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Evaluation of Arthralgia Induced by Aromatase Inhibitor Therapy

Aromataz İnhibitör Terapisinin Neden Olduğu Artraljinin Değerlendirilmesi

Gulabi Meşe[1], Hakan Sakallı[2], Didem Arslan Taş[3], Abdullah Canataroğlu[4]

[1]Adana Numune Training and Research Hospital, Internal Medicine Department, ADANA
[2]Metropark Hospital, Internal Medicine And Medical Oncology Department, ADANA
[3]Cukurova University, Internal Medicine And Rheumatology Department, ADANA
[4]Adıyaman University, Internal Medicine And Rheumatology Department, ADIYAMAN

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ABSTRACT

Purpose: In breast cancer treatment, aromatase inhibitors (AI) and tamoxifen (Tmx) are frequently used. In this study, the relationship between the hormonal therapy and arthralgia in women with breast cancer was studied.

Methods: Sixty-four patients of whom 32 taking AI and 32 taking Tmx were included in the study. VAS was used to determine the intensity of pain. Also five options Likert scale was applied to all patients to answer the question "what are your thoughts about the sources of your current pain?". As laboratory parameters, CBC, BUN creatinine, ALT, AST, alkaline phosphatase, calcium, CRP, ESR, ANA, RF, and estradiol levels of the patients were analyzed.

Results: The mean age of the AI group was 52.7 ± 8.2 years old and in the Tmx group, it was 47.4 ± 6.5 years old ($p<0.05$). According to Likert scale; the frequency of arthralgia attributed to drug was 43.8% in AI group and 0% in tamoxifen group ($p<0.05$). VAS of AI group (4.7 ± 3.0) was higher than VAS of Tmx group (1.7 ± 2.1) ($p<0.05$). Serum estradiol level of AI group (16.4 ± 13.2 pg/ml) was found to be lower when compared to that of Tmx group (34.2 ± 21.4 pg/ml) ($p<0.05$). There was no statistically significant differences between groups for other laboratory parameters ($p>0.05$, for each).

Conclusion: In our study, more frequent and severe arthralgia has been observed in patients under AI treatment when compared to tamoxifen. One of the causes that leads to arthralgia in patients using AI may be low levels of estradiol.

Key Words: Aromatase inhibitors, Arthralgia, Breast Cancer, Tamoxifen, Likert scale

ÖZET

Amaç: Meme kanseri hormon tedavisinde, aromataz inhibitörleri (AI) ve (Tamoksifen) Tmx sık olarak kullanılmaktadır. Bu çalışmada, meme kanserli kadınlarda görülen artralji yakınmalarının hormon tedavisinde kullanılan ajanlarla ilişkisi araştırılmıştır.

Yöntem: Meme kanseri olan ve AI grubu ilaç alan 32 hasta ve Tmx alan 32 hasta çalışmaya dahil edildi. Hastaların eklem ağrılarının şiddetini belirlemek için Görsel Analog Skalası (VAS) kullanıldı. Yine tüm hastalara „mevcut eklem ağrılarınızın kaynağı hakkındaki nedenlerle ilgili düşünceniz nedir?" sorusuna cevap arayan beş seçenekli Likert ölçeği uygulandı. Laboratuar parametresi olarak, hastaların CBC, BUN, kreatinin, ALT, AST, alkalen fosfataz, kalsiyum, CRP, ESR, ANA, Anti-DNA, RF, östradiol seviyelerine bakıldı.

Bulgular: AI kullanan hasta grubun yaş ortalaması 52,7±8,2 yıl, Tmx kullanan grubun yaş ortalaması 47,4±6,5 yıl idi ($p<0,05$). Likert ölçeğine göre; ilaca bağlı artralji sıklığı, AI grubunda % 43,8 iken, Tmx grubunda % 0 idi ($p<0,05$). VAS, AI grubunda (4,7 ± 3,0), Tmx grubundan (1,7 ± 2,1) daha yüksek idi ($p<0,05$). Serum östradiol düzeyleri, AI grubunda (16,4 ± 13,2 pg/ml), Tmx gubundan (34,2 ± 21,4 pg/ml) daha düşük olarak saptandı ($p<0,05$). Gruplar arasında, diğer laboratuar parametreleri açısından istatistiksel olarak anlamlı fark yoktu (her biri için $p>0,05$).

