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CLINICAL TRIAL

Randomized controlled trial of high-dose versus standard-dose vitamin D3 for prevention of aromatase inhibitor-induced arthralgia

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Abstract

Purpose Half of hormone receptor-positive (HR+) breast cancer patients will develop joint pain, termed aromatase inhibitor-induced arthralgia (AIA), while taking aromatase inhibitor therapy. Though there is no universally accepted effective treatment for AIA, there has been some evidence to support high-dose vitamin D as a treatment.

Methods We randomized post-menopausal women who were beginning adjuvant AI therapy to receive standard-dose vitamin D3 (800 IU daily for 52 weeks), or high-dose vitamin D3 (50,000 IU weekly for 12 weeks, followed by 2000 IU daily for 40 weeks). The primary end point was development of AIA. The trial was designed to enroll 184 patients. This futility analysis was performed after 93 patients were enrolled.

Results The high-dose vitamin D regimen was effective in raising serum vitamin D levels, but there was no significant difference in development of AIA between the two arms. In the high-dose arm, 25 patients (54%) developed AIA, compared to 27 patients (57%) in the standard-dose arm. The planned futility analysis was positive; thus, the study was terminated. Neither baseline vitamin D nor 12-week vitamin D level was predictive of AIA development.

Conclusion Although vitamin D levels were increased in the high-dose arm, there was no significant signal for benefit of high-dose vitamin D supplementation for AIA prevention in this unblinded trial. This study, along with several others, implies that vitamin D likely does not play a significant role in AIA for the majority of patients.

Keywords Aromatase inhibitor-induced arthralgia · Vitamin D · Cancer survivorship · Medication compliance

Background

Approximately, 70% of newly diagnosed breast cancers are positive for hormone receptors (estrogen receptor, ER; progesterone receptor, PR) [1]. In the post-menopausal setting, adjuvant endocrine therapy typically includes a third-generation aromatase inhibitor (AI), based on multiple studies demonstrating superior efficacy of adjuvant AI's over tamoxifen in early breast cancer [2–4].

Though they are extremely effective, AIs often trigger a syndrome of symmetrical joint pain, termed aromatase inhibitor-induced arthralgia (AIA). AIA typically affects the small joints in the hands and feet; pain is usually worse when sedentary, and improved when physically active [5]. The incidence of AIA is approximately 50% [5]. This common syndrome is significantly detrimental to women's quality of life, impairing functioning in household, recreational, and occupational activities [6, 7]. Therefore, it is not surprising that many women do not complete their prescribed course of AI therapy due to this plaguing arthralgia. The rate of adherence to adjuvant anastrozole therapy was only 50–68% at 3 years [8]. The most common reason for AI discontinuation is arthralgia.

To date, clinical trials have examined various potential treatment options for AIA, including steroids, diuretics, acupuncture, duloxetine, omega fatty acid, and exercise. However, there is still no standard, uniformly accepted treatment for AIA, and we do not know the etiology of this common syndrome.

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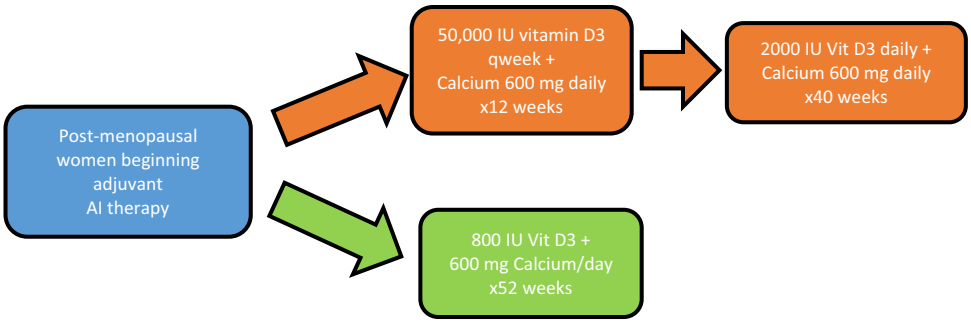

Fig. 1 Study schema

There are several studies which have examined vitamin D as a treatment for AIA, but results have been conflicting [9–12]. We therefore designed this randomized, prospective clinical trial in post-menopausal women with ER+ breast cancer, who are beginning adjuvant aromatase inhibitor therapy. Half of the women were assigned to receive high-dose Vitamin D (50,000 IU per week for 12 weeks, followed by 2000 IU daily for 40 additional weeks), and the other half of the women received standard-dose vitamin D (800 IU daily for 52 weeks). The goal of this trial was to show us whether high-dose vitamin D supplementation is a good preventative measure for AIA, and whether it is associated with increased AI compliance.

