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CLINICAL TRIAL

Effect of a switch of aromatase inhibitors on musculoskeletal symptoms in postmenopausal women with hormone-receptor-positive breast cancer: the ATOLL (articular tolerance of letrozole) study

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Abstract The objective of the present study was to evaluate the effect of the switch of aromatase inhibitors (AIs) on musculoskeletal symptoms in postmenopausal women with hormone-receptor-positive breast cancer. This was a 6-month, prospective, non-randomized, multicenter study. Patients who had discontinued anastrozole due to musculoskeletal symptoms were eligible to participate in this study, and received letrozole, which was initiated 1 month after anastrozole discontinuation. Musculoskeletal symptoms were systematically assessed for severity, location of the symptoms, presence of swelling and of morning stiffness by the oncologist patients when patients stopped taking their anastrozole, 1 month after the discontinuation of anastrozole, and 1, 3, and 6 months after initiating the letrozole therapy. The primary endpoint was the percentage of patients who discontinued letrozole due to the severe musculoskeletal symptoms. After switching from anastrozole therapy, and at the end of the 6-month letrozole treatment, 128 (71.5%) out of 179 patients (61.3 ± 8.4 years) continued with letrozole. Fifty-one patients (28.5%) discontinued treatment due to severe joint pain. At the end of the 6-month, 116 patients (73.9%) had arthralgia, 33 (21.0%) myalgia, 25 (15.9%) arthritis, 22 (14.0%) tendinitis, and 20 (12.7%) polyalgic syndrome. Bivariate analysis of the factors associated with letrozole discontinuation showed that the duration of a prior anastrozole treatment was a significant predictor ($P = 0.04$). This study shows that in patients intolerant to one AI, switching to another agent allows a higher proportion of patients to continue the therapy and maximize hormonal adjuvant therapy and disease outcome benefits.

Keywords Aromatase inhibitors · Letrozole · Musculoskeletal symptoms · Postmenopausal breast cancer

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Introduction

Aromatase inhibitors (AIs) have been rapidly replacing tamoxifen as the standard of care for adjuvant therapy for postmenopausal women with hormone-receptor-positive (HR+) breast cancer [1–6]. Several clinical studies have shown that the third generation AIs (e.g., anastrozole, letrozole, and exemestane) are superior to tamoxifen in reducing the risk of disease recurrence in an adjuvant setting irrespective of treatment strategy either at the start of adjuvant treatment or after 2–3 years of tamoxifen treatment [2–4].

The efficacy of AIs relies on inhibiting the aromatization of androgens which in turn causes estrogen depletion [7, 8], in contrast with tamoxifen, a selective estrogen receptor modulator, which blocks estrogen activity by binding to the receptors. An increase in the incidence of musculoskeletal symptoms such as arthralgia, arthritis, joint pain or myalgia, have been observed during AI therapy when compared to tamoxifen [9, 10], as expected with decreased estrogen concentration. Musculoskeletal symptoms have been

reported with each of the three AIs and are considered as an adverse event related to this class of drug. Of 200 patients who participated in one adjuvant AI study, 88 (44%) reported onset or worsening of joint pain, with nearly 5% discontinuing their treatment [10]. More recently, studies have revealed an increase in tenosynovial changes in women taking AIs compared to those on tamoxifen [11, 12]. The mechanism of AI-associated musculoskeletal symptoms is unclear, and it is has been reported that increased pain sensitivity on nociceptive fibers may be due to estrogen deprivation at the cartilage and periarticular tissues [8, 13]. Musculoskeletal symptoms can be severe, limiting normal daily activity and potentially lead to the discontinuation of an AI treatment. Partridge et al. [14] analyzed data from three large commercial health programs longitudinal databases and found that the adherence to adjuvant anastrozole therapy decreased from 69–78% in the first year and to 50–68% in the third year; however, in this study, reasons for non-persistence, including severe side effects or adverse events, were not evaluated.

Given the significant benefits of AIs on disease outcome, a majority of postmenopausal women with HR+ breast cancer will attempt to tolerate the musculoskeletal symptoms. When pain is severe and unresponsive to available treatment (analgesics, non-steroidal anti-inflammatory drugs), patients may be switched from one AI to another or possibly to another therapy such as tamoxifen. Renshaw et al. [15] reported that nearly 50% of patients experienced joint pain relief when switched from either anastrozole to letrozole or visa versa.