Sonuç: Çalışmamızda AI alan hastalarda Tmx alan hastalara göre daha sık ve daha şiddetli artralji olduğu saptanmıştır. AI kullanan hastalardaki artralji nedenlerinden biri de, düşük östradiol düzeyi olabilir.

Anahtar Kelimeler: Aromataz inhibitörleri, artralji, meme kanseri, Tamoksifen, Likert skalası

INTRODUCTION

The aromatase inhibitors (AI) are more frequently used for the breast cancer therapy when compared with tamoxifene because of the prolonged disease free survival and the lesser side effects like vascular side effects and endometrium cancer[1-3]. But in the course of the AI medication, some complaints like arthralgia, arthritis and muscular complaints could be raised that could not be predicted before[2,4,5]. The frequency of arthralgia as a side effect of AI medication was reported as 5.4 % and 35.6% in the literature[2,4,5]. Although the reason and the severity of the pain are not exactly known, it is generally attributed to the estrogen decrease[1]. But in this group of patients the presence and severity of pain seem not to depend on objective criteria. Recently, brief pain inventory is commonly used to evaluate the pain caused by AI[1] but there is no data for the reliability of VAS.

By using the VAS scale, patients could be able to declare their pain numerically, and also they can easily interpret the severity and their sensitivity for pain. As the registration and measurement of the VAS scale is practical and easy, it is widely used[2,3].

The Likert scale is a psychometric scale. It is used for measuring the behaviour of individuals about a subject; it is a bipolar measure commonly used for questionnaires, and accordingly it measures negative and positive answers[4,5].

In this study, we aimed to investigate the reason of the pain caused by AI therapy by the Likert scale, to measure the severity of pain by VAS, and to investigate the relationship between the pain and the serum estradiol level.

MATERIAL and METHODS:

Sixty-four breast cancer patients under AI or Tmx therapy, who are the attendees of the medical oncology outpatient clinic were included in this study. This study is approved by the local ethics committee and also the written informed consent was obtained from all patients. The patients; who were previously diagnosed as breast cancer and treated by surgery, radiotherapy or chemotherapy; were subsequently, according to the hormone receptor positivity, received the continuation of the therapy with Aromatase inhibitor (AI) (anastrazole, letrozole) or Tamoxifene (Tmx) (But the drug should not be switched for inclusion). The patients who were previously diagnosed as metastatic breast cancer, rheumatoid arthritis, other connective tissue diseases, fibromyalgia, spondyloarthropathies or other inflammatory musculoskeletal disease were excluded from the study.

The demographic data of the included patients were recorded. The date of diagnosis, the pathological type of the disease, the kind and number of chemotherapy cures, radiotherapy and its duration, and the AI or Tmx therapy and their duration were recorded.

Detailed physical examination was performed for all patients also detailed musculoskeletal examination was performed in order to record the pain, swelling, limitations or deformities of the joints. The number of tender or swollen joints and durations were all recorded.

The severity of the pain was measured by performing the VAS scale. This is a 10 cm long measure, patients are asked to mark the present pain that they have as grading it from 0 to 10 resembling their pain, this point is measured and reported as VAS scale. According to their medications, all patients had fulfilled the Likert scale with 4 alternatives. The scale consists of 5 attitude expressions. In the Likert scale, the patients were asked this question “As the reason of your present complaints, what is your opinion about the alternatives below”. The alternatives were: a) Osteoarthritis-OA (degeneration of the joints), b) Aromatase inhibitor group drugs (Brand name Arimidex or Femara) or Tamoxifene, c) The medications that you use other than these (antihypertensive, diabetes, cholesterol etc), d) Other reasons (congenital joint disease, accidents,

falls, previous joint surgery, articular prostheses, heavy exercise or work). The answer options are as follows; “completely agree”, “too much agree”, “moderately agree”, “lesser agree”, “do not agree” degree alternatives. In order to form the attitude scale, the attitude expressions were on the left side and the answer alternatives took part on the right side. After performing the scale, the values of the answers were summed and scores were gathered for each patient.

