Original Article

A Prospective Study of Aromatase Inhibitor-Associated Musculoskeletal Symptoms and Abnormalities on Serial High-Resolution Wrist Ultrasonography

N. Lynn Henry, MD, PhD[1]; Jon A. Jacobson, MD[2]; Mousumi Banerjee, PhD[3]; Jill Hayden, RN[1]; Jeffrey B. Smerage, MD, PhD[1]; Catherine Van Poznak, MD[1]; Anna Maria Storniolo, MD[4]; Vered Stearns, MD[5]; and Daniel F. Hayes, MD[1]

BACKGROUND: Nearly half of women treated with aromatase inhibitors (AI) develop AI-associated musculoskeletal symptoms (AIMSS) such as arthralgias, but to the authors' knowledge the etiology is unclear. The upper extremities are frequently affected, especially the wrists, hands, and fingers. AI use may also increase the risk of developing carpal tunnel syndrome. Tendon sheath fluid and tenosynovial changes have been demonstrated by imaging symptomatic patients who were treated with AIs. The authors hypothesized that these abnormalities are correlated with AIMSS. **METHODS:** Thirty consecutive patients in whom adjuvant therapy with letrozole or exemestane was initiated on a prospective clinical trial enrolled in a pilot study evaluating tendon and joint abnormalities at baseline and after 3 months of AI therapy. Patients underwent high-resolution ultrasonography of the wrists bilaterally and completed the Health Assessment Questionnaire (HAQ) and pain Visual Analog Scale (VAS). AIMSS were defined as an increase in the HAQ or VAS score during AI therapy that exceeded a predefined cutoff. **RESULTS:** Twenty-five patients completed both the baseline and 3-month assessments. During the first 12 months of AI therapy, 15 patients developed AIMSS, and 13 discontinued therapy because of musculoskeletal symptoms. There was a trend toward an association between the presence of tendon sheath abnormalities on wrist ultrasound at baseline and the development of AIMSS ($P = .06$). **CONCLUSIONS:** Clinically relevant musculoskeletal symptoms develop in women treated with AIs, leading to treatment discontinuation in a substantial percentage of these patients. However, in the current study, patient-reported symptoms were not found to be associated with changes visible on wrist ultrasonography. ***Cancer*** **2010;116:4360–7.** © *2010 American Cancer Society.*

KEYWORDS: breast cancer, aromatase inhibitor, arthralgia, ultrasonography, musculoskeletal.

Aromatase inhibitors (AI) substantially decrease circulating estrogen concentrations in postmenopausal women via blockade of aromatase, the enzyme responsible for the conversion of androgens to estrogens. This class of drugs is increasingly used for the adjuvant treatment of postmenopausal women with hormone receptor-positive invasive breast cancer, in part because of data to support their superiority compared with tamoxifen, a selective estrogen receptor modulator.[1-9] Although AIs were reported to be relatively well tolerated in the large prospective randomized clinical trials,[4,8,10,11] more recent studies have demonstrated that up to half of treated patients develop AI-associated musculoskeletal symptoms (AIMSS) such as arthralgias, joint stiffness, and carpal tunnel syndrome (CTS), which can lead to treatment discontinuation.[12-15] A previous study found that symptoms of AIMSS appear, on average, within 3 months of the initiation of AI therapy.[14]

To the best of our knowledge, the pathophysiology of AIMSS remains unclear. Previously reported studies using magnetic resonance imaging (MRI) have demonstrated tenosynovitis in a substantial proportion of patients with severe wrist symptoms.[16] A prospective study of 12 women who were treated with AIs demonstrated a high incidence of

Corresponding author: N. Lynn Henry, MD, PhD, Breast Oncology Program, University of Michigan Comprehensive Cancer Center, 300 North Ingalls, Room 3A04, Ann Arbor, MI 48109-5419; Fax: (734) 763-7672; norahh@med.umich.edu

[1]Breast Oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan; [2]Department of Radiology, University of Michigan, Ann Arbor, Michigan; [3]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan; [4]Department of Medicine, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, Indiana; [5]Breast Cancer Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, Maryland

DOI: 10.1002/cncr.25385, **Received:** January 20, 2010; **Revised:** March 22, 2010; **Accepted:** March 23, 2010, **Published online** June 14, 2010 in Wiley Online Library (wileyonlinelibrary.com)

MRI-detected wrist tenosynovitis after 6 months of AI therapy, and new abnormalities on imaging studies were associated with a decrease in grip strength.[17] However, in these studies, associations between the objective findings and the development of patient-reported musculoskeletal symptoms were not evaluated.