Methods

This is a multi-center, randomized, controlled, phase II study comparing high-dose vitamin D versus standard-dose vitamin D for post-menopausal breast cancer patients who are beginning adjuvant aromatase inhibitor therapy. The study was conducted at the Breast Oncology Clinics at Baylor College of Medicine and Harris Health Systems' Smith Clinic, as well as the Siteman Cancer Center at Washington University. The study was approved by the Institutional Review Board at all institutions. Written informed consent was obtained from all patients.

Patients

Eligible patients were ≥ 21 years old, with stage I-III hormone receptor-positive breast cancer, who were beginning adjuvant aromatase inhibitor therapy. All patients were post-menopausal, defined as any of the following: (1) age ≥ 60 years old; (2) history of bilateral oophorectomy; or (3) serum estradiol and FSH concentrations in the post-menopausal range, along with either amenorrhea for 12 months or previous hysterectomy. If the patient was < 60 years old at the time of study enrollment and had completed chemotherapy, post-menopausal status had to have been confirmed prior to chemotherapy.

Patients were excluded for any of the following reasons: aromatase inhibitor therapy in the last 6 weeks, history of kidney stones, hypercalcemia at baseline, history of symptomatic hypercalcemia or hyperparathyroidism, baseline 25-OH Vitamin D level > 50 ng/mL, currently taking phenytoin or phenobarbital, currently taking cholestyramine or orlistat, malabsorption syndrome, or chronic granulomata forming disorders, such as sarcoidosis or tuberculosis.

Procedures

Patients were randomized 1:1 to receive either 50,000 International Units (IU) oral vitamin D3 per week for 12 weeks followed by 2000 IU daily for 40 weeks, or 800 IU Vitamin D3 daily for 52 weeks. All women on both arms of the trial were also given calcium carbonate 600 mg daily, per Institute of Medicine Guidelines. See Fig. 1 for study design.

All patients were evaluable for toxicity from the time of their first treatment with vitamin D. All patients who were randomized were considered evaluable for response, regardless of how much treatment they received, consistent with an intention to treat analysis. Any patient who was randomized but did not complete the HAQ-II at 12 weeks was designated as a treatment failure, meaning that they were assumed to have developed AIA.

Throughout the 52-week study period, participating women completed the Health Assessment Questionnaire-II and grip strength measurement a total of three times (at baseline, week 12, and week 52) in order to assess their arthralgia while on AI therapy. AIA was defined as meeting any of the following criteria: (1) increase in HAQ-II score from baseline by 0.2 or greater; or (2) increase in visual analog pain score by 0.3 or greater. Compliance with aromatase inhibitor (AI) therapy was also assessed throughout the study via pill counts. Finally, study participants also had periodic assessments of serum calcium and 25-hydroxyvitamin D for safety purposes, and to assess whether vitamin D levels correlate with AIA.

Patient-reported outcome measures

The HAQ-II is the primary measure used to determine development of AIA in this study. It is commonly used in rheumatology literature, and has been substantiated across many trials [12–14]. This is a simple survey, which is a proven, reliable, and accurate indicator of joint pains and consequent disabilities [15, 16]. An abbreviated version of the HAQ-II, which takes about 5 min to complete, was used in the study. The questionnaire asks 20 questions in eight categories of functioning: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. For each question, the patient is scored on a scale of 0–3, depending on how much difficulty they have performing the task. A score of 0 correlates with no difficulty at all, and a score of three denotes that the patient is unable to do the task. The highest numerical score from each category is used, and the average of these 8 numbers is the composite score on the HAQ-II. Scores of 0–1 are considered to represent mild to moderate difficulty, 1–2 represents moderate to severe disability, and 2–3 represents severe to very severe disability. Average score in a population-based study is 0.49, whereas patients with osteoarthritis and rheumatoid arthritis have average scores of 0.8 and 1.2, respectively. The widely accepted "minimal clinical important difference" is 0.2 [17]. Thus, the study uses this as a cut-off point to define AIA development.

