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# Arthralgia- the principal side effect in Breast Cancer Patients Receiving Aromatase Inhibitors and its management

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**ABSTRACT**

Breast cancer is the common cause of cancer death in women. In the adjuvant setting, Aromatase inhibitors (AIs) such as letrozole, anastrozole, and exemestane play an important role in treating postmenopausal women (PMW) with hormone receptor-positive breast cancer. Since estrogen endorses the growth of breast cancer cells, AI's act by inhibiting aromatase enzyme which is involved in peripheral synthesis of estrogen in PMW. Standard duration of AI therapy is 5 years to achieve good prognosis but AI's are principally associated with skeletal symptoms where arthralgia is the primary reason for early discontinuation. The purpose of the study was to assess the incidence of arthralgia in south Indian population and to conclude its management. The retrospective case review included 81 breast cancer patients with positive hormone receptor status, who were receiving adjuvant AI therapy. The Incidence of arthralgia was 49% in the AI treated group and it is high among young adults (50 vs. 65, p value= 0.0278) when compared to the elderly patients. The incidence of arthralgia in bisphosphonates treated AI group is less when compared to Non bisphosphonates group (P value = 0.0277). Hence bisphosphonates can be an initial choice of therapy in patients with AI induced arthralgia.

## INTRODUCTION

Breast cancer is the most common cause of cancer death in women. The third generation AIs include anastrozole, letrozole, exemestane, have been investigated as substitutes to tamoxifen as they demonstrated improved efficacy in reducing the risk of recurrences when used as upfront, switch, and extended adjuvant therapy in the adjuvant setting of early, hormone-responsive breast cancer (Del *et al*., 2007). The primary adverse effects include fatigue, insomnia (Bauml *et al.,* 2015), premenopausal symptoms, vaginal dryness, sexual dysfunction which doesn't affect the course of therapy and can be managed symptomatically but the skeletal symptoms with risk of osteoporosis and fracture, arthralgia, bone loss and myalgias are associated with premature termination of treatment (Gaillard and Stearns, 2011; Chim *et al.,* 2013)which may adversely impact disease free and overall breast cancer survival (Hershman *et al.,* 2011). Hence this study was intended to identify the real time incidence of skeletal symptoms in south Indian population who were treated with AI for breast cancer and its management to prevent early withdrawal of AI by improving the quality of life thus encouraging patients to continue the AI therapy for ≥ 5 years, to achieve good prognosis and an improved overall disease free survival (Katherine *et al.,* 2007).

**Probable Mechanism of AI induced Bone loss:**

As growth of many breast cancer tumors is stimulated or maintained by estrogen, these AIs inhibit the P450 cytochrome enzyme aromatase (CYP19), which involved in the peripheral synthesis of estrogens which are primary source of estrogens in post-menopausal women by converting the peripheral androgens to estrogens(Gaillard and Stearns, 2011).But Estrogen deprivation is believed to be a key contributing factor for AI-associated musculoskeletal side effects since current evidence suggests that estrogen is involved in bone and collagen maintenance, peripheral and central nervous system pain perception, and inflammation (Jones *et al.,* 2012).

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**Management with bisphosphonates**

Bisphosphonates inhibits bone resorption by inhibiting osteoclastic resorptive activity partly through inhibition of farnesyl diphosphate synthase and protein prenylation; thereby they prevent skeletal complications (Kimmel *et al.,* 2007) in patients with aromatase inhibitor induced bone loss and is the presently evolving intervention strategy which is under investigation. They also reduce the risk of developing musculoskeletal symptoms in breast cancer patients diagnosed with bone metastasis, as well as delaying the time to musculoskeletal symptoms. Certain bisphosphonates may also ease bone pain thus improves quality of life (Wong *et al.,* 2012).

In addition to adequate calcium and vitamin D supplementation, bisphosphonates are currently the intervention of choice for patients with low bone mineral density or patients with confirmation of rapid bone turnover, along with a healthy lifestyle (Robert *et al.,* 2008). Currently there are no treatments are specifically approved for AI induced bone loss, Hence an attempt is made to identify the role of bisphosphonates in post-menopausal breast cancer patients and to conclude the management of AI induced skeletal symptoms.

