REVIEW ARTICLE

Current management of aromatase inhibitor-induced arthralgia

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Summary

Aromatase inhibitors (AIs) are standard of care in the adjuvant setting of postmenopausal women with hormone receptor positive breast cancer. Despite their beneficial effects on survival outcomes in breast cancer, AIs-induced arthralgia (AIA) is a common side effect which may lead to drug discontinuation and decreased AIs adherence among patients. So far, the exact pathophysiology of AIA is still an unclarified condition that explains why the optimal treatment in its management has not yet been established. Moreover, studies regarding the alternative treatment options for AIA are limited due to small sample size. Herein, we report a summary of current treatment options and their effectiveness in AIA with a practical algorithm in light of the relevant literature.

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

Introduction

AIs are widely used in the adjuvant setting of hormone therapy to improve the survival of postmenopausal patients with hormone receptor positive breast cancer [1]. Recent studies have demonstrated that AIs are superior to tamoxifen in terms of favorable survival outcomes [2] and the American Society of Clinical Oncology suggests AIs as the adjuvant hormone therapy for postmenopausal breast cancer with positive hormone receptors [3,4]. Although AIs produce beneficial survival outcomes, some severe adverse effects which may result in poor AI adherence develop during treatment. Among them, joint pain and arthralgia are well-known as the severe side effects of AIs with an incidence up to 50 % in all patients [5]. However, there is only little information concerning the management of AIA. Hence, understanding the main pathophysiology and developing an optimal treatment recommendation for arthralgia are required for patients to increase the quality of life as well as to prevent drug discontinuation.

Possible mechanisms

Estrogen (ER) deficiency has been suggested as a main cause of arthralgia, led by some possible mechanisms including direct local effect on joint tissues, indirect effects of increased inflammatory parameters such as IL-6 and affecting central and peripheral nociception [6]. The decrease in serum estradiol levels has been supposed to be correlated with both decrease in the bone mineral density and increase in the articular symptoms [7]. Previous studies have demonstrated that ER regulate the inflammation and spinal processing of nociceptive input via the inhibition of microglial activation and inflammatory mediators and also has an anti-nociceptive effects through opioid pain fibres

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in the cranio nervous system [8,10]. Diminished serum estradiol levels may lead to a decrease in the endogenous opioid levels, explaining thus the severe pain in patients [11]. ER are also known to have chondroprotective effects by preventing collagen degradation. Additionally, aromatase is found in synovial cells and cartilages. Thus, ER deficiency due to AIs may impair the regulation in cartilage structure [12]. Another mechanism contributing to AIA is an inflammatory process presenting with an increased risk of wrist joint effusion [6]. Previous imaging studies have shown some inflammatory tenosynovial changes in AIA [13]. Patients with AIA have been found to have higher rates of joint effusions and electromyography findings compatible with carpal tunnel syndrome [12].

Patients at high risk

So far, various factors have been defined to be linked with developing higher risk of AIA. Among them, obesity has been consistently shown to be associated with AIA. The ATAC trial had shown that obese women with body mass index (BMI) above 30 had a higher incidence of AIA compared with normal weight women with BMI below 30 [14]. Prior hormone replacement therapy, history of previous chemotherapy, such as taxanes, existence of arthralgia or osteoarthritis at baseline and genetic polymorphisms have been shown to be associated with a higher risk of developing AIA [15].

Current management

AIA has remained a therapeutic challenge since the exact pathophysiology is still under debate. Recently, a lot of studies concerning the alternative treatment options in AIA have been performed to provide a good quality of life and to allow uneventful continuation of adjuvant hormone therapy. Herein, we report a step by step algorithm for AIA in light of the evidence-based studies.

Patient's education regarding the possible side effects as well as the drug advantages may be beneficial in managing AIA and also may help patient adherence to AI treatment. Follow-up of patients receiving AIs should be scheduled at 2 to 6 months following treatment initiation [16]. Further follow-up may be performed according to the patient symptoms. The attending physician should emphasize the drug benefits on decreasing the risk of disease recurrence so that to increase her adherence to AI treatment. The non-pharmaceutical acupuncture method was recently reported to produce effective and favorable results on AIA and also to increase the AIs adherence in patients [17]. In a year-long randomized trial, another non-pharmaceutical exercise method exercise has been shown to lead to improvement in AIA in 121 breast cancer survivors receiving AIs [5]. Lifestyle alterations such as regular exercise and weight reduction in patients with AIA may increase muscle strength, joint mobility and flexibility in order to control the joint symptoms [16]. In addition, yoga is suggested to be an effective method in the management of AIA. However, more trials are required to confirm these results [18].