High-resolution ultrasound is an effective and readily accessible tool that identifies abnormalities of the tendon sheath, can quantify changes in the median nerve in CTS,[18] and may be applicable for the evaluation of musculoskeletal changes that occur with AI therapy. The objective of the current pilot study was to prospectively evaluate the anatomy of the wrist using serial high-resolution ultrasonography in women initiating treatment with AIs as part of their adjuvant breast cancer treatment plan. We hypothesized that the presence of ultrasound-detected abnormalities of the wrist before treatment initiation, or their appearance during AI therapy, may be correlated with the development of AIMSS.

MATERIALS AND METHODS

Patients

Women who enrolled in the multicenter, prospective, randomized Exemestane and Letrozole Pharmacogenomics (ELPh) clinical trial (ClinicalTrials.gov #NCT00228956) between October 2007 and September 2008 at the University of Michigan Comprehensive Cancer Center were offered concomitant enrollment in this ultrasound substudy. As per the parent study, patients were randomized to receive exemestane (Aromasin; Pfizer, New York, NY) at a dose of 25 mg orally daily or letrozole (Femara; Novartis, East Hanover, NJ) at a dose of 2.5 mg orally daily. Key eligibility criteria included female gender, postmenopausal status, age $\geq$18 years, early stage hormone receptor-positive breast cancer, and intent to initiate adjuvant therapy with an AI. No prior AI therapy was permitted. All participants indicated that surgery, radiotherapy, and chemotherapy for breast cancer were completed before study enrollment. This substudy excluded patients with a history of prior significant wrist injury, wrist surgery, or CTS. The protocol was approved by the Institutional Review Board, and all enrolled patients provided written informed consent.

Study Design and Interventions

This prospective study of high-resolution wrist ultrasonography was conducted as a substudy of the ELPh trial. The study design of the ELPh trial has been reported previously.[14] Briefly, patients were evaluated at baseline and after 1, 3, 6, and 12 months of AI therapy to assess changes in medical history and concomitant medications, and to complete symptom questionnaires and the modified Health Assessment Questionnaire (HAQ),[19] which includes a pain Visual Analog Scale (VAS).

AIMSS were previously reported to develop in the majority of patients treated with AIs within 3 months of the initiation of therapy.[14] Therefore, all patients in this substudy also completed the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire[20] and underwent evaluation of the bilateral wrists with high-resolution ultrasonography using 12 to 17 megahertz linear transducers (Model iU22; Philips, Bothell, WA) at baseline and after 3 months of AI therapy.

Definition of AIMSS

In the ELPh trial, AIMSS were defined as meeting $\geq$1 of the following criteria at any point during study participation: 1) HAQ score increased by $>$0.4 over the baseline score; 2) pain VAS score $\geq$5 cm (of 10-cm VAS) for patients with no pain (VAS of 0) at baseline; and 3) the pain VAS score increased and the pain was rated as much worse or very much worse on a self-rated clinical global impression scale (graded as 6 or 7)[21] for patients reporting pain at baseline (VAS of $>$0).[14]

Wrist Ultrasonography

Patients underwent baseline and 3-month bilateral, high-resolution ultrasound imaging of the wrist. The ultrasound examination included static images and video clips, as well as a written report of imaging findings. Imaging data included: 1) the presence or absence of fluid (compressible anechoic or hypoechoic distention), hyperemia on color or power Doppler imaging, or synovitis (noncompressible, hypoechoic distention) in the volar or dorsal joint spaces (distal radioulnar, radiocarpal, and midcarpal); 2) the presence or absence of fluid, hyperemia, or synovitis in the flexor or extensor tendon sheaths; 3) the presence or absence of tendinosis (hypoechoic and enlarged), full-thickness tear (complete discontinuity), or partial thickness tear (partial anechoic cleft) in the flexor or extensor tendons; 4) median nerve area (in mm^2) measured at the wrist crease (using circumferential trace) at the level of the pisiform; and 5) the presence of subcutaneous edema (hypoechoic, linear, and branching distended lymphatics). Images were analyzed in a blinded manner by an academic musculoskeletal radiologist after all patients had undergone both evaluations.