To date, no clinical study has documented the course of musculoskeletal symptoms in postmenopausal women with HR+ breast cancer after switching from one AI to another due to severity of the musculoskeletal symptoms. The objective of this study was design to evaluate the effect of the switch of AIs on musculoskeletal symptoms in postmenopausal women with HR+ breast cancer, and to identify the factors associated with subsequent discontinuations from AI therapy. This trial also evaluates the prevalence and severity of the musculoskeletal symptoms.

Patients and methods

Study design

This was a prospective, non-randomized, open-label, and multicenter trial. This study was conducted between 2005 and 2007 in 37 clinical centers across France. The observation period lasted for 7 months from enrollment and included a 1-month washout followed by 6 months of letrozole treatment (Fig. 1). At visit 1 (baseline visit) patients stopped taking their anastrozole due to lasting presence of musculoskeletal symptoms. Visit 2 was scheduled 1 month after the discontinuation of anastrozole, and visits 3, 4, and 5 were scheduled at months 1, 3, and 6, respectively, after initiating the letrozole therapy.

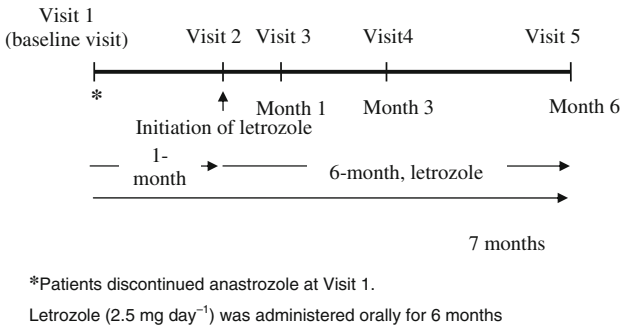

Fig. 1 Study design representing the visit schedule for aromatase inhibitor (AI) switching. * Patients discontinued anastrozole at visit 1. Letrozole (2.5 mg day^{-1}) was administered orally for 6 months

Patients and eligibility criteria

Eligible patients were postmenopausal women with HR+ breast cancer treated with adjuvant anastrozole who were experiencing lasting and severe musculoskeletal symptoms to the point of stopping their treatment. Patients who wanted to stop anastrozole were proposed to be switched to letrozole after a 1-month washout and were included in a 6-month open study. Patients were required to have adequate hematopoietic function (PNN $\geq$ 1200 mm^{-3}, platelets $\geq$ 100000 mm^{-3}, Hb $\geq$ 10 g dl^{-1}) and satisfactory liver function (bilirubin $\leq$ 30 µmol l^{-1}, transaminases $<$ 3 N). They were excluded from the study if they (i) were hypersensitive to any component of letrozole, (ii) had metastatic disease, (iii) had bone fracture-related pain, (iv) were on a hormonal therapy (e.g., tamoxifen, GnRH agonists) other than anastrozole, and/or (v) if they were incapacitated or had poor cognitive function preventing them to comply with the required assessments.

The study was approved by a central institutional review board, a local review boards, and the local ethic committee for medical research. This study was conducted in accordance with the Declaration of Helsinki (revised in 1983). Written and oral informed consents were obtained from all patients.

Treatment

One month after stopping anastrozole, letrozole 2.5 mg per day was administered (orally) for 6 months or until the treatment was discontinued due to intolerance or disease progression. After the 6-month treatment, the decision of continuation or not of letrozole was left to the physician of the patient.

Endpoints

The primary endpoint of the study was the percentage of postmenopausal women who discontinued the letrozole treatment due to severe musculoskeletal symptoms after switching from anastrozole. The secondary endpoints of the study included the following: (i) characterization of the musculoskeletal symptoms (e.g., location, severity, and impact of pain on daily life), (ii) persistence to letrozole treatment using patient report, and (iii) identification of the predictors of letrozole discontinuation.