As anthropometric measures, length, weight, blood pressure for all the patients were recorded. After length and weight measure, the body mass index (BMI) was calculated with this formula “ BMI=[weight (kg)/length (m^2)]”. Common blood count (CBC), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), Estradiol (E2), Alkalen phosphatase (ALP), calcium (Ca) were measured and recorded. ANA and anti-dsDNA tests were studied by Western Blot (WB) Immunoassay (ImmuBlot International Immuno – Diagnostics, USA) method. For excluding other organic reasons, some biochemical parameters like Blood urea nitrogen (BUN), creatinin, Na, K, AST, ALT were also measured. The blood samples were collected after 10–12 hours fasting and centrifuged at + 4^oc.

The serum BUN (Blood urea nitrogen), Na, K, Ca, AST and ALT levels were detected by colorimetric method using Beckman Coulter LX20 device; the serum ALP levels were detected by spectrophotometric method using Beckman Coulter LX20 device; the RF and CRP were detected by nephelometric method using Beckman Coulter Image device; and the serum estradiol levels were detected by chemiluminescent microparticule enzime immunoassay (CMIA) method using Advia Centaur XP device.

Statistical Analysis:

For the statistical analysis, SPSS 18.0 software program was used. The categorical measures were defined as number and percentage, and the numeric measures were defined as mean and standard deviation (minimum-maximum when needed). For the comparison of categorical measures between the study groups, chi-square test statistics were used. When comparing the numeric measures between the groups, two different criteria were taken into consideration; whether the hypotheses is provided the T test was used for dependent groups, whether the hypotheses is not provided, the Mann Whitney U test was used. For the non-parametric correlation analysis in both groups, Spearman’s method was used. For all the tests, statistical significance level was accepted as $p<0.05$.

RESULTS

Of the 64 study patients, 32 have received AI and 32 have received Tmx therapy. The median age of AI group was 54 (34-66) years old, and the median age of the Tmx group was 46 (40-55) years. The demographic data of the groups are given in Table 1. The arthralgia was 25 (78.1 %) in AI group and 15 (46.9 %) in Tmx group ($p<0.019$). When the Likert scale was performed, the possible aetiology of arthralgia in the patients’ opinion, there was statistically significant difference between the groups ($p<0.05$). In the AI group, up to 5 (15.6 %) patients, it was due to the osteoarthritis; up to 14 (43.8 %) patients, it was due to the drug therapy and up to 6 (18.8 %) patients, it was due to other reasons; 7 (21.8 %) patients had no pain. In the Tmx group, up to 5 (15.6 %) patients, it was due to the osteoarthritis; up to 10 (31.2 %) patients, it was due to other reasons; no patient has reported that the arthralgia was due to Tmx and 17 (53.1%) patients had no arthralgia, (Table 2).

In the AI group, arthralgia was in ankle joint in 9 (36%) patients, in elbow in 7 (28%) patients, in cervical spine in 6 (24%) patients, in talocalcaneal joint in 6 (24%) patients and in wrist joint in 5 (20%) patients. In the Tmx group, arthralgia was in ankle joint in 4 (26%) patients, in elbow joint in 3 (20 %) patients, in cervical spine in 3 (20%) patients, in wrist joint in 3 (20%) patients, and in talocalcaneal joint in 2 (13%) patients.