Table 1. Patient Characteristics[a]

Characteristic		Baseline N = 29	3 Months N = 25	*P*
Median age (range), y		61 (47-83)	59 (47-83)	
Race/ethnicity	Non-Hispanic White	25 (86%)	22 (88%)	
	Hispanic White	2 (7%)	1 (4%)	
	Black	1 (3%)	1 (4%)	
	Asian	1 (3%)	1 (4%)	
BMI, kg/m^2	<25	9 (31%)	8 (32%)	
	25-30	4 (14%)	4 (16%)	
	>30	16 (55%)	13 (52%)	
Prior chemotherapy	Any	15 (52%)	13 (52%)	
	Taxane	12 (41%)	11 (44%)	
Prior tamoxifen		10 (34%)	9 (36%)	
Median HAQ score (range)		0 (0-0.625)	0 (0-0.750)	.97
Median VAS score (range)		2.8 (0-8.1)	2.6 (0-5.7)	.49
Median DASH score (range)		5.8 (0-44.8)	6.9 (0-55)	.95
Patient-reported joint pain	None	11 (38%)	7 (28%)	.41
	Mild	8 (28%)	7 (28%)	
	Moderate/severe	10 (34%)	11 (44%)	
Patient-reported neuropathy	None	13 (45%)	16 (64%)	.44
	Mild	11 (38%)	4 (16%)	
	Moderate/severe	5 (17%)	5 (20%)	

BMI indicates body mass index; HAQ, Health Assessment Questionnaire; VAS, Visual Analog Scale; DASH, Disabilities of the Arm, Shoulder, and Hand questionnaire.
[a] Values are given for patient-reported outcomes at baseline and after 3 months of aromatase inhibitor therapy.

Statistical Analyses

The primary objective of the current study was to estimate the 1) incidence of tendon sheath, joint space, and tendon abnormalities; and 2) increase in median nerve cross-sectional area before and 3 months after the initiation of AI therapy, and to quantify those changes based on high-resolution ultrasonography of the wrist. The secondary objective was to evaluate associations between objective, ultrasound-detected changes in the median nerve and tendon sheaths and treatment-emergent musculoskeletal symptoms.

For analysis, the ultrasound abnormalities were grouped into those affecting the tendon, the tendon sheath, and the joint space. Change in the average median nerve area before and 3 months after the initiation of AI therapy was tested using the Student *t* test for paired data. Univariate associations between baseline findings and the development of AIMSS or early treatment discontinuation were tested using chi-square tests. Logistic regression was used to model the probability of developing AIMSS or early treatment discontinuation (2 separate models) as a function of baseline characteristics and changes in VAS, HAQ, and DASH scores between baseline and 3 months. A P value $<.05$ was considered to be statistically significant.

RESULTS

Patient Characteristics

Characteristics of the 29 eligible patients are listed in Table 1. One patient was found to be ineligible for the parent study because she was not postmenopausal, and therefore she was excluded from all analyses. Of the 29 eligible patients, 25 underwent repeat evaluation at 3 months. Two patients discontinued AI therapy before the 3-month study visit because of musculoskeletal symptoms. One patient developed intolerable aches and pains, and the other had fatigue, headache, and myalgias. Of the other 2 patients who did not undergo ultrasonography at the 3-month time point, 1 had been noncompliant with study procedures and was taken off study and 1 developed fatigue, headaches, and an inability to concentrate and discontinued AI therapy.

Wrist Ultrasonography Findings

Abnormalities on the baseline high-resolution ultrasound of the wrist were common, especially in the joint recess (Table 2); a representative finding is shown in Figure 1, Top. Nearly half of the patients developed new findings on ultrasound after 3 months of AI therapy, also primarily located in the joint recess (Table 3) (representative finding

Table 2. Proportion of Patients (n=29) With Abnormalities Noted on Wrist Ultrasonography Prior to the Initiation of AI Therapy[a]