Study assessments

Demographic data, a clinical assessment, and the Eastern Cooperative Oncology Group (ECOG) score were collected when patients stopped taking anastrozole (visit 1—V1, baseline), 1 month after the discontinuation of anastrozole (visit 2—V2), 1 month (visit 3—V3), 3 months (visit 4—V4), and 6 months (visit 5—V5) after the beginning of letrozole. The ECOG Performance Status Rating measures how cancer affects the daily living abilities of the patient, the scale ranges from 0 (fully active, no restrictions) to 5 (dead). At each visit, the presence and level of musculoskeletal symptoms systematically assessed for severity, location of the symptoms, presence of swelling and of morning stiffness was evaluated by the oncologist. Arthralgia excluded swelling and synovitis and arthritis indicates joint inflammation leading to pain and swelling. Muscle and tendon pain were also assessed; chronic widespread pain, non-restorative sleep, adverse events, concomitant treatments including analgesics were also collected. Polyalgic syndrome was defined by multiple tender points, general asthenia and leading to altered sleep.

At each visit, a French version of the brief pain inventory (BPI) was used to assess the severity of pain and the impact of pain on daily function. The BPI short questionnaire asks questions about pain relief, quality of the pain, and the patient's perception in relation to the possible cause of the pain. The BPI is based on a scale from 0 to 10, a score of 7 or higher on the scale represents a more severe level of (versus mild or moderate) pain [16, 17]. Quality of life (QoL) was assessed with French versions of the Health Assessment Questionnaire (HAQ) (a scale ranging from 0 to 3; higher values indicating more disability), and the SF-12®. The SF-12 is a subset of 12 questions from the SF-36® Health Survey which assesses subscales for a physical and a mental component in relation with quality of life [17–19]. The scores could range from 0 to 100, where higher scores indicated better QoL. Routine hematology and biochemistry parameters (erythrocyte sedimentation rate (ESR), C-reactive protein, muscle enzymes, vitamin D, calcium, and phosphorus) were also assessed at baseline and 6 months after initiation of letrozole.

Data analysis and statistical methods

It was hypothesized that there would be a 50% discontinuation rate due to musculoskeletal pain with letrozole. Therefore, it was calculated that the study would require 171 evaluable patients out of a possible 200 patients to obtain a 95% CI of 50 ± 7.5% (NQuery Advisor v 4.0). All the analysis were performed on the intent-to-treat (ITT) population which included all patients who received one dose of letrozole. Demographics and clinical characteristics were analyzed using descriptive analyses (mean ± SD, median and range) for continuous variables, and the percentage as well as frequency for nominal variables. Continuous and ordinal secondary parameters were described at each time point and in terms of change from baseline. Wilcoxon's signed rank test was used for comparisons to baseline. Categorical parameters were described using frequency tables at each time point. Finally, a search for possible predictors of letrozole discontinuation was explored by a chi-square test and the data was analyzed using SAS v8.02.

Results

This study enrolled 179 patients over 2 years. Patient demographic data and baseline characteristics are shown in Table 1.

Characteristics of patients who discontinued anastrozole (baseline visit)

All patients who were enrolled in this study discontinued anastrozole due to severe and lasting musculoskeletal symptoms. The mean duration of anastrozole treatment before discontinuation was 14.3 months (Table 1). At the baseline visit, 156 patients (87.2%) reported symptoms of arthralgia, 71 (39.7%) myalgia, 49 (27.4%) polyalgic syndrome, 36 (20.1%) tendinitis, and 31 (17.3%) arthritis (Fig. 2a). The most commonly affected joints were those located in the hands, knees, and spine (Fig. 2b). The joint symptoms were associated with morning stiffness in 55 (34.1%) of patients. There were 130 (72.6%) of patients who reported at least four or more affected joints (Fig. 2c). 27.9% of patients reported joint symptoms at the hands. The pain intensity assessed as a mean BPI score was 4.9 ± 1.6 (Table 1). There were 70% of patients who reported mean BPI scores between 4 and 7, with 40.8% of them taking over minor analgesics and 22.9% on moderate

Table 1 Patient demographics and baseline characteristics (visit 1)