## MATERIALS AND METHODS

This retrospective study was carried out in the oncology department of a multispecialty hospital. All medical records of breast patients from January 2008 to December 2015, were thoroughly revised for possible inclusion. Consent from the hospital authorities and oncologists were obtained before accessing patient medical records. All patient linked data were obtained from the EMR's and were accessible only by the investigators. The study protocol was approved by the institutional ethics committee and a case report form was designed as per study requirements. 81 charts were included after apply inclusion and exclusion criteria.

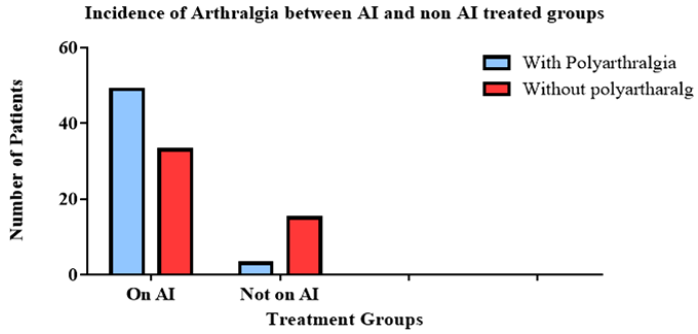


**Fig. 1:** Incidence of arthralgia between on AI treated group (P value =0.0118).

**Inclusion criterion**

1. Female breast cancer patients who received adjuvant AI therapy with Hormone receptor status: Estrogen receptor positive AND/OR Progesterone receptor positive as the aromatase inhibitor work by binding to Estrogen/ Progesterone receptor.

**Exclusion criterion**

Patients with documented pre- existing rheumatoid arthritis were avoided as the patients may experience skeletal symptoms irrespective of AI therapy and it cannot be attributed to AI.

**Statistical Analysis**

All statistical analyses were done using IBM SPSS 17.0 and Graph pad prism 6.0. A p-value of less than 0.05 (95% CI) was considered significant throughout the study. Incidence of dichotomous categorical variables was calculated by chi square test.

## RESULTS

The study population included hormone positive breast cancer patients receiving Aromatase inhibitors and were on regular visit to the hospital for either of the following reasons: to monitor the response to AI therapy, to keep a check on the relapse of disease, to manage any other secondary health problems.

After applying inclusion and exclusion criteria, 81 patient medical records remained for evaluation where 49 patients took letrozole, 19 anastrozole and 13 exemestane. The Incidence of arthralgia was found to be 49% in the studied population. 59.7% patients experienced arthralgia in the aromatase inhibitor (AI) treated group whereas the incidence of arthralgia in non-aromatase inhibitor (NAI) treated group was found to be 16.6%. Statistically significant difference was found in the incidence of arthralgia between AI and NAI treated group (P value = 0.0118). 25% Elderly patients experienced arthralgia after taking aromatase inhibitors (AI) whereas the incidence of arthralgia in non-elderly patients group was found to be 53.4% (P value = 0.0278).

The significant side effects were found to be fatigue (53.65%), Arthralgia (47%), generalized body pain (22%), cough and cold (14.6%), insomnia (8.53%), pathological fracture (3.65%) and Deep Vein Thrombosis (1.21%). Patient suffered from deep vein thrombosis eventually discontinued AI therapy and managed symptomatically. At the initiationof AI therapy, Bisphosphonates were also prescribed to prevent bone loss and to reduce the incidence of musculoskeletal symptoms but certain patients (non-Bisphosphonates group) didn't receive bisphosphonates due to poor renal status and in patients with increased risk of renal failure.23% patients reported the musculoskeletal symptoms after the bisphosphonate therapy whereas as non-Bisphosphonates group reported 55% of patients reported musculoskeletal symptoms (P value = 0.0277).

## DISCUSSION

Patients received letrozole were 59.7 %, 23.17% patients received anastrozole, and 15.8% patients received exemestane. Out of all the skeletal symptoms, arthralgia is the most common side effect noticed and is the frequently cited reason for the discontinuation of therapy (Chim *et al.,* 2013) hence the incidence of arthralgia between AI therapy and non AI therapy group was