The visual analog scale is the other major component of the HAQ-II. In this, the patient is asked to mark, with a vertical line, where her pain lies on a horizontal line which is 15 cm long, with the far left side of the line representing no pain at all, and the far right side representing unbearable pain. To obtain the individual's score, the distance between the far left side of the line and the patient's mark is multiplied by 0.2. This converts the number of centimeters into the appropriate score and will yield a value from 0 to 3.

For the purposes of this study, AIA will be defined as any of the following criteria: (1) increase in HAQ-II score from baseline by 0.2 or greater; or (2) increase in visual analog pain score by 0.3 or greater. The HAQ-II questionnaire and its visual analog pain score are used in the definition of AIA because the questionnaire has been validated through many other studies which examine joint pain, and it is very simple to do in the office in less than 5 min. Though grip strength will be measured at various time points throughout the study, it will only be used in the exploratory analysis to see whether it may be an appropriate measure for AIA. Grip strength measurement is a relatively easy, inexpensive, objective criterion which may help to more clearly define AIA. These data will be very useful in the future, as it may serve to support a clearer, more objective definition of AIA for use in future studies, and for use in clinical practice.

Statistics

The primary endpoint for this study was development of AIA in each arm after 12 weeks of AI therapy, as determined by patient questionnaires. Secondary endpoints included compliance with AI therapy, as well as correlation of low-baseline vitamin D levels with development of AIA. Grip strength was explored as a potential surrogate for the development of AIA as an exploratory endpoint.

The primary objective of this study was to determine if supplementation with high-dose Vitamin D can prevent AIA in women being treated with adjuvant aromatase inhibitors. The Health Assessment Questionnaire-II (HAQ-II) was used to assess joint pain symptoms. Previously published estimates of AIA incidence showed that 33% of women on standard dose of vitamin D, and 19% of women on a high dose of vitamin D, developed AIA [18]. Assuming a one-sided test with $\alpha = 0.10$, $\beta = 0.20$, we would need 88 women in each arm to detect a different rate of AIA development using the Chi-square test. Assuming 5% dropout rate in the first 12 weeks, we planned to accrue 92 women to each arm, for a total of 184 women. Sample size calculations were conducted using nQuery Advisor 7.0, Statistical Solutions, USA.

Group differences in AIA rate were assessed using the Chi-square test. Development of AIA at week 12 was used to test the primary objective.

Compliance rates were summarized descriptively between the two arms. Serum vitamin D levels at baseline and week 12 between the treatment groups were compared using Wilcoxon rank-sum tests. The association between low-baseline vitamin D levels and AIA was assessed using the multivariate logistic regression model with adjusting for treatment effect. For each patient on the study, change in grip strength at week 12 was correlated with AIA development using summary statistics and Wilcoxon rank-sum test.

We conducted an interim futility analysis when half of the patients had been enrolled (46 patients on each arm). A non-binding O'Brien–Fleming spending function is used to calculate the futility boundary. Calculations were performed using nQuery Advisor + nTerim 3.0 (Statistical Solutions. Boston, MA).

The following table summarizes the futility boundary at each analysis when 50% and 100% patients are enrolled and evaluable at the interim analysis and the final analysis. The futility boundary in the term of p value scale at the interim analysis is calculated as $p = 0.47$ (or $Z = 0.076$). If the one-tailed p value exceeds 0.47, it will be recommended that the trial stops for futility.

Looks	Information (%)	*n* per group	Futility boundary (*Z* value)	Futility boundary (one-tailed *p* value)
1	50	46	0.076	0.47
2	100	93	1.28	0.05

In order to preserve power and compensate for the interim futility analysis which tends to reduce power, the sample size of the study was increased from 88 per group to 93 per group, which is 196 total, if considering a 5% drop out rate.

Results

Accrual and eligibility

At the time of the futility analysis, 93 patients had been randomized from Feb 2014 through July 2017. Patients were enrolled from all three clinical sites. Based on intention to treat analysis, all 93 patients were evaluable for efficacy analysis. Because six patients did not start treatment with vitamin D, only 87 patients were evaluable for safety.

Patient characteristics

Baseline patient characteristics were similar between the two groups (see Table 1). Median age was 64 years. A majority of the patients were minorities, with 44% Latina patients and 18% African American patients. A majority of the patients were also overweight or obese, as 86% of the patients had a BMI > 25. Forty-three percent of the patients received chemotherapy, which included a taxane for 95% of these patients.