Characteristics of women who stopped anastrozole	$N = 179$
Age (years)	61.3 ± 8.4
Weight (kg)	68.8 ± 14.1
BMI (kg m^{-2})	26.1 ± 4.7
ECOG score (0–5)	0.7 ± 0.6
Previous osteoarthritis (%)	72 (40.2)
Duration of menopause (years)	10.4 ± 8.9
Mood disorder treated, *n* (%)	34 (19)
Duration of prior treatment of anastrozole (months)	14.3 ± 10.5
Previous intake of anastrozole, *n* (%)	
<6 months	49 (27.4)
≥6 and <12 months	43 (24.0)
≥12 and <24 months	54 (30.2)
>24 months	33 (18.4)
BPI short-form score (0–7)	4.9 ± 1.6
SF-12® physical score (0–100)	37.1 ± 8.5
SF-12® mental score (0–100)	40.8 ± 11.0
HAQ (0–3)	2.0 ± 0.5
ESR (mm/first hour) (≤30 mm)	15.6 ± 13
C-reactive protein, mg m^{-1} (normal ≤5 mg $m^{-1)}$	5.0 ± 12.6
Calcium, mmol l^{-1} (2.2–2.6)	2.39 ± 0.1
Phosphorus, mmol l^{-1} (0.9–1.3)	1.21 ± 0.20
Creatinine phosphokinase, ukat l^{-1}(normal <3.3)	1.55 ± 1.0
Serum 25-OH-vitamin D, nmol l^{-1} (normal ≥ 75 nmol/l)	50 ± 31.7

All values are shown mean ± SD

BPI brief pain inventory, *BMI* body mass index, *ECOG* Eastern Cooperative Oncology Group, *ESR* erythrocyte sedimentation rate, *HAQ* health assessment questionnaire, *SF-12* 12-item short-form

opioids. At the baseline visit, biochemical markers of inflammation (ESR and C protein reactive) were assessed and within the normal range.

Characteristics of patients at the end of letrozole treatment

At the end of the 6-month study, 128 (71.5%) of patients were still taking letrozole (95% CI = 64.9–78.1) and 51 (28.5%) had discontinued their treatment (95% CI = 21.9–35.1) due to musculoskeletal symptoms.

Among the patients who stopped letrozole for joint symptoms, 17 (9.5%) patients stopped before the end of the first month of treatment. In these patients, the most commonly reason for treatment discontinuation was due to joint pain of spine (64.7%), hands (52.9%), knees (52.9%), and ankles (52.9%).

At the end of the 6-month treatment with letrozole, 116 (73.9%) patients had arthralgia, 33 (21.0%) myalgia, 25 (15.9%) arthritis, 22 (14.0%) tendinitis, and 20 (12.7%) polyalgic syndrome. There were 24 (15.3%) patients who did not report any joint pain. Joint pain was associated with morning stiffness in 38 (24.2%) women. Overall, fewer women reported arthralgia, arthritis, tendinitis, and polyalgic syndrome after the switch (Fig. 2a). The effect of switching to letrozole was observed across all commonly affected joints (Fig. 2b). The most common joints affected were hands (45.9%), knee (41.4%), and spine (40.8%) (Fig. 2b). Most of women, 59 (37.6%), had at least four joints from which they reported some level of discomfort (Fig. 2c).

After the 1-month or washout period, the mean BPI, HAQ, and SF-12® for the physical and mental scores were 3.7 ± 2.7, 1.7 ± 0.6, 41.5 ± 8.9, 44.1 ± 11.2, respectively (Tables 2, 3, and 4). After completing 6 months of letrozole treatment, the mean BPI was 3.8 ± 2.4 (median = 3.5; range = 0–9.3) decreasing 19% from baseline when the patient had previously been on anastrozole (Table 2). Additionally, a significant improvement in QoL was also observed after switching to letrozole (Tables 3 and 4). This improvement is reflected by the mean change in the scores after 6 months of letrozole from the baseline visit: there was a significant decrease in BPI (−1.2 ± 2.3, $P < 0.001$) and HAQ (−0.3 ± 0.5, $P < 0.001$) with a significant improvement in the SF-12® physical and mental scores of +5.2 ± 9.5, $P < 0.001$, +2.7 ± 11.3 ($P = 0.01$, respectively) (Tables 2, 3, and 4). There was also a decrease in the usage of analgesics observed in 49 (31.2%) patients who were taking minor analgesics and 35 (22.7%) patients on moderate opioids. There were no significant changes in biochemical markers of inflammation during the 6-month study (data not shown here).