Site	No. With Abnormalities Unilaterally	No. With Abnormalities Bilaterally	Total No. With Anormalities	Total No. With Abnormalities
Tendon sheath (flexors)	3 (10.3%)	1 (3.4%)	4 (13.8%)	14 (48.3%)
Fluid	3 (10.3%)	1 (3.4%)	4 (13.8%)	
Synovitis	0	0	0	
Hyperemia	0	0	0	
Tendon sheath (extensors)	6 (20.7%)	5 (17.2%)	11 (37.9%)	
Fluid	6 (20.7%)	5 (17.2%)	11 (37.9%)	
Synovitis	1 (3.4%)	0	1 (3.4%)	
Hyperemia	1 (3.4%)	0	1 (3.4%)	
Tendon (flexor + extensor)	1 (3.4%)	1 (3.4%)	2 (6.9%)	2 (6.9%)
Tendinosis	1 (3.4%)	1 (3.4%)	2 (6.9%)	
Partial thickness tear	0	0	0	
Full thickness tear	0	0	0	
Joint recess (volar)	6 (20.7%)	7 (24.1%)	12 (41.4%)	24 (82.8%)
Fluid	4 (13.8%)	6 (20.7%)	10 (34.5%)	
Synovitis	2 (6.9%)	3 (10.3%)	5 (17.2%)	
Hyperemia	0	0	0	
Joint recess (dorsal)	12 (41.4%)	18 (62.1%)	24 (82.8%)	
Fluid	5 (17.2%)	16 (55.2%)	21 (72.4%)	
Synovitis	4 (13.8%)	9 (31.0%)	13 (44.8%)	
Hyperemia	5 (17.2%)	2 (6.9%)	7 (24.1%)	

AI indicates aromatase inhibitor.
[a] Numbers do not necessarily add up to totals because some patients had >1 abnormality present (eg, both fluid and synovitis of the extensor tendon sheath).

shown in Fig. 1 Bottom). Abnormalities of the tendon itself were noted only rarely. Change in the mean median nerve area with 3 months of AI therapy was not statistically different (10.4 ± 2.2 mm at baseline vs 10.8 ± 2.5 mm at 3 months).

Changes in Patient-Reported Symptoms

After 3 months of AI therapy, 72% of patients reported joint pain, with 44% of the total study population reporting moderate to severe pain (Table 1). Median scores on the HAQ and VAS for all patients were unchanged between baseline and 3 months. It is interesting to note that approximately half of the study patients reported preexisting neuropathy, primarily of mild severity, and this symptom decreased during AI therapy. Because patients with CTS were excluded from participation, baseline neuropathy symptoms were likely the result of alternate etiologies.

Patients were followed on AI therapy until treatment discontinuation or for at least 1 year. Fifteen patients (51.7% of the eligible cohort) developed AIMSS after a median of 6.2 months of AI therapy (range, 1.2-18.6 months). Thirteen patients (44.8% of eligible cohort) discontinued AI therapy because of musculoskeletal symptoms after a median duration of 10.7 months of therapy (range, 0.9-21.2 months). The majority of patients subsequently switched to a different AI therapy. One additional patient discontinued AI therapy after the 3-month time point because of intractable diarrhea.

Associations Between Baseline Findings and AIMSS or Early Treatment Discontinuation

On univariate analysis, a higher body mass index (BMI) was found to be associated with a decreased risk of early treatment discontinuation (odds ratio [OR] across BMI groups, 0.16; 95% confidence interval [95% CI], 0.03-0.84 [$P = .03$]) (Table 4). There also was a trend toward prior tamoxifen use and a lower risk of early treatment discontinuation (OR, 0.05; 95% CI, 0.002-1.0 [$P = .05$]). No other significant associations were noted between baseline patient characteristics or questionnaire scores and either the development of AIMSS or early treatment discontinuation because of musculoskeletal symptoms (Table 4). There was a trend toward an association between the presence of tendon sheath abnormalities on ultrasound at baseline and the subsequent development of

