thorough assessment of time to first joint symptoms in patients with BC receiving AI therapy

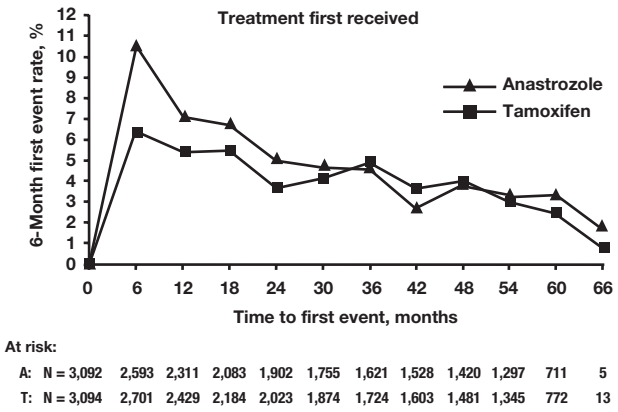

FIGURE 1 Time to onset of first joint symptom event in the ATAC trial. The 6-month first event rate = D/S, where D is the decrement in the Kaplan-Meier event-free estimate over the previous 6 months and S is the Kaplan-Meier estimate 6 months before the time point. Reprinted with permission from Mackey J, Gelmon K. Adjuvant aromatase inhibitors in breast cancer therapy: significance of musculoskeletal complications. *Curr Opin Oncol*. 2007;19:S9-S18,[31] originally appeared in poster by Buzdar AU, presented at 2006 ASCO meeting.

was conducted in the ATAC study (Figure 1).[10,30,31] This subanalysis showed that the event rate for joint symptoms peaked within 6 months after initiation of AI therapy and decreased thereafter. The majority of events (anastrozole, 68%; tamoxifen, 59%) were reported within 24 months of AI therapy initiation.[10] Among patients reporting joint symptoms, 46% had exacerbation of an existing condition.[10] In addition, patients who received prior chemotherapy had a higher incidence of joint symptoms and a shorter median time to onset (TTO).[31] A recent analysis of the Breast International Group (BIG) 1-98 study showed that the incidence of arthralgia/myalgias in patients who received letrozole was higher in years 1 and 2 than in years 3-5 (26% vs. 14%, respectively).[32] A recent 1-year, prospective, joint-symptom evaluation in a clinical practice involving 58 postmenopausal women who initiated AI therapy showed that MSS were increased from baseline at both 3 and 6 months after treatment began.[33] Rheumatologic evaluation of the hands showed worsening function, stiffness, and pain at 3 months; however, only function continued to worsen at the 6-month evaluation, when a significant decrease in pinch grip strength was noted ($P = .05$). The 1-year results were not available.

Several AI studies have reported a median TTO of arthralgia, which yields more precise timing of onset. In a study involving 97 postmenopausal women who were randomized to either exemestane or letrozole for 1 year, 44 women met the criteria for rheumatologic evaluation.[34] Among those evaluated, the median TTO was 1.6 months (range, 0.4-10 months). In another study involving 24 patients who were referred for rheumatologic evaluation, the median TTO was 2.5 months.[5] The timing of arthralgia in these two AI studies was similar to what was observed in 102 premenopausal women receiving leuprolide, a drug that reduces hormone production to menopausal levels; the timing suggested that estrogen deprivation may be involved in the development of arthralgia.[35] In fact, the prevalence of arthralgia peaks in women during menopause (age 50-59 years).[15,35] In this study, the AEs of estrogen deprivation (such as vaginal dryness) began 2 weeks after leuprolide initiation and corresponded to the decline of estradiol to menopausal levels. The development of arthralgias and myalgias began during weeks 3-7 of therapy, with 25% of patients experiencing symptoms.[35] Symptoms resolved at 2-12 weeks after discontinuing leuprolide treatment. In a separate study, conjugated estrogen therapy in postmenopausal women reduced the risk of developing MSS by up to 38%, compared with placebo.[35]

These studies suggest that a high percentage of postmenopausal women with breast cancer may be predisposed to develop joint symptoms, or may have a preexisting joint condition. Therefore, in general, arthralgia that is related to estrogen suppression may worsen or develop within the first few months of AI treatment initiation, and subside within a few months after treatment has been discontinued.

