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Aromatase inhibitor–associated musculoskeletal pain: An overview of pathophysiology and treatment modalities

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Abstract

Since their introduction into clinical use in the 1970s, aromatase inhibitors have been a cornerstone of therapy for estrogen-receptor positive breast cancer in postmenopausal women. Unfortunately, this therapy leads to estrogen depletion in the body, which can lead to unpleasant side effects such as menopausal symptoms like hot flashes, insomnia, slightly increased risk of ischemic heart disease, accelerated bone loss leading to higher osteoporosis risk, and most significantly, arthralgias. The joint pain induced by aromatase inhibitor therapy is frequently cited as the leading cause of premature discontinuation; approximately 50% of patients will report new onset or worsening joint pain 1 year after therapy initiation, approximately 30% of patients discontinue therapy after 1 year, and only 50%–68% of patients remain fully compliant with therapy after 3 years. This article will describe risk factors for aromatase inhibitor–associated musculoskeletal syndrome, including genetic predispositions correlated with an increased risk of this syndrome, explain the currently understood pathophysiology, and give an overview of effective treatment options in managing this syndrome.

Keywords

Oncology, palliative medicine, anesthesia/pain

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Introduction

Since their introduction into clinical use in the 1970s, aromatase inhibitors (AIs) have been a cornerstone of therapy for estrogen-receptor positive breast cancer in postmenopausal women. The American Society of Clinical Oncology recommends the initiation of 5–10 years' worth of AI therapy after breast cancer surgery, depending on risk of recurrence.[1,2] Unfortunately, this therapy leads to estrogen depletion in the body, which can lead to unpleasant side effects such as menopausal symptoms like hot flashes, insomnia, slightly increased risk of ischemic heart disease, accelerated bone loss leading to higher osteoporosis risk, and most significantly, arthralgias.[3] This adverse effect presents as joint pain affecting the hands, wrists, knees, lower back, hips, shoulders, and feet, with the fingers being most commonly affected. Extra-articular issues such as carpal tunnel syndrome, trigger finger, morning stiffness, decreased grip strength, and improvement of symptoms with movement have also been reported.[4] The mean time to symptom onset is 1.6 months after initiation of therapy, and symptom severity often peaks at 6 months.[5]

The joint pain induced by AI therapy, or "aromatase inhibitor–associated musculoskeletal syndrome" (AIMSS), is frequently cited as the leading cause of premature discontinuation; approximately 50% of patients will report new onset or worsening joint pain 1 year after therapy initiation,[6] approximately 30% of patients discontinue therapy after 1 year, and only 50%–68% of patients remain fully compliant with therapy after 3 years. This leads to an increasing risk of breast cancer relapse and mortality.[4] This article will describe risk factors for AIMSS, including genetic predispositions correlated with an increased risk of this syndrome, explain the currently understood pathophysiology, and give an overview of effective treatment options in managing this syndrome.

Pathophysiology

Risk factors positively correlated with the development of AIMSS include being less than 5 years from menopause, history of taxane-based chemotherapy, obesity, and a past medical history of arthritis or osteoporosis.[4] The exact

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pathophysiology behind this syndrome is not fully understood, but the prevailing theories point to estrogen deprivation as the key factor leading to degradation of bone and cartilage leading to development of the syndrome. This hypothesis is supported by studies that have shown how the CYP19A1 gene, which is responsible for coding aromatase, has many polymorphisms in the population, which can affect the risk of developing AIMSS.[7] A 7-repeat allele of TTTA is correlated with decreased levels of estrogen in postmenopausal women during AI therapy and conferred a slightly higher risk of AIMSS, while a different 8-repeat allele of TTTA is correlated with increased estrogen levels and conferred a decreased risk of AIMSS.[8] Indeed, another study found that patients suffering from AIMSS had decreased estrogen levels compared to women on AI therapy not experiencing arthralgias.[9]

Estrogen decreases osteoclast maturation and overall decreases osteoclast lifespan, as well as promoting osteoblast maturation and maintaining their lifespan. Estrogen also helps to maintain the integrity of joints by inhibiting the breakdown of the cartilaginous extracellular matrix, as chondrocytes contain E2 receptors.[10] Estrogen also has an anti-inflammatory effect on the body by decreasing the synthesis of inflammatory cytokines such as tumor necrosis factor (TNF)-a and interleukin (IL)-1b, and increased levels of C-reactive protein (CRP), eotaxin, and monocyte chemoattraction protein 1 (MCP-1) have been detected in patients.[11] Magnetic resonance imaging (MRI) studies in women experiencing AIMSS have shown fluid surrounding the flexor sheaths, thickening of the flexor/extensor tendons in the hands, and fluid in the metacarpal joints, suggesting underlying inflammation caused by the medication.[12]