The serum estradiol level was 16.41±13.27 pg/ml in AI group and 34.28±21.48 pg/ml in Tmx group (p<0.05). ANA and anti-dsDNA were negative in all patients. The VAS score was 4.7±3.0 in AI group and 1.7±2.1 in Tmx group (p<0.05) (Table 3). In AI group, there was negative correlation between the VAS and the serum estradiol level (r=-0.49, p=0.04), whereas there was no such correlation in Tmx group.

When the patients with arthralgia in both of the groups were evaluated, there was no significant correlation between the VAS score and the age, the duration of AI therapy, the duration of Tmx therapy or menopause period (p>0.05 for each group).

In our study, we have divided both of the groups into three subgroups according to the BMI; such as: BMI<25, BMI=25-30 and BMI>30. There was significant difference between the BMI of the AI and Tmx groups (p<0.05), but this result has no effect on the serum estradiol level and the VAS score (p>0.05 for each).

Table 1: The demographic data of the patients

	Aromatase Inhibitor Group	**Tamoxifen Group**	**p**
Age[a]	54 (34-66)	46 (40-55)	0.006
Infiltratif Ductal Carcinoma	28 (87.5)	30 (93.8)	0.238
Infiltratif Lobular Carcinoma	4 (12.5)	1 (3.1)	
Medullary Ca	0 (0)	1 (3.1)	
Stage [b]			
E2a	16 (50)	5 (15.6)	0.017
E2b	14 (43.8)	25 (78.1)	
E3a	2 (6.3)	1 (3.1)	
E3b	0 (0)	1 (3.1)	
Cure count [b]			0.188
0-6 cure	24 (75)	18 (56.2)	
8-14 cure	8 (25)	14 (43.8)	
Radiotherapy (RT) [b]			0.999
Received	19 (59.4)	20 (62.5)	
Not received	13 (40.6)	12 (37.5)	
BMI *			
BMI<25 (normal)	5 (15.6)	8 (25)	0.016
BMI: 25-30 (preobese)	24 (75)	12 (37.5)	
BMI:Class 1:30-35 (obese)	3 (9.4)	11 (34.4)	
BMI:Class 2:35-40 (morbid obese)	0 (0)	1 (3.1)	
Duration of therapy[a] **(Months)**	21.34±16.45	20.16±11.43	0.898

[a] mean± standard deviation, median (min-max) [b] Count (Percent)

* BMI Classification,World Health Organization

Table 2: The results of joint pain, VAS score and Likert scale of the patient groups

	Aromatase Inhibitor Group	Tamoxifene Group	p
JOINT PAIN [b]			0.019
Present	25 (78.1)	15 (46.9)	
Not present	7 (21.9)	17 (53.1)	
PAINFUL JOINT COUNT [b]			0.016
0	7 (21.9)	17 (53.1)	
1-3	8 (25)	8 (25)	
4+	17 (53.1)	7 (21.9)	
VAS SCORE [a]	4.70 ± 3.07	1.79 ± 2.13	<0.001
LIKERT SCALE [b]			<0.001
- No pain	7 (21.8)	17 (53.1)	
-Pain due to osteoarthritis	5 (15.6)	5 (15.7)	
- Pain due to medication	14 (43.8)	0 (0)	
- Pain due to other reasons	6 (18.8)	10 (31.2)	

[a] Mean±standard deviation, median (min-max) [b] Number (Percent)

Table 3: Laboratory test of the groups (Mean ± Standard deviation)

	Aromatase Inhibitor group	**Tamoxifen Group**	**p**
Latest menstrual period (Months)	70.56±51.33	28.75±30.69	<0.001
RF, IU/ml (Rheumatoid factor)	17.61±4.14	18.19±4.13	0.600
ESR, hours (erythrocyte sedimentation rate)	19.09±21.30	19.47±11.92	0.234
CRP mg/ml (C-reactive protein)	0.93±1.23	0.77±0.52	0.634
Calcium mg/dl	9.43±0.44	9.44±0.75	0.935
Phosphor mg/dl	3.16±0.53	2.93±0.71	0.152
ALP IU/L	92.2±28.0	84.0±34.3	0.107
LDH U/L	212.03±124.44	195.56±50.03	0.819
Estradiol (pg/ml)	16.41±13.27	34.28±21.48	<0.001