Potential etiologies for MSS with AI use

Despite increased awareness of the clinical importance of AI-associated MSS, the mechanisms underlying symptom development remain poorly understood. Given symptom variability, multiple etiologies likely can lead to the development of MSS in individual patients on AI therapy.[5] Several potential mechanisms have been discussed in recent reviews, including estrogen deprivation, inflammatory or autoimmune response, the direct off-target effect of AIs or their metabolites, and vitamin D deficiency.[5,36,37] Identification of the mechanisms leading to MSS may facilitate the development of directed approaches for symptom management.

A recent case-control, genomewide association study of patients in the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.27 phase III study of anastrozole and exemestane identified four single-nucleotide polymorphisms that were related to the incidence of grade 3 or 4 musculoskeletal symptoms.[38] Genetic polymorphisms in CYP19A1 (the final enzyme in estrogen synthesis) is also associated with patient-reported arthralgia.[39] Further investigation of these genetic variations may lead to a better understanding of the mechanism, more effective symptom management, and earlier identification of patients at risk of developing arthralgia.

Estrogen deprivation is thought to be a crucial contributing factor for AI-associated MSS because estrogen is involved in various signaling pathways that are implicated in MSS etiology.[5,8,15,35,37] Current evidence suggests that estrogen is involved in bone and collagen maintenance, peripheral and central nervous system pain perception, and inflammation.[5,8,15,35,37] Accordingly, patients with osteoporosis have an increased risk for MSS during AI therapy.[40] Estrogen deprivation also seems to lower the pain threshold, and the increased pain perception may expose an underlying joint pathology.[15] Low estrogen levels may alter the natural melatonin cycle, leading to morning joint stiffness.[41] However, a definitive relationship between decreased estrogen levels and the development arthralgia has not been established.

Several recent studies have reported conflicting results with regard to the involvement of inflammation in the development of MSS.[34,42,43] Currently, there is no consistent evidence based on inflammatory biomarkers, but a link may exist. Localized inflammation in the joint may activate nociceptive fibers that innervate the joint capsule and ligaments.[35,37] Joint inflammation may also lead to an expansion of the nociceptive fields, thereby sensitizing nociceptive receptors to pain signals that might otherwise be ignored, or to pain signals originating from other parts of the body.[35,37] Therefore, if inflammation surrounding the joints is promoted by AI-induced estrogen deprivation, then a peripheral nociceptive mechanism may explain the development of joint pain. One case-control study of 30 participants that was part of a larger, prospective, randomized clinical trial found no statistically significant changes in 36 inflammatory cytokines and lipid mediators that were assayed after AI treatment, compared with pretreatment levels.[44] However, further research is necessary to clearly define the role of inflammation in the development of AI-associated arthralgia.

Although it is possible that AIs or their metabolites may affect the development of arthralgia through a direct off-target mechanism, this is less likely than other proposed mechanisms, based on the observation that musculoskeletal AEs are common to steroidal and nonsteroidal AIs as well as to gonadotropin-releasing hormone antagonists.[5,45] Further studies investigating AI metabolism are necessary to elucidate whether this is a viable hypothesis.

Another potential mechanism is exacerbation of an existing vitamin D deficiency. Vitamin D deficiency can lead to musculoskeletal pain and joint stiffness/discomfort, and a recent study reported that 88% of women with early breast cancer had vitamin D deficiency.[46] Nevertheless, the data supporting this hypothesis are inconsistent. An intervention study showed a significant inverse correlation between arthralgia symptoms and vitamin D levels, and lowered pain scores were reported in a randomized study with high-dose vitamin D supplementation (50,000 IU weekly), compared with placebo.[47-49] Another prospective study suggested that a vitamin D target concentration of 40 ng/mL may prevent the development of AI-induced arthralgia.[50] In contrast, a study in postmenopausal women receiving anastrozole or placebo reported no effect of baseline vitamin D levels on arthralgia incidence.[51] Interestingly, one prospective study noted that vitamin D levels increased significantly from baseline during 6 months of AI treatment ($P = .004$), although this study also found no association between AI-associated symptoms and vitamin D concentration.[52] In summary, several of these potential mechanisms may play a role, but further study is needed.