Studies have been carried out to evaluate the influence of single-nucleotide polymorphisms (SNPs) on the development of AIMSS. Osteoprotegerin (*OPG*) is a protein that has been shown to have osteoprotective effects by inhibiting downstream signaling of the osteoclastic RANKL. OPG rs2073618, an allele coding for a missense mutation in the protein commonly found among Caucasians (~45%) and Asians (~25%), is associated with a 3.33-fold increased risk of AIMSS after 3–6 months of therapy.[13] Interestingly, this SNP is also positively correlated with an increased risk of postmenopausal osteoporosis and fractures, and decreased levels of OPG have been observed in patients experiencing acute flares of rheumatoid arthritis.[14] Another study showed that blockade of the estrogen-dependent SNP rs11849538 located on TCL1A leads to increased transcription of NF-kB, which in turn mediated joint inflammation.[15]

A genome-wide study identified 70 SNPs in women who had received at least 1 month of a third-generation AI that were positively correlated to increased risk of arthralgias. Many of these genes, such as BLS1, PLAA, and TRPV3, have been studied to be associated with joint erosion, increasing chemoattraction of CD4+ cells into joint synovium, upregulation of NF-kB; all elements that are indicated in inflammatory diseases such as rheumatoid arthritis. This suggests that patients who experience AIMSS are more likely to experience an overall increased risk of inflammatory arthritis outside of AI therapy.[16]

SNPs that are potentially protective against AIMSS have also been identified. The Fok-I variant of the Vitamin D receptor has a prevalence of ~33% in Caucasian women, and it is associated with a ~50% decrease in levels of IL-1b, a cytokine that is strongly positively correlated with arthralgia. Patients with this variation were less likely to report AIMSS 6 months after initiation of AI treatment.[17]

Treatment

There are currently no standardized guidelines or universally accepted treatments for AIMSS, but there have been many studies, including randomized control trials and cross-sectional studies, examining pharmacologic and non-pharmacologic routes of treatment, some of which are summarized here.

Nutritional supplementation with vitamins and glucosamine/chondroitin has been explored as a possible treatment option. The liver's CYP3A4 protein metabolizes all AI's currently in use (letrozole, anastrozole, exemestane), and Vitamin D is necessary for induction of this enzyme; therefore, patients on AI therapy are believed to have increased needs for Vitamin D. Indeed, AI patients in one study were Vitamin D deficient (less than 30 ng/mL) at a rate nearly two times higher than the average postmenopausal woman living in the same region, even though these women were being supplemented with 665 IU Vitamin D supplements and spending an average of 39 min/day outside in the sun.[18] Studies by Khan et al.[19] and Rastelli et al.[20] have suggested that high-dose Vitamin D3 or D2 supplementation for 12 weeks (50,000 IU daily compared to the standard daily dose of 600 IU) significantly decreased debilitating symptoms, while studies by Shapiro et al.[21] and Khan et al.[22] with lower doses (4000–30,000 IU) did not lead to decreased symptoms. Supplementation with daily over-the-counter glucosamine sulfate (1500 mg/day) and chondroitin sulfate (1200 mg/day) for 24 weeks lead to a significant decrease in joint stiffness, Range of Motion (ROM), and improved grip strength in 46% of patients.[23] Supplementation with 2500 µg of sublingual vitamin B12 for 90 days leads to improvement in pain severity scores in 34% of women in a study by Campbell et al.[24]

Various other medications have been studied in the treatment of AIMSS. As described above, as fluid in the flexor/extensor sheaths and in the joints has been observed via MRI in these patients, diuretics have been studied as an effective medication. In a very preliminary study by Alhanafy et al.,[25] women treated with furosemide 20 mg and spironolactone 50 mg every 2 days for 4 weeks demonstrated improvement in pain, joint stiffness, and grip strength in over two-thirds of patients, beginning in the first week of treatment. Duloxetine,

a selective serotonin-norepinephrine reuptake inhibitor commonly used to treat chronic pain in both depressive and non-depressed patients, has also been studied. A 2018 study by Henry et al. in which AIMSS patients took 30 mg of duloxetine for 1 week followed by 60 mg for a further 11 weeks demonstrated that >50% of patients experienced a >50% reduction in joint pain and stiffness after 6 weeks,[26] with obese patients experiencing a greater reduction in pain scores than non-obese patients.[27]

As AIMSS can potentially result from an inflammatory process arising from low estrogen states, glucocorticoid therapy has also been studied. A non-randomized study by Kubo et al.[28] examined the effects of low-dose prednisolone (5 mg daily) for 1 week in patients with typical arthralgias due to AIMSS. Two-thirds of women experienced immediate joint pain relief, and this effect lasted for 2 months after discontinuation of steroid therapy in one-third of women.