Bivariate analyses assessing the possible factors associated with the discontinuation with letrozole found only one statistically significant predictor which was the prior duration of anastrozole therapy. A shorter duration of anastrozole treatment was associated with a higher risk of letrozole discontinuation ($P = 0.04$). There was no significant association between the discontinuation of letrozole treatment with respect to age, duration of menopause, body mass index (BMI), socio-demographic status, and a history of osteoarthritis.

Discussion

Despite the established benefits of AI therapy on improving disease-free survival, AIs result in increased musculoskeletal symptoms compared to tamoxifen which may limit treatment persistence and long-term observance [9–13]. These effects must be anticipated, managed by non-

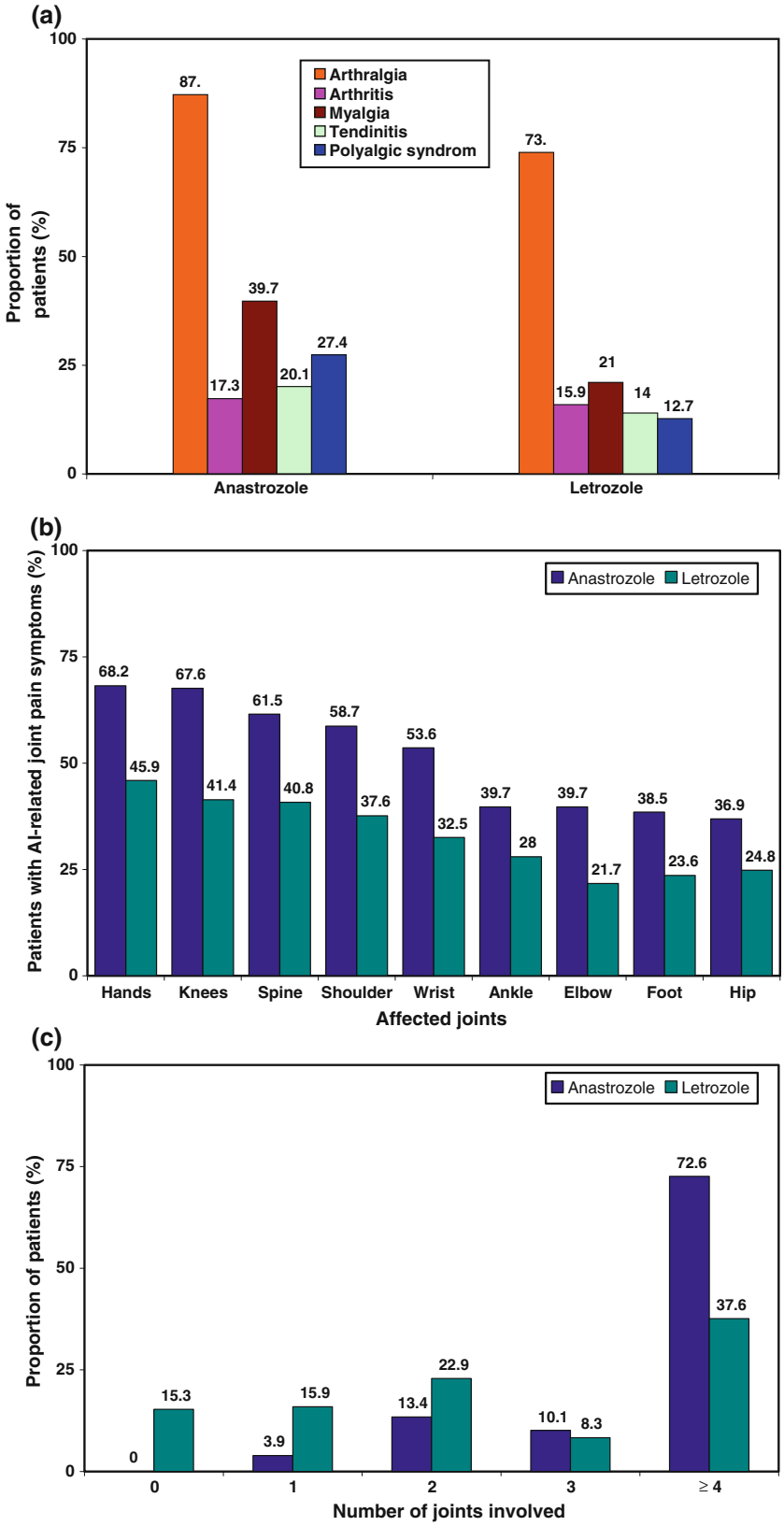

Fig. 2 First aromatase (anastrozole) and a 6-month second aromatase inhibitor treatment (letrozole)-related musculoskeletal symptoms: **a** proportion of patients with symptoms, **b** proportion of patients with the most commonly affected joints as assessed by the investigator, **c** proportion of patients with the number of affected joints