Limitations to determining etiology

Analysis of MSS etiology during AI therapy in postmenopausal women with breast cancer is complicated by a variety of factors, including prior or concomitant anticancer therapy and/or comorbidities. For example, MSS may occur as a result of chemotherapy.[53] In a neoadjuvant docetaxel study involving 45 patients with operable breast cancer, 6.7% developed grade 3 myalgia/arthralgia during chemotherapy.[54] Among 18 patients who received chemotherapy for a variety of tumor types and then developed arthralgia, their joint symptoms arose about 6 months after the first chemotherapy session and lasted for a mean of 3 months with treatment.[55] Therefore, MSS may overlap between treatments, or may arise during subsequent treatment but be related to the prior treatment. Arthralgias are also known to occur after treatment with certain antihypertensives, statins, and vaccines.[20,53]

To add to the complexity, there are 41 preferred terms for MSS in the CTCAE (version 4.0).[29] In Common Toxicity Criteria (version 2.0), there are just seven preferred terms for MSS (arthralgia, arthritis, muscle weakness, myalgia, myositis, osteonecrosis, and other).[56] Indeed, arthralgia arising during AI therapy is difficult to distinguish from bone diseases, inflammatory and degenerative arthropathies, and secondary pain from other causes.[20] Clearly, a uniform assessment of arthralgia/MSS in AI-treated patients is lacking.[35] To facilitate the identification of AI-induced arthralgia, we propose a diagnostic algorithm (Figure 2) rather than a more comprehensive rheumatologic evaluation, which may not be applicable.

Optimal management

Management of MSS is usually palliative, with patients primarily receiving nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors (coxibs), and opioids (for severe symptoms).[15] Interventions to reduce ar-

