Editorial

Duloxetine for AI-associated joint pain in breast cancer patients

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Aromatase inhibitors (AIs) are the standard of care for treatment of both early and advanced hormone-sensitive breast cancer in postmenopausal women. Although AIs have been considered to be well-tolerated, only 50 % of patients can complete the full course of the treatment, at the optimal schedule (1). A prospective randomized trial revealed that 32% of patients discontinued initial AI therapy within 2 years of initiation, because of adverse events, and 75% of them did so due to AI-associated musculoskeletal symptoms (AIMSS), including joint pain and stiffness (2). AIMSS reportedly occurs in up to 50% of breast cancer patients treated with AIs (3,4). Therefore, effective management of AIMSS is necessary for continuing AIs without compromising the quality of life (QOL). However, a standard of care for AIMSS, especially in terms of pharmacological interventions, is yet to be validated.

Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is thought to enhance descending pain inhibitory pathways by inhibiting the re-uptake of serotonin and norepinephrine. Clinical trials have revealed that duloxetine decreases chronic pain related to various etiologies including diabetic neuropathy, fibromyalgia, and osteoarthritis, along with chronic low back pain (5).

Henry *et al*., conducted a randomized, multi-center, placebo-controlled clinical trial, to assess the efficacy of duloxetine in relieving pain related to AIMSS in early breast cancer patients (6). A total of 299 early-stage breast cancer patients with an average joint pain score of ≥4 out of 10 in whom pain developed or worsened since AI therapy initiation, were randomly assigned to duloxetine or placebo for 12 weeks (1:1), which was then tapered off over a period of 1 week. Patients who had been taking AIs for a period of 21 days to 3 years were included in the study. Joint pain, pain interference, functioning, QOL, and depression were assessed at weeks 2, 6, and 12 (during intervention), as well as at week 24 (12 weeks after discontinuing the full-dose intervention). Patients were stratified by baseline pain score assessed by the Brief Pain Inventory (BPI), and prior taxane use. The duration of AI use was within 1 year in 64% of the patients. Results showed that the average pain score through 12 weeks, which was the primary endpoint, was reduced to a slightly greater extent (by 0.82 points) in the duloxetine arm than in the placebo arm (95% CI, –1.24 to –0.40, P=0.0002). Importantly, 52% of the patients treated with duloxetine immediately achieved clinically meaningful improvement in pain (defined as a ≥2-point decrease from baseline), within 2 weeks after initiation of the therapy. At week 6, this increased to 68% and was sustained until discontinuation of duloxetine. Although adverse events were seen more frequently in the duloxetine arm, most were of grade 1–2 severity and included fatigue, nausea, dry mouth, and headache.

Methodological assessment of pain related to AIMSS was the strength of this study. AIMSS are often underreported by physicians in clinical practice, as they are highly subjective and difficult to be recognized, classified, and graded systematically. In this trial, patient-reported outcomes were simultaneously assessed by four questionnaire tools. As a result, reliable and consistent

improvement with duloxetine in terms of average pain, worst pain, stiffness, pain interference, and functioning was noted.

In this trial, more than half of patients in the duloxetine arm reported clinically meaningful (≥2 points) improvement in pain. However, the benefit noted with duloxetine over placebo was only 0.82 points, which may not be enough to suggest a dramatic change in clinical practice. Several factors including natural history of AIMSS without intervention, patient selection, active ingredients within the placebo itself, and "placebo effect" caused by patients' expectations for interventions, may probably have a role in this (7).