pharmacological and pharmacological interventions. One such approach could be to switch from one AI to another as shown in this study. Our data suggests that switching from one AI to another allowed 70% of patients to continue their treatment for over 6 months and is a mean to maximize the benefits from their AI therapy on disease outcome.

Table 2 BPI (brief pain inventory) score changes over the study

	N	BPI score (mean ± SD)	Change from baseline (mean ± SD)	*P* value
Visit 1 baseline	176	4.9 ± 1.6		
Visit 2	175	3.7 ± 2.2	−1.1 ± 1.9	<0.001
Visit 3	171	3.5 ± 2.1	−1.4 ± 1.9	<0.001
Visit 5 or premature stop	149	3.8 ± 2.4	−1.2 ± 2.3	<0.001

Table 3 HAQ (health assessment questionnaire) score changes over the study

	N	HAQ score (mean ± SD)	Change from baseline (mean ± SD)	*P* value
Visit 1 baseline	176	2.0 ± 0.5		
Visit 2	176	1.7 ± 0.6	−0.3 ± 0.5	<0.001
Visit 3	175	1.7 ± 0.5	−0.3 ± 0.5	<0.001
Visit 5 or premature stop	150	1.7 ± 0.6	−0.3 ± 0.5	<0.001

Table 4 SF-12 (physical and mental) scores changes over the study

	N	SF-12 physical score			SF-12 mental score		
		Physical score (mean ± SD)	Change from baseline (mean ± SD)	*P* value	Mental score (mean ± SD)	Change from baseline (mean ± SD)	*P* value
Visit 1 baseline	168	37.1 ± 8.5			40.8 ± 11.0		
Visit 2	165	41.5 ± 8.9	4.6 ± 8.4	<0.001	44.1 ± 11.2	3.8 ± 9.1	<0.001
Visit 3	157	42.1 ± 9.2	5.0 ± 9.4	<0.001	44.4 ± 11.0	3.8 ± 11.2	<0.001
Visit 5 or premature stop	146	41.7 ± 9.5	5.2 ± 9.5	<0.001	43.1 ± 9.9	2.7 ± 11.3	0.01

Few studies have assessed the symptomatic effects of switching AIs on musculoskeletal symptoms in postmenopausal women with HR+ breast cancer. In a study of 170 patients that compared anastrozole, letrozole, and a switching regimen, 131 (77%) reported joint pain with AI therapy and 10 patients reported joint stiffness [15]. There was no difference in the incidence of joint stiffness or pain between patients receiving anastrozole or letrozole. Of the patients who reported joint symptoms with either anastrozole or letrozole, and switched at 12 weeks to another AI, about half had persistent symptoms and about half did not [15]. In a single-blind crossover trial which aimed to assess whether tolerance for either letrozole or anastrozole can differ in terms of early quality of life (QoL), 72 breast cancer patients who had experienced tamoxifen failure were randomized to letrozole or anastrozole (either letrozole or anastrozole for 4 weeks, 1 week off, then crossover for 4 weeks) [20]. 68% of patients preferred to continue letrozole compared to 32% of those who were receiving anastrozole ($P < 0.01$) [20].

Hormonal changes in postmenopausal women affect their musculoskeletal health. As a consequence of estrogen deprivation, the occurrence of joint pain increases with age and reaches a peak in women aged 50–59 years [8, 21, 22]. Postmenopausal status is a strong independent predictor associated with increased musculoskeletal symptoms in women [8]. Therefore, AI-related effects may have additive consequences in these patients.