determined to confirm that AI is associated with arthralgia. Non AI therapy group consisted of patients who were on tamoxifen, statistically significant difference found in the incidence of arthralgia between these groups (P value = 0.0118). This result comprises with the ATAC trial, concluded that postmenopausal women (30.3 %) on tamoxifen 20mg daily reported less joint symptoms when compared to those women (35.3 %) on anastrozole 1 mg daily.(OR 1.25 [1.11–1.40]) (Sestak *et al.,* 2008). The proposed explanation is that ERs and aromatase are both expressed in bone, and estrogen has been shown to regulate bone remodeling by stimulating the expression of antiresorptive factors such as osteoprotegerin. This results in the attenuation of receptor activator of NF-kappa-B (RANK) and RANK ligand (RANKL) signaling, leading to inhibition of osteoclastogenesis and attenuated bone turnover. Since aromatase inhibitors deprives peripheral estrogen levels which is the primary source of estrogen in post-menopausal women, deficiency of estrogen is associated with increased expression of measurable markers of bone resorption and bone formation(Gaillard and Stearns, 2011), all these may factors may contribute to musculoskeletal symptoms.

No medical intervention was provided for the primary side effect fatigue but advised adequate rest and insomnia was managed by anti-anxiety group of drug Alprazolam with a dose ranging from 0.25 mg to 0.50 mg depended on severity of insomnia. Patients with generalized body pains (mild to moderate) were managed by OTC pain relievers.

The incidence of arthralgia is high among young adults (relative risk: 0.4677 and odds ratio: 0.2903, P value= 0.0278) when compared to the elderly patients (over 65) (Orimo *et al.*, 2006). Since there is demonstrated age difference among patients who experienced arthralgia, the reasonable explanation for this could be that young old and old age patients might have not felt the effect of sudden drop in peripheral estrogen levels as much as young adults do with AI therapy and therefore they may report less frequently (Menas *et al.,* 2012).

A consistent treatment algorithm is developed based on the anecdotal experience and literature review. Incidence of musculoskeletal symptoms in patients treated with bisphosphonates along with AI therapy is less compared to patients who were treated only with aromatase inhibitors. This results comprises with N03CC (Alliance) trial, this study concludes that immediate treatment with zoledronic acid prevented bone loss compared with delayed treatment in postmenopausal women receiving letrozole (Wagner *et al.,* 2015).

Bisphosphonates are the first therapeutic option for AI induced bone loss and should be continued as long as AI-treatment is maintained, being IV zoledronic acid 4mg every 6 months the best tolerated option. Lifestyle modifications and adequate calcium and vitamin D supplementation have been documented to have good impact in long-term bone health (Cepa and Vaz *et al.,* 2015). Patients who are at risk of vertebral fractures can be prescribed with alendronate as it has been proved in the Fracture Intervention Trial (FIT). The study therefore establishes that a combination of 5 mg of alendronate and 0.5 mcg calcitriol is effective for preventing the bone loss induced by AI. To maintain bone health in women taking anastrozole, 150 mg Ibandronate once monthly has proved effective (Lester *et al.,* 2012).

Zoledronic acid is the most prevailing among the bisphosphonates available, it was approved for the prevention and treatment of bone metastases, Zometa-Femara Adjuvant Studies Synergy (ZO-FAST) have shown that zoledronic acid administered at dose of 4 mg infusion every two years in patients treated with letrozole has significantly improved bone mass even with normal BMD at baseline (Bundred *et al.,* 2008).

## CONCLUSION

This study has demonstrated that higher incidence of arthralgia is associated with aromatase inhibitor therapy in breast cancer patients when compared to Non AI therapy and the skeletal symptoms must be identified at the earliest to prevent the premature discontinuation of AI therapy as they are required to be taken for a minimum period of 5 years to achieve improved survival and to prevent the relapse. Incidence of arthralgia in elderly patients is less when compared to young adult patients and able to continue therapy for longer period without progression, hence aromatase inhibitors can be a first choice of therapy in elderly patients with positive hormone receptor breast cancer. Since aromatase inhibitors are found to be strongly associated with arthralgia and musculoskeletal symptoms and bisphosphonates are found to reduce the incidence of AI induced musculoskeletal symptoms, bisphosphonates should be added to therapeutic regimens containing aromatase inhibitors irrespective of musculoskeletal symptoms. Bisphosphonates can also be an initial choice of therapy in patients with AI induced musculoskeletal symptoms.

All patients initiating AIs need advice regarding exercise, calcium/vitamin D supplements, baseline BMD monitoring (when available), and bone-directed therapy if T-score $\leq 2.0$. This study emphasizes the need for patient counselling regarding the possibility of arthralgias with AI and the need for the continuation of therapy.

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