Issues associated with Aromatase Inhibitor–Associated Musculoskeletal Symptoms in Breast Cancer

Tsai-Ju Chien¹,²

¹Institute of Traditional Medicine, National Yang-Ming University, Taipei, Taiwan
²Division of Hemato-Oncology, Department of Internal Medicine, Branch of Zhong-xing, Taipei City Hospital, Taipei, Taiwan

Correspondence: Tsai-Ju Chien
E-mail: silence021@gmail.com
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Since Aromatase inhibitors are the standard therapy in hormone receptor positive postmenopausal breast cancer females. What we are concerned is the related complications named Aromatase Inhibitor–associated musculoskeletal symptoms (AIMSS) such as arthralgia, osteoporosis, loss of bone mineral density or musculoskeletal pain which will lead to poor compliance of patients and treatment failure. The further understanding the role and mechanism of aromatase inhibitors will help dealing with the AIMSS. Meanwhile, how to measure or diagnose the AIMSS may need more consensuses because so far no definite marker can define the AIMSS and functional tests are most subjective report from patients. In clinical practice, some therapeutic trials have focused on the treatment of AIMSS but still no exclusive agreement. Accordingly, we review and highlight the related issues about AIMSS in breast cancer and hope for more comprehensive understanding about this issue then come up with the consensus.


The role of Aromatase inhibitor in breast cancer and related musculoskeletal symptoms

Aromatase inhibitors (AIs) are, has been used as a first-line standard adjuvant endocrine therapy in postmenopausal women with hormone receptor–positive breast cancer because higher levels of estrogen and aromatase expression have been noted in breast cancer cells [1]. Compared with some anti–estrogen medications such as tamoxifen, aromatase inhibitors are superior because they do not have the intendency of increasing the risk of endometrial cancer and thromboembolism [2]. Aromatase inhibitors has been approved by the Food and Drug Administration with their crucial role in adjuvant and first-line metastatic breast cancer settings [3]. For two kinds of aromatase inhibitor, steroidal (anastrozole or letrozole) and nonsteroidal (Exemestane), both were found to be equal efficient in terms of breast cancer outcomes in 5-year initial adjuvant therapy for postmenopausal breast cancer [4]. However, accelerated bone resorption from estrogen suppression is a potential risk with the use of aromatase inhibitors. This is an annoying symptom involving Aromatase Inhibitor–associated musculoskeletal symptoms (AIMSS) including bone fracture, osteoporosis, loss of bone mineral density or musculoskeletal pain and arthralgia [5]. Studies showed 28%–47% of patients receiving AI therapy experienced musculoskeletal disorders [6, 7]. The ATAC trial which analyzed the related data of musculoskeletal events from AI and tamoxifen alone or in combination indicated significantly more women without preexisting joint symptoms developed arthralgias when treated with anastrozole, compared with the women treated with tamoxifen (36.5%:30.9%;p< .001) [8]. AIMSS is the primary reason leading to withdrawal from AI treatment in breast cancer patients and successful AI treatment depends on patient compliance [9]. Therefore, this issue is worthy of attention as AIMSS is increasingly used.
**Mechanism of AIMSS**

The possible pathophysiology of AI-associated arthralgia is obscure. The varied levels of estrogen lead to bone loss, which in turn contribute to arthralgia [9]. In an MA 27 Aromatase inhibitor clinical trial focusing on patients with postmenopausal, ER-positive breast cancer who were treated with one of two AIs, anastrozole or exemestane, though the outcome was similar for both two drugs, exemestane may have more effect on bone health [10,11]. Though the important role aromatase inhibitor play in treating breast cancer, we should remember that aromatase can lead to local conversion of androstenedione to estrone and estradiol, and estrogen is accompanied chondro-protective effects by decreasing collagen degradation [12]. So AI which induces estrogenic deficiency may impair cartilage maintenance [13]. Further, the related muscular pain may due to various articular structures innervated with nociceptive fibers, such as the joint capsule, periosteal bone, ligaments, synovium, and even the periarticular structures. Accordingly, the inflammatory related cytokines, including prostaglandins and bradykinin, make the joints more sensitive to pain and mechanical related muscular pain may due to various articular structures innervated with nociceptive fibers, such as the joint capsule, periosteal bone, ligaments, synovium, and even the periarticular structures. Accordingly, the inflammatory related cytokines, including prostaglandins and bradykinin, make the joints more sensitive to pain and mechanical stimuli via activating receptors on peripheral nociceptors [14]. A further study indicated the expression of cytokine influenced by SNPs - near the 3’ terminus of TCL1A, is also involved in the AIMSS mechanism [15]. The deeper pharmacogenomics explanation is estradiol (E2) increased TCL1A expression and, in a TCL1A SNP-dependent manner, also adjusted the expression of IL-17, IL-17RA, IL-12, IL-12RB2 and IL-1R2 [15]. Through the phosphoinositide 3-kinase/Akt signaling pathway, the expression of TCL1A will increase which related to CD4+ and CD8+ T-cell activation [16], and TCL1A also serves as a cofactor of Akt1 that enhances Akt1 kinase activity [17]. Illustration of the mechanism associated with AIMSS in women with breast cancer may help in the clinical treatment of AIMSS.