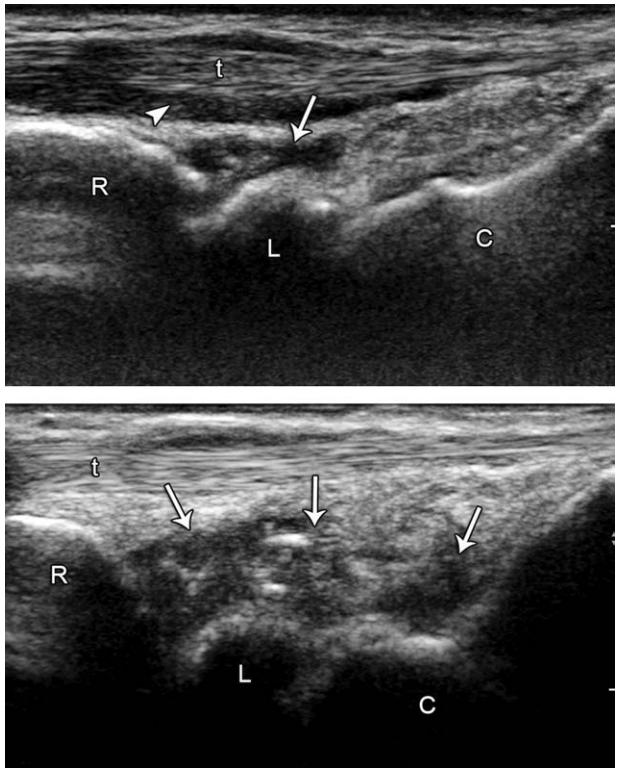

Figure 1. Joint recess and extensor tendon abnormalities are shown. (*Top*) Baseline sagittal ultrasound image over the dorsal wrist demonstrates hypoechoic fluid distending the (arrow) dorsal recess of the radiocarpal joint and (arrowhead) surrounding the extensor tendon. (*Bottom*) A 3-month sagittal ultrasound image over the dorsal wrist demonstrates heterogeneous hypoechoic fluid and synovitis distending the (arrows) dorsal recesses of the radiocarpal and midcarpal joints. R indicates radius; t, extensor tendon; L, lunate; C, capitate. The right side of the image is distal.

AIMSS (Fig. 2 Top). Ten of the 15 patients (67%) who developed AIMSS during 12 months of AI therapy had tendon sheath abnormalities at baseline, compared with 4 of 14 patients (29%) who did not develop AIMSS ($P = .06$). No statistically significant associations between baseline ultrasound findings and either the development of AIMSS (Fig. 2 Top) or early treatment discontinuation (Fig. 2 Bottom) were noted.

Associations Between Changes in Findings After 3 Months of AI Therapy and AIMSS or Early Treatment Discontinuation

No associations were noted between changes from baseline to after 3 months of AI therapy in HAQ, VAS, or DASH scores and the development of AIMSS or early treatment discontinuation (Table 4). Similar to the findings at baseline, we did not observe statistically significant associations between new findings on ultrasonography and either the development of AIMSS or early treatment discontinuation (Fig. 3).

Although a previous analysis suggested that the majority of AI-treated patients develop symptoms within 3 months of treatment initiation, the median time to the development of AIMSS in the cohort enrolled in the current substudy was 6.2 months. Patients enrolled in this substudy completed the HAQ and VAS questionnaires at multiple additional time points as part of the parent study. Therefore, we performed an unplanned analysis of the correlation between the development of AIMSS and early treatment discontinuation and changes in the HAQ and VAS scores from baseline to either 12 months or the time of early treatment discontinuation, whichever came first. We found a significant association between changes in the VAS score and the development of AIMSS (OR, 2.11; 95% CI, 1.1-4.2 [$P = .03$]) and early treatment discontinuation (OR, 2.12; 95% CI, 1.1-4.1 [$P = .02$]). A similar finding was not noted with changes in the HAQ score (Table 4).

DISCUSSION

In the current study, abnormalities of the tendon sheath and joint space at the bilateral wrist detected on high-resolution ultrasound were very common in women before the initiation of AI therapy. We observed a trend toward an association between tendon sheath abnormalities on ultrasonography before treatment initiation and the development of AIMSS. The identification of factors predictive of the increased likelihood of developing AIMSS would be useful for counseling and managing patients who are initiating treatment with adjuvant endocrine therapy. Although this study does not provide new insight into the mechanism of AIMSS, our results suggest that pre-existing abnormalities within the tendon sheath may predict which women are likely to experience AI-associated musculoskeletal pain.

The findings of the current study are similar to those of previous reports, the majority of which have been cross-sectional studies.[16,17,22] A strength of the current study is the prospective, serial assessment of patients using both high-resolution ultrasound and patient self-report questionnaires.