Bisphosphates such as zoledronic acid are widely used by postmenopausal women to decrease the risk of osteoporosis and increase bone mineral density and have also been shown to decrease inflammation by depleting proinflammatory cytokines such as TNF-a, IL-1, and IL-6. The Zoledronic Acid Prophylaxis (ZAP) trial compared the incidence of AIMSS against historical controls; 52 women (similarly matched to the control cohort) received zoledronic acid prior to initiating letrozole and 6 months later. During the first year of AI therapy, 37% reported AIMSS in the ZAP group compared to 67% in the controls.[29]

Various non-pharmacologic agents have also been explored. Perhaps the best-studied approach not involving the use of medications is acupuncture. A large randomized controlled trial (RCT) conducted in 2018 by Hershman et al. examined AIMSS patients undergoing two 30-min sessions of full-body acupuncture per week for 6 weeks, followed by one session per week for an additional 6 weeks. Pain scores were twofold lower in the treatment cohort compared to women undergoing sham acupuncture after 6 weeks; improvements in average pain and joint stiffness were also seen at 12 weeks.[30] Indeed, a 2017 meta-analysis examining five RCTs for acupuncture in AIMSS supported this assertion, with all of the trials finding significant decreases in joint pain and stiffness after 6–8 weeks of acupuncture, but no significant differences at 3–4 weeks. Acupuncture is proposed to exert its analgesic effects through the higher circulation of endogenous opioids and could potentially have an anti-inflammatory effect on the body. Patients have been shown to have decreased circulating levels of IL-17 and a decreased erythrocyte sedimentation rate (ESR) after 6 weeks of treatment; however, decreases in levels of other proinflammatory markers such as CRP were not observed.[31]

The role of exercise in the management of musculoskeletal symptoms caused by AIs is still being investigated. Studies by Varadarajan et al.[32] and Nyrop et al.[33] demonstrated improvements in grip strength, joint stiffness, increased exercise tolerance, and an overall improvement in mobility while following an 8-week supervised exercise program. However, a 2020 Cochrane review did not demonstrate any additional benefit on overall disability or pain scores for women following supervised exercise programs. Despite this, the authors noted that exercise is overall very safe for cancer patients and should be included and encouraged as part of their treatment plan, as it has been shown to be helpful in reducing exhaustion, increasing adherence to medical therapies, and reducing the incidence of depression in cancer patients.[34]

Symptoms can also be managed by switching between different AIs. A study by Briot et al.[35] examined patients who stopped taking anastrozole due to musculoskeletal symptoms, switching to letrozole after a 1-month washout period. 71.5% of patients continued to take letrozole after 6 months, suggesting that patients can be switched between the three approved AIs (letrozole, anastrozole, exemestane)

A multidisciplinary approach can be useful in the diagnosis and treatment of AIMSS. Rheumatologic consultation is often the trigger for diagnosis if the primary treatment team (e.g. oncology) does not recognize it immediately.[36] In addition, pathologic linkages with other autoimmune diseases such as Sjogren syndrome, systemic sclerosis, and systemic lupus erythematosus (SLE) are more likely to be recognized through rheumatologic consultation.[37]

Conclusion

AIs are a standard therapy used in women with estrogen-receptor positive breast cancer. Unfortunately, the hypoestrogenic state that results is strongly associated with the development of adverse musculoskeletal symptoms such as joint pain, stiffness, decreased grip strength, and decreased exercise tolerance in up to 50% of patients. These symptoms are primarily responsible for the high rate of medication discontinuation in these patients, leaving them at increased risk of cancer recurrence and growth.

Palliative medicine providers, oncologists, and primary care providers are frequently called on to manage the adverse side effects of cancer treatment medications and often treat pain caused by AIs. Although there are currently no standardized guidelines or universal treatments for AIMSS, there are numerous accessible treatment options that can provide short-term and long-term relief in these patients. Many of them are easily accessible, such as nutritional supplementation, acupuncture, exercise, and well-studied pharmacological agents such as duloxetine. Providers should be aware of the varying length of treatment and duration of relief of the different management options available so that they can be best tailored to suit the needs of individual patients.

Limitations of this review

This is not a systematic review or meta-analysis, simply an informational review of the literature and overview on this

topic. For definitive data that would affect standard of care, multi-center, randomized, placebo-controlled, double-blinded studies are required.

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