**Measurement of AIMSS**

Since pain is a subjective feeling, most studies related to AIMSS designate pain and joint stiffness as the primary outcomes, and quality of life or well-being as the secondary outcomes [18, 19]. Pain score assessment includes the Brief Pain Inventory-Short Form (BPI-SF) [20-22]; Western Ontario and McMaster Universities Osteoarthritis Index(WOMAC) [21, 23]; Functional Assessment of Cancer Therapy–General (FACT-G), and the Handgrip strength test [20, 21]. In objective measurement, some studies check the cytokine level as IL-1,IL-6, IL-8,IL-10,IL-12,IL-17; IFN-β; TNF-α compared to the degree of inflammation [24] or the estradiol change because estrogen is associated with chondroprotective effects through decreasing collagen degradation [12]. Bone mineral density may also serve as a target in monitoring AIMSS, such as in a IBIS-II bone sub-study [25, 26] where Kyvernitakis et al examined the effects of AI on the serum levels of sclerostin, dickkopf-1 (DKK-1) and osteoprotegerin (OPG), as markers of bone turnover and bone mineral density, concluding sclerostin levels are an indication of the central role of osteocytes in bone turnover in women with breast cancer [27]. Thus far, no definite marker has been identified as an indicator of AIMSS. Different research studies have chosen different markers or tools from various perspectives.

**Treatment recommendations in AIMSS**

There is still a lack of knowledge of the explicit mechanism of arthralgia and anti-inflammatory agents are not as effective as we expected. Patients who experience severe musculoskeletal discomfort may need to switch to different kind endocrine agent such as tamoxifen [28]. Thus, some complementary therapies have been tried in clinical practice. Related research, including the use of Omega-3 fatty acids (O3-FAs) in reducing pain and stiffness, has not met the standard for clinical significance [29]. A double-blind placebo-controlled randomized phase II trial suggested a high weekly dose of Vitamin D2 supplementation may improve AIMSS and positively affect bone health with FIQ pain (p = 0.0045), BPI worst-pain (p = 0.04), BPI average-pain (p = 0.0067), BPI pain-severity (p = 0.04), and BPI interference (p = 0.034) scores which were better in the high dose Vitamin D2 than the placebo group [30]. Van Poznak C et al showed the addition of risdroronate may prevent and treat osteoporosis, resulting in favorable effects on bone mineral density in postmenopausal women at risk of fragility fracture who were receiving adjuvant anastrozole for early breast cancer [31]. A systemic review noted third-generation bisphosphonates positively affect the bone mineral density of patients who are suspected to or have suffered from bone loss, osteopenia, or osteoporosis due to treatment with aromatase inhibitors in hormone responsive breast cancer [32]. Immediate treatment with zoledronic acid demonstrated a significantly higher risk of increasing bone mineral density than patients with delayed zoledronic acid [33, 34]. One unique case report proposed Kampo medicines (Japanese traditional medicines) may improve Als-induced side-effects [35]. Other complementary therapies include Tai chi, which was demonstrated to improve wellbeing for breast cancer patients with AI related arthralgia [36]; yoga, leading to improvement in objective functional outcomes, pain, and health-related quality of life as measured by the Brief Pain Inventory (BPI), self-reported Patient Specific Functional Scale (PSFS), and electro-acupuncture, which will be exclusively discussed in the following paragraph [22, 39, 40].
The role of Acupuncture in AIMSS

Oncology acupuncture is a new and emerging field of research and clinical practice \[41\]. Acupuncture has also been applied in AIMSS, with an increasing number of physicians focusing on this issue \[42\]. In our previous study, we systematically reviewed the RCTs related to the efficacy of needle acupuncture in AIMSS in early breast cancer and lead to a conclusion that acupuncture seems to result in alleviating severity of joint pain and stiffness in AIMSS but has no obvious changes on inflammatory biomarkers \[19\]. The associated mechanism is supposed that through increasing the levels of endogenous opioid peptides in the central nervous system will lead to the effect of analgesia, \[43\] and down regulating pro-inflammatory cytokines, such as interleukin and TNF-α, but still requires more direct experimental proof \[44\]. The signaling molecules level such as serotonin, noradrenalin, dopamine, cholecystokinin octapeptide, glutamate, and γ-aminobutyric acid may change after acupuncture, leading to improvement in pain and stiffness \[45\]. The meridian theory of traditional Chinese Medicine and its integration with western medicine is worth further investigation.

Future perspective

Considering the importance and benefit of aromatase inhibitor treatment in breast cancer, we should strive to reach a possible solution to AIMSS to improve patient compliance. Deeper studies related to AIMSS in terms of mechanisms, measurement tools and complementary therapy are needed to reach a consensus on Aromatase Inhibitor–associated musculoskeletal symptoms.

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