A higher than anticipated number of patients discontinued therapy because of musculoskeletal symptoms, possibly because of chance in this small patient cohort, or possibly because they were enrolled in a clinical trial with a specific focus on musculoskeletal symptoms, which may

Table 3. Proportion of Patients (n=25) With New Abnormalities Noted on Ultrasonography After 3 Months of AI Therapy[a]

Site	No. With Abnormalities Unilaterally	No. With Abnormalities Bilaterally	Total No. With Abnormalities	Total No. With Abnormalities
Tendon sheath (flexors)	1 (4%)	0	1 (4%)	5 (20%)
Fluid	1 (4%)	0	1 (4%)	
Synovitis	0	0	0	
Hyperemia	0	0	0	
Tendon sheath (extensors)	4 (16%)	0	4 (16%)	
Fluid	4 (16%)	0	4 (16%)	
Synovitis	1 (4%)	0	1 (4%)	
Hyperemia	0	0	0	
Tendon (flexor + extensor)	0	0	0	0
Tendinosis	0	0	0	
Partial thickness tear	0	0	0	
Full thickness tear	0	0	0	
Joint recess (volar)	3 (12%)	3 (12%)	5 (20%)	12 (48%)
Fluid	3 (12%)	2 (8%)	5 (20%)	
Synovitis	1 (4%)	2 (8%)	3 (12%)	
Hyperemia	0	0	0	
Joint recess (dorsal)	7 (28%)	4 (16%)	11 (44%)	
Fluid	1 (4%)	4 (16%)	5 (20%)	
Synovitis	5 (20%)	2 (8%)	7 (28%)	
Hyperemia	2 (8%)	0	2 (8%)	

AI indicates aromatase inhibitor.
[a] Numbers do not necessarily add up to totals because some patients had >1 abnormality present (eg, both fluid and synovitis of the extensor tendon sheath).

Table 4. Associations Between Subject Characteristics and Patient-Reported Outcomes and Development of AIMSS and Early Treatment Discontinuation Due to Musculoskeletal Symptoms

	Development of AIMSS		Early Treatment Discontinuation	
Baseline Characteristic	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (<55 y vs ≥55 y)	0.18 (0.01-3.1)	.24	0.23 (0.01-4.2)	.32
BMI (<25, 25-30, >30 kg/m^2)	0.43 (0.11-1.7)	.22	0.16 (0.03-0.84)	.03
Prior tamoxifen (no vs yes)	0.21 (0.02-3.1)	.26	0.05 (0.002-1.0)	.05
Prior chemotherapy (no vs yes)	0.26 (0.04-1.9)	.19	0.19 (0.02-1.74)	.14
HAQ score	0.59 (0.31-1.1)	.11	0.73 (0.38-1.43)	.36
VAS score	1.26 (0.77-2.1)	.36	0.90 (0.52-1.55)	.70
DASH score	1.04 (0.92-1.2)	.52	1.09 (0.96-1.25)	.17
Change in measurement (baseline and 3 mo)				
HAQ score	1.15 (0.57-2.3)	.70	1.39 (0.68-2.88)	.37
VAS score	1.56 (0.42-5.8)	.51	1.43 (0.46-4.48)	.54
DASH score	1.05 (0.91-1.2)	.52	1.09 (0.93-1.29)	.28
Change in measurement (baseline and 12 mo)				
HAQ score	2.76 (0.3-26.6)	.38	6.02 (0.4-83.8)	.18
VAS score	2.11 (1.1-4.2)	.03	2.12 (1.1-4.1)	.02

AIMSS indicates aromatase inhibitor-musculoskeletal symptoms; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; HAQ, Health Assessment Questionnaire; VAS, Visual Analog Scale; DASH, Disabilities of the Arm, Shoulder, and Hand questionnaire.

have led to greater awareness of toxicity on the part of both the patient and physician. Similar to other reports, patients in this cohort who were previously treated with tamoxifen were less likely to discontinue AI therapy.[13] However, contrary to other reports,[12,13] there was an association noted between obesity and a decreased risk of