In a cross-sectional survey of 200 patients who were receiving an adjuvant AI therapy, nearly half of them reported arthralgia of the hands, knees, and spine [10]. In the present study, we observed that patients who switched to letrozole after experiencing severe musculoskeletal pain with anastrozole reported similar musculoskeletal symptoms (type and location) (Fig. 2a, b). We observed a good persistence over 6 months, although there was only a slight decrease of 6–18% in the number of patients experiencing arthralgia, myalgia, or tendinitis after switching from anastrozole to letrozole (Fig. 2a). There was a substantial decrease in the number of patients (~35%) with four or more afflicted joints (Fig. 2b, c), and a 19% decrease in the severity of pain (mean BPI) was noticed after switching.

The incidence of the joint pain symptoms reported in this study is higher (70%) compared to that reported in another clinical setting study (50%) (10) and the adjuvant trials (20–30%) [2–4]. This may well be attributed to the inclusion criteria of our study that limited enrollment to postmenopausal women with HR+ breast cancer on

anastrozole who were experiencing more severe joint pain, and decide to stop treatment because of these symptoms.

In this study, the single predictor for second AI discontinuation was the duration of the previous one suggesting that some patients may be intolerant to any of AI. We evaluated other potential predictor factors such as age, BMI, years since menopause, previous osteoarthritis, but these variables were not correlated with the presence or severity of musculoskeletal symptoms in our patient's population. Previous studies have identified factors which may influence the onset and the severity of AI-related arthralgia. Crew et al. [10] found more than a fourfold increase in the risk of AI-related arthralgia in patients who received prior taxane chemotherapy. A retrospective exploratory analysis of the ATAC trial showed that the major risk factors for developing joint symptoms are previous use of hormonal replacement treatment, hormone-receptor positivity, previous chemotherapy, obesity and treatment with anastrozole [23]. All of these factors are potentially linked with a great decrease in estrogen concentrations. Although, studies are conflicting concerning the influence of body weight, in fact, Crew et al. [10] found that patients who were overweight (BMI, 26–30 kg/m^2) were less likely to have AI-related joint pain compared with those who had a normal BMI (25 kg/m^2) or were obese (BMI $>$ 30 kg/m^2). Increased adiposity and increased sex hormone levels may explain the lower prevalence of AI-related joint pain in overweight women compared with women with a normal BMI [24]. The protective effect was lost among obese women, may be because of an increased risk of osteoarthritis obesity.

Actually comparisons of results of different studies must take into account the baseline characteristics of the patients: we included only patients who reported pain as a criterion of entry in our trial, in contrast with Sestak et al. [22] who studied patients without any pre-existing joint symptoms. Musculoskeletal pain is an adverse event often reported with this class of agent, AIs can trigger symptoms which can be completely resolved after treatment discontinuation [23]. However, in our study, we have noticed that the 1-month washout of AI was associated with a slight decrease in musculoskeletal pain, but the symptoms did not resolve completely. Other studies have suggested that switching from one AI to another may alleviate symptoms in some women [15].

Our study has several limitations. It is an open study, and the assessed endpoints are qualitative in nature leaving some room for patient's personal subjectivity. Due to the short duration (6 months) of follow-up, we could not exclude the occurrence of additional musculoskeletal symptoms after the 6-month treatment period with letrozole. In a single center study of 77 postmenopausal women, Donnellan et al. [9] showed that the range of the median duration of initiation of anastrozole intake to the onset of symptoms can be large from 8 weeks to 16 months. We cannot exclude that the decrease in symptoms is related to time rather to the switch. Patients may attempt to tolerate the second AI after considering that these symptoms are related to this class of drugs, and that stopping such therapy may be a loss of chance. We evaluated persistence to letrozole using the patient report and we can not check that they really took the treatment. Finally, this observational study is not a comparative one, and these results cannot lead to comparison of the tolerance of the 2 AIs.

Aromatase inhibitors use results in increased musculoskeletal symptoms which can be managed by non-pharmacological and pharmacological interventions. This study suggests that switching from one non-steroidal AI to another one can result in prolong treatment with the adjuvant hormonal therapy in postmenopausal women with HR+ breast cancer troubled by musculoskeletal symptoms.