DISCUSSION

AI group drugs are widely used for early stage breast cancer with positive hormone receptor in postmenopausal women and prolonged adjuvant therapy[6,8]. The AI drugs decrease the serum estradiol level which has an important effect on breast cancer aetiology and on management by inhibiting the conversion of androstenedione (AS) to estron in the periferal tissue. The increase in the articular symptoms and decrease in the bone mineral density as being the most significant side effects of AI are supposed to be correlated with the decrease in the serum estradiol level[9].

Previously, it was reported that, the arthralgia due to AI medication appeared in the first year of the therapy [10]. In our study, in 71 % of the patients who has the opinion that the arthralgia is due to the AI therapy; arthralgia has occurred in the first year of the medication. It could be hypothesized that the reason may be the immediate fall in the estradiol level in the early period of AI medication[7,10.]

Although the aetiology is not clear, recently, some of the defined side effects of the AI therapy are accepted to be a result of the decrease in the estradiol level in the circulation[11]. It is suggested that complex communications between the ligament, joint capsule, synovium, periost, subchondral bone tissue, that all have nerve endings that conducts the pain, could play roles in the pain formation and conduction in the joint[11].

Estradiol modulates the local inflammation via the synoviocytes and chondrocytes in the joint[12]. The synovial fibroblasts are sensitive to active protein production. Collagen increase in the joint could decrease the elasticity of the ligaments and tendons and this could lead to the stiffness and pain.

The immediate fall in the serum estradiol level could be the reason of the decrease in the endogen opioid level and this may be an explanation of severe pain[13,14]. In our study, the lower level of serum estrogen in AI group when compared to the Tmx group, besides, the correlation between the increase in VAS scale measures and the decrease in serum estradiol levels in AI group ($r=-0.49$, $p<0.05$), are important clues for modulation of pain by estradiol.

The high level of pain threshold in the pregnant women with high serum estrogen level supports the role of estrogen level variations for the occurrence of arthralgia[18]. Ockene et. al. have reported that, the occurrence of arthralgia 8-12 months after cessation of the therapy; in the patients under estrogen and progesterone therapy for hormone replacement[19] also supports the role of estrogen level variations for occurrence of arthralgia. Similarly, Donnellan et. al. have reported that, after cessation of the AI therapy, the relief of pain also suggests the effect of variation of serum estradiol level on pain[20].

In a study conducted by Friedman et. al., in 25 % of the premenopausal patients who had no arthralgia and who were under leuprolide medication for leiomyoma, recent arthralgia symptoms have occurred; nevertheless this symptom has spontaneously disappeared 2-12 weeks after the cessation of the medication[15]. These additional findings also support the effect of the variations in serum estrogen level on patients' pain severity via the mechanisms that mentioned before and also suggest that lower estradiol levels affect the severity of pain.

When the relationship between the AI therapy and arthralgia was taken into consideration, it is suggested that the AI, via the class effect, start the tenosynovial variations that results with pain[16], also the decrease in serum estrogen level increases the severity of pain. The VAS score could be successfully performed in this group of patients, because it is more appropriate when used to measure the severity of pain, and also it is easily understood, patients can coordinate quickly and it can be repeated and re-evaluated when needed. It is an extremely reliable test because of the regular distribution of the measurements[2,3].

In ATAC study, after the patients with musculoskeletal pain were excluded, arthralgia was found in 949 of 2698 patients (35.6 %) who were under anastrazole therapy, and in 829 of 2735 patients (30.3 %) who were under tamoxifene therapy[7].