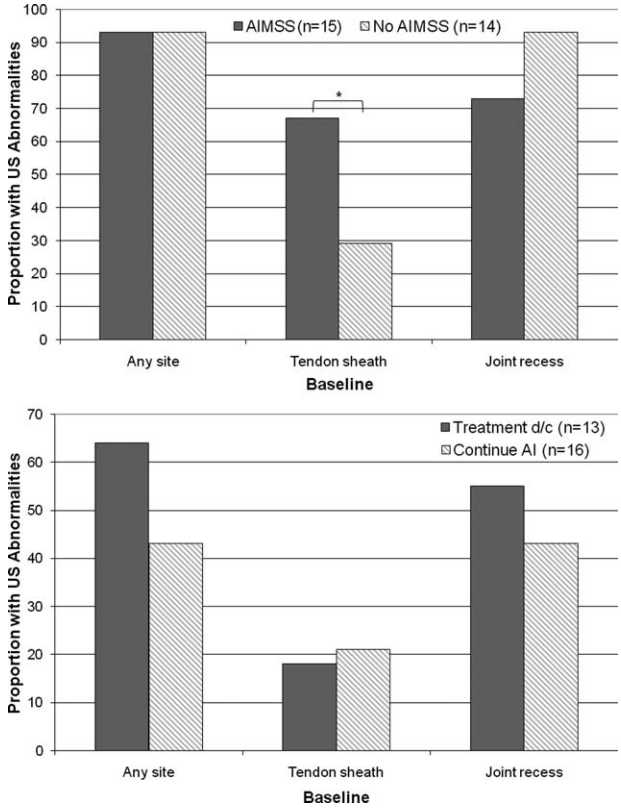

Figure 2. Associations between (*Top*) the presence of ultrasonographic (US) abnormalities at baseline and treatment-emergent aromatase inhibitor (AI)-associated musculoskeletal symptoms (AIMSS) and (*Bottom*) early treatment discontinuation because of musculoskeletal symptoms are shown. d/c indicates discontinue. All comparisons were found to nonstatistically significant. *p=.06.

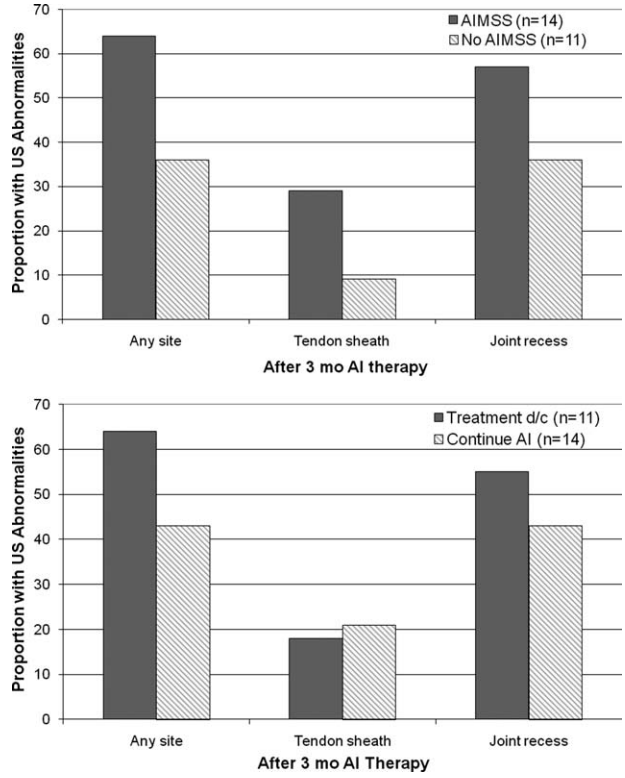

Figure 3. Associations between (*Top*) the percentage of new ultrasonographic (US) abnormalities after 3 months of aromatase inhibitor (AI) therapy and treatment-emergent AI-associated musculoskeletal symptoms (AIMSS) and (*Bottom*) early treatment discontinuation because of musculoskeletal symptoms are shown. d/c indicates discontinue. All comparisons were found to be nonstatistically significant.

treatment discontinuation because of musculoskeletal symptoms.

A limitation of the current study is the lack of multiple, long-term ultrasound assessments during AI therapy. Patients were assessed after 3 months of therapy, but the median time to reported AIMSS in this cohort was approximately 6 months. Therefore, it is possible that we were unable to detect a statistically significant association between ultrasound-detected abnormalities and patient-reported symptoms because of insufficient time point assessments. This restriction to analysis of the data from the 3-month time point may also have led to the lack of a noted association between changes in the HAQ and VAS scores and the development of AIMSS or early treatment discontinuation, which is also supported by our finding of a statistically significant association between changes in the VAS score between baseline and 12 months and both the development of AIMSS and early treatment discontinuation. A second limitation of the current study is the relatively small subject cohort, which was further decreased by early treatment discontinuation by 5 patients, thereby reducing statistical power.