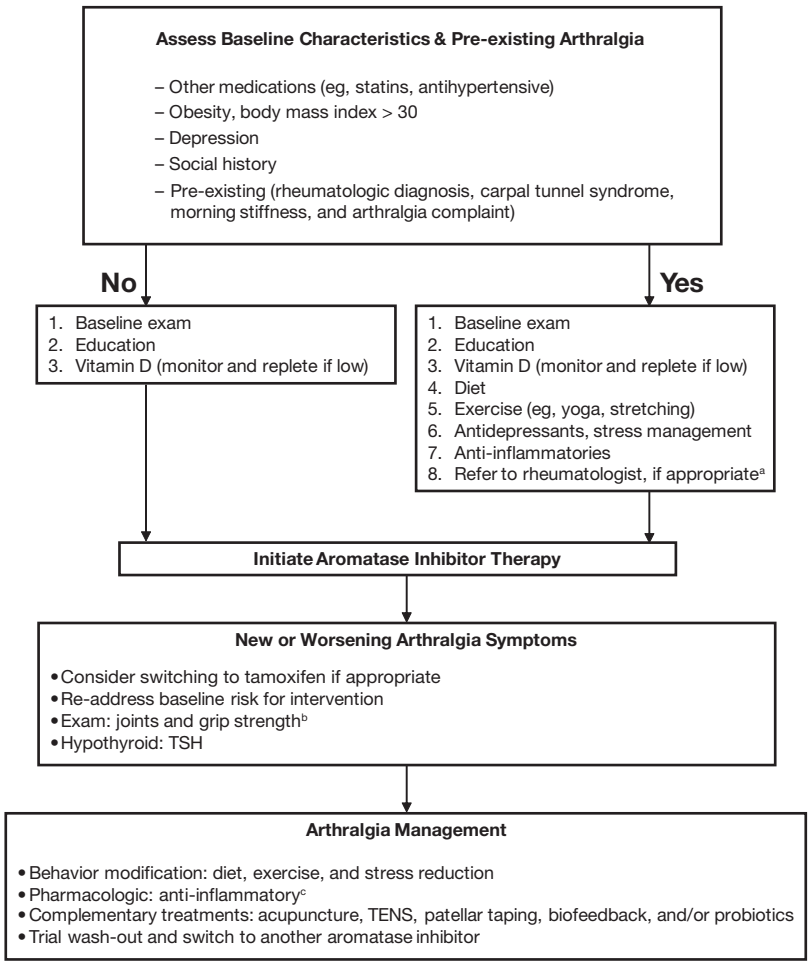

FIGURE 2 Algorithm for diagnosis and management of AI-associated arthralgia. TSH indicates thyroid-stimulating hormone; TENS indicates transcutaneous electrical nerve stimulation. [a]Criteria for referral include ≥ 3 swollen joints, metatarso-/metacarpophalangeal involvement, and morning stiffness that lasts ≥ 30 minutes. [b]Joint examination is for absence of effusion and pain (mild tenderness permissible), with no associated joint changes (if positive, refer to rheumatologist); grip strength should be normal. [c]Treatment is with a nonsteroidal anti-inflammatory agent, ibuprofen, naproxen, or diclofenac, or a cyclo-oxygenase-2–specific inhibitor such as celecoxib, if not contraindicated.

thralgia symptoms during AI treatment have not been formally studied; they have been extrapolated from the current management of arthritis and other related entities. Treatment of MSS symptoms should be individualized based on symptoms, differential diagnoses, and concomitant therapies. Furthermore, arthralgia symptoms could be an early sign of rheumatoid arthritis, requiring referral to a rheumatologist (Figure 2).[53]

Published recommendations from experts in the field and an arthralgia working group for the management of arthralgia symptoms in patients receiving AI therapy suggest a sequential use of lifestyle changes and pharmacologic interventions, depending on symptom severity (Figure 2).[6,15] The recommendations also stress patient counseling and education as important components of arthralgia management. Advising patients that arthralgia is common with AI treatment—and that symptoms can be managed—may increase the likelihood that patients will report these events. This, in turn, promotes appropriate symptom management and discourages AI therapy discontinuation or nonadherence.

Lifestyle changes—including dietary changes, weight loss, and exercise—are suggested for patients with either preexisting or new-onset symptoms.[15] Weight loss may decrease the risk for joint symptoms, as obese women (BMI > 30 kg/m^2) in the ATAC study were more likely to report joint symptoms than were overweight or normal-weight women (BMI ≥ 30).[17] In a prospective study of tenosynovial changes in patients who were treated with an AI or tamoxifen, a regression analysis suggested that grip strength decreased more for patients with high or low body mass index (BMI).[57] Yoga, exercise (especially weight-bearing exercise) with regular stretching, and physical therapy with joint-mobility exercises have been suggested for the management of mild arthralgia pain.[5,53,58] Such measures may also support breast cancer treatment goals, for example, in patients without hot flashes who were effectively treated for breast cancer, dietary changes that were maintained over 4 years were also shown to reduce the risk of breast cancer.[59] Exercise may also contribute to improved survival after adjuvant breast cancer treatment.[60] Other nonpharmacologic approaches to MSS management include heat (eg, hot packs), footwear with lateral-wedge insoles (for knee-associated symptoms), massage therapy, and acupressure (Figure 2).[5,6,53]

Pharmacologic treatment options for AI-associated arthralgia that reportedly provide symptom relief include conventional NSAIDs (eg, ibuprofen),[11,16] analgesics (eg, acetaminophen),[16] coxibs (eg, celecoxib), tramadol, glucosamine plus chondroitin sulfate,[16] opioids,[16] probiotics

(eg, VSL#3), bisphosphonates, vitamin D supplements, antidepressants, sleep aids, nerve-pain medication, and topical capsaicin plus methylsalicylate.[5,15,20,53] Recently, testosterone undecanoate was reported to reduce joint symptom morbidity.[61] According to one recommendation, conventional NSAIDs and coxibs should be started at a high dose to provide rapid symptom relief, followed by titration down to the minimum effective dose.[15] Duloxetine (a selective serotonin norepinephrine reuptake inhibitor that has been used to treat chronic pain) has recently been tested in a randomized phase II study for 29 patients with AI-induced MSS.[62] Results were promising; 72% of patients receiving duloxetine had at least 30% reduction in average pain.[62] By allowing normal joint function to resume quickly, these drugs may encourage patients to continue AI treatment.