The "placebo effect" has been reported to have a significant role in studies related to symptom management. Previous reports revealed that the magnitude of placebo effect was as high as 30–50% in trials investigating pharmacological management of cancer treatment-induced toxicities such as vasomotor symptoms, fatigue, and neuropathy (7). In a trial comparing omega-3-fatty acids (O3-FAs) versus placebo for 24 weeks in patients with AIMSS, no significant difference in pain improvement was noted between the two arms (61% and 57% of patients reported improvement of pain, in O3-FAs, and placebo arms, respectively), despite significant improvement in the O3-FAs arm compared to baseline (8). Contrarily, two randomized trials evaluating non-pharmacological management for AIMSS reported significant improvement following such interventions, without any placebo effect. One was a trial comparing true acupuncture with sham acupuncture, which revealed 50% decrease in pain with true acupuncture, whereas there was no change in pain intensity with sham acupuncture (9), and the other trial comparing exercise intervention with usual care reported 29% decrease in pain score following exercise, whereas there was no change in pain intensity with usual care (10). Importantly, Henry *et al*. demonstrated superiority of duloxetine to placebo, regardless of significant improvement in the placebo arm (6). Furthermore, 71% of patients in the duloxetine arm reported that the intervention was beneficial, while only 49% in the placebo arm noted beneficial effects. Hence, it can be suggested that duloxetine is effective in the management of AIMSS.

However, the efficacy of placebo cannot be ignored. While the magnitude of "placebo effect" would be lesser in clinical practice (compared to clinical trials), its advantages in terms of biochemical safety and reduced cost (compared with the actual drug), may need to be considered. Placebo as an option for treatment of AIMSS as well as the ethical implications will need further research. A recent randomized controlled trial related to irritable bowel syndrome (IBS) revealed that placebo worked effectively even without blinding (11). Patients were randomized to either open-label placebo pills (presented as "placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes") or no-treatment (control group), with the same quality of interaction with providers. A significant improvement in IBS symptoms and a better QOL were noted in the open label placebo group compared to the control group. Similar results were also reported in a small pilot study evaluating antidepressant drugs in patients with depression (12). Several national studies revealed that most physicians regularly prescribe placebo, and consider it ethical (13,14). However, further trials are needed to confirm the possibility of placebo as a treatment option, especially in view of long-term efficacy and toxicity.

Epidemiologically, nearly 50% of healthy postmenopausal women develop joint and muscle pain without AIs (15). However, no specific biomarker or symptom classification has been established to distinguish AIMSS from other etiologies of musculoskeletal pain. The pathophysiology of AIMSS is also not clear. It has been hypothesized that estrogen deprivation caused by AIs results in musculoskeletal pain through numerous mechanisms. Preliminary evidences have demonstrated anti-nociceptive and anti-inflammatory effects of estrogens. Additionally, the protective effect of estrogens on structural integrity of articular cartilage has been suggested (15). Dizdar *et al*. reported increased tendon thickness and higher rates of effusion in hand joints/tendons on musculoskeletal sonography in women with AI-induced arthralgia compared to those who never received AIs (16). Although several factors such as dehydroepiandrosterone sulfate (DHEAS), insulin-like growth factor-I (IGF-I), interleukin-17 (IL-17), and vitamin D, have been suggested to be associated with the development of AIMSS, the underlying mechanisms are not known (15,17).

Assessment of the relationship between AIMSS and survival outcomes also revealed mixed results. In retrospective exploratory analyses of the Tamoxifen Exemestane Adjuvant Multinational (TEAM), Arimidex, Tamoxifen, Alone or in Combination Trial (ATAC), and Breast International Group (BIG) 1-98 trial, musculoskeletal symptoms were suggested to be associated with better

survival outcomes (18-20). In contrast, the MA.27 study revealed no association between these aspects (21). Interestingly, the incidence of AIMSS was higher in ATAC than in MA.27. However, an adherence rate of 88% among patients with symptoms, and 84% among those without symptoms was noted in ATAC patients, whereas it was only 70% in MA.27 patients; 31.6% of all patients in the MA. 27 study discontinued AIs mainly due to AIMSS (21). These results suggest that AIMSS can potentially be a prognostic factor of AIs when associated with good adherence. Therefore, management of AIMSS is essential to ensure long term adherence to life-saving AIs.

A new step in the management of AIMSS is suggested. Duloxetine can potentially be a new standard of care for patients with AIMSS. Further understanding of etiology would be helpful to improve the management of AIMSS and increase adherence to AIs.

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Footnote

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