In our study in 25 (78.1%) patients of AI group and in 15 (46.9%) patients of Tmx group arthralgia has occurred ($p<0.05$). When Likert scale is performed to our patients, 14 (43.8 %) patients in AI group had exclaimed that their pain is due to the AI therapy. In Tmx group, the patients had reported that none of their symptoms is attributable to the Tmx therapy ($p<0.05$).

These data obtained from the Likert scale is in accordance with the literature results of arthralgia of aromatase inhibitor therapy because the behavioral scales like Likert scale are prepared with additional line-up technique, each individual is replaced in the scale according to the total sum and it determines the behavioral position of the individual about this subject. For this reason, in order to evaluate subjective characteristics like pain, the Likert scale would be appropriate.

In previous studies, for grading the pain of arthralgia that has occurred as a result of AI therapy, most commonly, the French version of BPI (Brief Pain Inventory) was performed[1].

In our study, we performed VAS, in order to measure the severity of pain, a score that is not used for this reason before, which is more reliable, easy to perform and inexpensive than the other pain scores. The VAS score of the patients under AI therapy was higher than the patients under Tmx therapy. More frequent and severe arthralgia was found in AI group when compared with the Tmx group.

In ATAC study, one of the risk factors for arthralgia was determined to be obesity. In ATAC study, in the patients with BMI>30; arthralgia has occurred more commonly[7] whereas in the study conducted by Crew et. al., in the patients with BMI=25-30, the musculoskeletal pain was less when compared to the patients with normal weight, and the BMI>30 does not have any protective effect on arthralgia[1].

It is suggested that increased weight could be a reason of arthralgia via causing osteoarthritis. In a cross-sectional survey of 4.517 women ages 20 to 70 years reported by Dennerstein et. al., found that using a self-report questionnaire that included general health information and a checklist of 36 symptoms of the patients, age and body weight were closely correlated to the joint complaints[17]. In our study, the patients were divided into three groups according to the BMI, but no relationship has been found. The reason may be: **1)** The relationship between the BMI and articular symptoms is variable and even may be affected from geographical features[10]. **2)** Sestak et. al., have reported that patients with BMI 25-30 kg/m2 and with BMI>30 kg/m2 have more common articular symptoms whereas patients with BMI <25kg/m2 have lesser symptoms [10]. In a study reported by Crew et. al., articular symptoms were not common in patients with BMI 25-30 kg/m2 or less whereas in the other two groups: BMI<25 kg/m2 and BMI>30 kg/m2 they were more common[1].

The relationship between the BMI and arthralgia is not clear; increased body weight could be a reason of osteoarthritis and arthralgia[18], increased secretion of estrogen in obese individuals could be protective against arthralgia[19]. For this reason, we suggest that the relationship between the BMI and arthralgia should be considered carefully in detail.

In the studies conducted by Morales[16] and Crew[1] et. al., it was stated that, arthralgia was found not to be related to presence of menopause, duration of menopause, age, aromatase inhibitor drug generation and the duration of therapy. In our study, despite of the age, the duration of the therapy were found to be significantly different in both of the groups. There was no significant correlation between the VAS score and the menopause duration, age and arthralgia. Depending on these data, it could be suggested

that: the arthralgia occurs as a result of aromatase inhibitor therapy but not due to age or menopause period; and the severity of pain is affected from the serum estrogen level. In the previous studies several blood tests studied but found not to be appropriate for explaining the aetiology of arthralgia that occurred as a result of aromatase inhibitor therapy. Also depending on our data, we propose that the biochemical and inflammatory parameters were not appropriate for the diagnosis.

As a result; the aromatase inhibitor therapy causes arthralgia more frequently than tamoxifene therapy and the reason seems to be related to the impaired pain modulation occurred as a result of variability of serum estrogen level.

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Yazışma Adresi / Address for Correspondence:

Dr. Didem Arslan Taş

Cukurova University

Internal Medicine and Rheumatology Deparment

ADANA

e-mail: arslan_didem@yahoo.com

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