Switching to another AI may reduce arthralgia symptom severity. Although all three AIs reduce estrogen levels through inhibition of the aromatase enzyme, they differ in terms of their pharmacokinetics and their effects on lipid parameters, aldosterone levels, and cortisol levels.[63] The dissimilarities among AIs may lead to variations in tolerability, and switching agents may allow patients to continue AI therapy. Several studies have evaluated this strategy.[64-66] Among 182 patients randomized to receive 12 weeks of letrozole followed by 12 weeks of anastrozole and vice versa, joint pain was reported by 131 patients.[64] However, 56% of those who reported joint symptoms with upfront letrozole did not report these symptoms after they switched to anastrozole; similar results were observed with the opposite sequence. Patients who discontinued anastrozole because of grade 2 or 3 arthralgia or myalgia and switched to letrozole after a 1-month period without AI therapy experienced a significant improvement in pain and disability scores after 6 months.[65] Another similarly designed study involved patients who discontinued anastrozole because of musculoskeletal pain; among those who switched to letrozole, about 30% fewer patients reported pain after 6 months.[66] Therefore, switching to another AI may allow patients to continue treatment and maximize benefits.[43]

Resolving MSS

Spontaneous resolution of arthralgia-related AEs associated with AI therapy occurs slowly during treatment, but resolution is common after cessation of AI therapy.[8,15] In one study, 53% (56 of 106 patients) with joint pain and/or stiffness reported use of oral medications for symptom relief (including NSAIDs, acetaminophen, and opiates), as well as oral supplements (eg, glucosamine, chondroitin sulfate, omega fish oils); 46% used a nonpharmacologic intervention (eg, exercise).[16] Among patients who used oral medications, 78% reported moderate to complete relief of joint symptoms. Among 34 patients reporting arthralgia and/or bone pain in a clinical setting, 50% stated that NSAIDs were effective for pain relief.[11] Testosterone and dehydroepiandrosterone-sulfate have each been reported to reduce the severity of pain and stiffness (as measured by visual analog score or questionnaire) in patients receiving AI therapy.[61,67]

Although there are few published clinical studies for nonpharmacologic interventions, three small studies in postmenopausal women with early breast cancer who reported MSS during AI therapy showed that acupuncture reduced pain severity, reduced joint symptoms, improved joint function, and was well tolerated.[68-70] However, supporting data from larger studies are necessary to establish benefits from acupuncture.

Temporary discontinuation of an AI with or without initiation of tamoxifen may be useful to establish MSS causality and health care providers may then decide whether to switch to another AI or to tamoxifen. Completion of adjuvant endocrine therapy is important for the cancer patient to receive maximum treatment benefit. To that end, physicians may improve adherence to therapy through patient education about arthralgia and effective symptom management.[15]

Conclusion

Adjuvant AI therapy is associated with arthralgia/MSS in approximately one-third of patients with hormone-sensitive early breast cancer. Although the reported symptoms are primarily mild to moderate, the development of more severe arthralgia does occur in approximately 2%-12% of patients treated with an AI.

Because of variability in the definition of arthralgia, the limitations in the data establishing causality, and the high baseline incidence of MSS in postmenopausal women, an accurate estimate of the incidence and etiology of AI-associated arthralgia is difficult to establish. Nonetheless, the risk-benefit ratio favors adjuvant AI therapy.[32,71-73] Therefore, steps to manage MSS should be taken in order for patients to complete AI therapy and receive its full clinical benefit. These steps include a baseline examination and patient education before initiating AI therapy, as well as lifestyle changes and pharmacologic treatment, if necessary, when arthralgia develops or worsens during AI therapy. Because the majority of patients who develop new or worsening arthralgia during AI therapy report ameliorated symptoms with palliative treatment—and algorithms to aid in optimal arthralgia management are available—arthralgia should not be a deterrent to using AIs in this patient population.

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