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Conflict of interest statement K Briot and C Roux received honoraria of Novartis. M Tubiana-Hulin has no conflict of interest to disclosure. L Bastit has no conflict of interest to disclosure. Ioana Kloos is medical oncologist, and an employee of Novartis

References

1. Winer EP, Hudis C, Burstein HJ et al (2005) American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor positive breast cancer: status report 2004. J Clin Oncol 23:619–629
2. Howell A, Cuzick J, Baum M et al (2005) Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 365:60–62
3. Coombes RC, Kilburn LS, Snowdon CF et al (2007) Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomized controlled trial. Lancet 369:559–570
4. Coates AS, Keshaviah A, Thürlimann B et al (2007) Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol 25:486–492
5. Poole R, Paridaens R (2007) The use of third generation aromatase inhibitors and tamoxifen in the adjuvant treatment of postmenopausal patients with hormone-dependent breast cancer: evidence based review. Curr Opin Oncol 19:564–572
6. Morales L, Neven P, Paridaens R (2005) Choosing between an aromatase inhibitor and tamoxifen in the adjuvant setting. Curr Opin Oncol 17:559–565

7. Dowsett M, Howell A (2002) Breast cancer: aromatase inhibitors take on tamoxifen. Nat Med 12:1341–1344
8. Felson DT, Cummings SR (2005) Aromatase inhibitors and the syndrome of arthralgias with estrogen deprivation. Arthritis Rheum 52:2594–2598
9. Donnellan P, Douglas S, Cameron D, Leonard RC (2001) Aromatase inhibitors and arthralgia. J Clin Oncol 19:2767
10. Crew KD, Greenlee H, Capodice J, Raptis G, Brafman L, Fuentes D, Sierra A, Hershman DL (2007) Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol 25:3877–3883
11. Morales L, Pans S, Verschueren K et al (2008) Prospective study to assess short-term intra-articular and tenosynovial changes in the aromatase inhibitor-associated arthralgia syndrome. J Clin Oncol 26:3147–3152
12. Morales L, Pans S, Paridaens R et al (2007) Debilitating musculoskeletal pain and stiffness with letrozole and exemestane: associated tenosynovial changes on magnetic resonance imaging. Breast Cancer Res Treat 104:87–91
13. Coleman RE, Bolten WW, Lansdown M, Dale S, Jackisch C, Merkel D, Maass N, Hadji P (2008) Aromatase inhibitor-induced arthralgia: clinical experience and treatment recommendations. Cancer Treat Rev 34:275–282
14. Partridge AH, LaFountain A, Mayer E, Taylor BS, Winer E, Asnis-Alibozek A (2008) Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. J Clin Oncol 26:556–562
15. Renshaw L, McHugh M, Williams L et al (2007) Comparison of joint problems as reported by patients in a randomized adjuvant trial of anastrozole and letrozole. Breast Cancer Res Treat 106:S108
16. Cleeland CS (1989) Measurement of pain by subjective report. In: Chapman CR, Loeser JD (eds) Issues in pain measurement. Advances in pain research and therapy, vol 12. Raven Press, New York, pp 391–403
17. Roth SH, Fleischmann RM, Burch FX, Dietz F, Bockow B, Rapoport RJ, Rutstein J, Lacouture PG (2000) Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. Arch Intern Med 160:853–860
18. Ware J Jr, Kosinski M, Keller SD (1996) A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 34:220–233
19. Guillemin F, Briançon S, Pourel J (1992) Validity and discriminant ability of the HAQ Functional Index in early rheumatoid arthritis. Disabil Rehabil 14:71–77
20. Thomas R, Godward S, Makris A, Bloomfield D, Moody AM, Williams M (2004) Giving patients a choice improves quality of life: a multi-centre, investigator-blind, randomised, crossover study comparing letrozole with anastrozole. Clin Oncol (R Coll Radiol) 16:485–491
21. Croft P, Rigby AS, Boswell R, Schollum J, Silman A (1993) The prevalence of chronic widespread pain in the general population. J Rheumatol 20:710–713
22. Sestak I, Cuzick J, Sapunar F, Eastell R, Forbes JF, Bianco AR, Buzdar AU, ATAC Trialists' Group (2008) Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis. Lancet Oncol 9:866–872
23. Buzdar AU, The ATAC Trialists' Group (2006) Clinical features of joint symptoms observed in the "Arimidex, Tamoxifen, alone or in combination (ATAC) trial". J Clin Oncol 24:551
24. Zumoff B (1982) Relationship of obesity to blood estrogens. Cancer Res 42(8 Suppl):289–294