Another possible limitation is the use of ultrasonography as opposed to MRI. One potential criticism of ultrasonography is operator-dependent variability. In the current study, we attempted to decrease this variability as much as possible through the collection and storage of both static images and cine clips for each subject at each time point for later analysis by a single, blinded reviewer. Advantages of high-resolution ultrasound include lower cost, shorter evaluation time, and a lack of factors that can preclude assessment with MRI, such as claustrophobia and the presence of metal in the body.

In summary, the findings of the current pilot study suggest that the presence of abnormalities of the wrist tendon sheath before the initiation of AI therapy may be predictive of the subsequent development of AIMSS both at

the wrist and at other anatomic sites. Future studies are warranted to confirm the trend noted in this pilot study, and to further elucidate the predictive role for imaging when making treatment decisions concerning adjuvant endocrine therapy.

CONFLICT OF INTEREST DISCLOSURES

Supported by Pharmacogenetics Research Network Grant U-01 GM61373 from the National Institute of General Medical Sciences, National Institutes of Health (NIH), Bethesda, Maryland (Indiana University) and Grant M01-RR000042 to the University of Michigan from the National Center for Research Resources (NCRR), a component of the NIH. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NCRR or NIH. Grants also were received from Pfizer (to Dr. Hayes); Novartis Pharma AG (to Dr. Hayes); the Barbara Padnos Breast Cancer Research Fund, University of Michigan Comprehensive Cancer Center (to Dr. Henry); and the Expedition Inspiration Fund for Breast Cancer Research (to Dr. Henry). ClinicalTrials.gov number: NCT00228956. Drs. Hayes, Stearns, and Storniolo received research funding from Pfizer and Novartis. Drs. Henry and Hayes received research funding from AstraZeneca. Dr. Stearns received honoraria from AstraZeneca. Dr. Jacobson received other support (equipment) from Philips, SonoSite, and Terason; has acted as a consultant for BioClinica; and has received book royalties from Elsevier.

REFERENCES

1. Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol.* 2008;9:45-53.
2. Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. *J Clin Oncol.* 2005;23:5138-5147.
3. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet*. 2007;369:559-570.
4. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst.* 2005;97:1262-1271.
5. Winer EP, Hudis C, Burstein HJ, et al. 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.* 2005;23:619-629.
6. Mamounas EP, Jeong JH, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol.* 2008;26:1965-1971.
7. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet*. 2005;366:455-462.
8. Coates AS, Keshaviah A, Thurlimann B, et al. 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.* 2007;25:486-492.
9. Jakesz R, Greil R, Gnant M, et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *J Natl Cancer Inst.* 2007;99:1845-1853.
10. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*. 2005;365:60-62.
11. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet.* 2007;369:559-570.
12. Sestak I, Cuzick J, Sapunar F, et al. Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis. *Lancet Oncol.* 2008;9:866-872.
13. Crew KD, Greenlee H, Capodice J, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. *J Clin Oncol.* 2007;25:3877-3883.
14. Henry NL, Giles JT, Ang D, et al. Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. *Breast Cancer Res Treat.* 2008;111:365-372.
15. Mao JJ, Stricker C, Bruner D, et al. Patterns and risk factors associated with aromatase inhibitor-related arthralgia among breast cancer survivors. *Cancer*. 2009;115:3631-3639.
16. Morales L, Pans S, Paridaens R, et al. Debilitating musculoskeletal pain and stiffness with letrozole and exemestane: associated tenosynovial changes on magnetic resonance imaging. *Breast Cancer Res Treat.* 2006;104:87-91.
17. Morales L, Pans S, Verschueren K, et al. Prospective study to assess short-term intra-articular and tenosynovial changes in the aromatase inhibitor-associated arthralgia syndrome. *J Clin Oncol.* 2008;26:3147-3152.
18. Wiesler ER, Chloros GD, Cartwright MS, Smith BP, Rushing J, Walker FO. The use of diagnostic ultrasound in carpal tunnel syndrome. *J Hand Surg Am.* 2006;31:726-732.
19. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol.* 2003;30:167-178.
20. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). *Am J Ind Med.* 1996;29:602-608.
21. Guy W. Clinical global impressions. In: Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US National Institute of Health, Psychopharmacology Research Branch; 1976.
22. Dizdar O, Ozcakar L, Malas FU, et al. Sonographic and electrodiagnostic evaluations in patients with aromatase inhibitor-related arthralgia. *J Clin Oncol.* 2009;27:4955-4960.