Vitamin D is suggested to play a crucial role in the management of AIA and is well-known to increase the proximal muscle strength which is essential for musculoskeletal health [19]. ER increase 1-a hydroxylase enzyme activity to convert the 250HD to active 1,25-dihydroxyvitamin D form and also increase vitamin D receptor activity. Decline of ER levels due to AIs may lead to a decrease in vitamin D levels [15]. In a study evaluating the effect of vitamin D in the management of AIA, 40 ng/ml of serum 250HD concentration was found to decrease the risk of developing AIA [6]. However, the authors reported that, despite supplementation, many women on the study had not reached adequate vitamin D levels. On the same topic there is an ongoing larger prospective randomized placebo-controlled trial to assess the vitamin D supplementation in AIA.

Pharmaceutical approaches, such as acetaminophen, should be initially tried in order to control the joint pains. If the pain persists, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen may be subsequently prescribed. Tricyclic antidepressants or opioids should be used for difficult and resistant cases [16]. NSAIDs are commonly used in clinical practice in the management of AIA, whereas no clinical trial is still available to support this approach. Moreover, physicians should also remember that despite the beneficial effects of NSAIDs in AIA, they have many serious adverse effects including gastrointestinal bleeding and acute renal failure [15].

Steroids are not frequently recommended in the management of AIA. However, in a study of low-dose, short-term (5-day) oral prednisolone therapy, AIA was significantly improved. This study also suggested that prednisolone may take the place of NSAIDs, acetaminophen or cyclooxygenase-2 (COX-2) inhibitors in patients with AIA [20].

Switching one AI to another has been more widely accepted as an effective method in the management of AIA. This approach was assessed in the Articular Tolerance of Letrozole (ATOLL) study which was a prospective, non-randomized and multicenter trial [21]. ATOLL study demonstrated that switching to another AI could be more tolerable and beneficial in terms of controlling the joint symptoms. Also the outcomes of a previous study suggest that switching to another AI or a final switch to tamoxifen may be a reasonable method in the management for difficult cases [16].

Despite the presence of several recommendations in the literature, the management of AIA still remains a therapeutic challenge in clinical practice due to absence of prospective, randomized, controlled trials. So far, studies on this issue are uncontrolled, small-sized and with short duration.

Discussion

So far, no standard management guideline for AIA is currently available and no optimal treatment has yet been established. AI discontinuation is commonly considered as the optimal and safe management way to improve and control the symptoms [6]. Switching to another AI or to tamoxifen for the AIA management may be an effective strategy although there is no much information on this issue. Hence, further comparative studies of tamoxifen and AIs should be performed to evaluate and illustrate the effect of switching. Other therapeutic options including antidepressants, anti-irritants, hypnotics, gabapentin, steroid injections, essential fatty acids, duloxetine and some sport activities or lifestyle alterations such as weight loss, yoga, cardiovascular aerobics and water aerobics may be partly efficient [22].

In our practice, case-by-case and step-by-step treatment approach is the key of the management. We initially aim to encourage patients with AIs therapy to have a normal lifestyle and also to keep their body form by joining some sport activities. We initiated supplements including vitamin D, biphosphonates and calcium to patients who have a lower bone mineral density showing osteoporosis in DEXA scan, according to the United States Preventative Task Force guidelines. If the pain persists, we initiate acetaminofen or NSAIDs according to the severity of the pain and drug response. Although selective NSAIDs (COX-2 inhibitors) seem to have less side effects, they are reported to downregulate aromatase, leading thus to serious side effects such as heart attack and stroke. Therefore, we do not recommend selective COX-2 inhibitors in the treatment of AIA. If the pain persists despite all of the management methods, we switch letrozole to anastrozole and vice versa. Furthermore, in appropriate patients we perform a final switch to tamoxifen in difficult and resistant cases.

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