Treatment completion

Most randomized patients completed at least 12 weeks of vitamin D treatment (83 of 93 patients, or 89%). The patients who did not complete treatment were equally split between the two arms, with five patients in each group completing less than 12 weeks of vitamin D. Seven patients withdrew consent, two patients were found to be ineligible, and 1 patient was non-compliant with treatment. One patient on the high-dose arm discontinued treatment after 12 weeks of therapy because of kidney stones. There were no other discontinuations due to adverse effects. (See Fig. 2 for CONSORT diagram.)

Development of AIA

Twelve weeks after randomization, 27 patients in the standard-dose arm (57%) and 25 patients in the high-dose arm (54%) developed AIA. Per the planned futility analysis, the one-tailed p value was 0.3818, and the *Z*-score was 0.3, yielding only a 38% conditional power that that study would find a significant difference between the two arms. Thus, the study was terminated early for futility.

At 12 weeks, 67 of the 93 randomized patients completed the HAQ-II questionnaire. Thirty-two patients in the standard-dose arm and 35 patients in the high-dose arm completed their 12-week questionnaires. As per protocol, the remaining patients were counted as failures. At 52 weeks, only 47 of the 93 trial patients completed the questionnaire. This was composed of 26 patients in the standard-dose arm, and 21 patients in the high-dose arm.

When the futility analysis was repeated with only the 67 patients who had evaluable HAQ-II scores at 12 weeks, the study still met criteria for futility.

At 52 weeks, 26 patients in the standard-dose arm (55%) and 29 patients in the high-dose arm (63%) developed AIA. These values were not significantly different (two-sided $p = 0.4487$). The principal reason for the apparent increase of AIA development in the high-dose arm is because only 21 patients in this arm completed the follow-up HAQ-II at 52 weeks. The remaining 25 patients with no questionnaire were considered to have developed AIA.

Vitamin D level

The vitamin D regimen on the high-dose arm (50,000 IU vitamin D3 weekly × 12 weeks) was effective in raising the vitamin D level. The mean baseline vitamin D level was 24.2 and 21.7 ng/mL in the standard-dose and high-dose arms, respectively. This level was not statistically significantly different between the two arms. At 12 weeks, the mean vitamin D level in the standard-dose arm was 29.3 ng/mL, compared to 50 ng/mL in the high-dose arm (see Fig. 3). The increase and the week 12 level were both significantly higher in the high-dose arm ($p < 0.0001$ for both comparisons).

There was no correlation between baseline vitamin D level and later development of AIA. Similarly, vitamin D level at 12 weeks was also not predictive of AIA development (see Fig. 4).

Compliance with AI therapy

Measurement of compliance was challenging because patients would sometimes forget to bring their pill bottles to follow-up appointments. Also, some patients were lost to follow-up at 52 weeks due to moving away, or transferring care. Only eight patients in the standard-dose arm and six patients in the high-dose arm had data available at all

Table 1 Patient characteristics

	All ($n=93$)		High dose ($n=46$)		Standard dose ($n=47$)	
	n	%	*n*	%	*n*	%
Age						
Median (range)	64 (44–82)		64 (45–76)		63 (44–82)	
Race						
White	72	77	33	72	39	83
Black or African American	17	18	11	24	6	13
Unknown	4	4	2	4	2	4
Ethnicity						
Hispanic or Latino	41	44	19	41	22	47
Non-Hispanic	50	54	26	57	24	51
Unknown	2	2	1	2	1	2
BMI						
Underweight	1	1	1	2		
Normal weight	12	13	4	9	8	17
Overweight	23	25	12	26	11	23
Obese	57	61	29	63	28	60
Clinical stage						
Stage I	42	45	22	48	20	43
Stage IIA	29	31	12	26	17	36
Stage IIB	13	14	5	11	8	17
Stage IIIA	7	8	5	11	2	4
Stage IIIB	2	2	2	4		
Histopathologic type						
IDC	74	80	35	76	39	83
ILC	15	16	9	20	6	13
Other	4	4	2	4	2	4
Histologic grade						
Grade I	24	26	13	28	11	23
Grade II	43	46	23	50	20	43
Grade III	25	27	9	20	16	34
Missing	1	1	1	2		
Received chemotherapy						
No	53	57	26	57	27	57
Yes	40	43	20	43	20	43
Received taxanes ($n=40$)						
Yes	38	95	19	95	19	95
No	2	5	1	5	1	5
Received HRT						
Never	65	70	32	70	33	70
Used before, stopped	11	12	7	15	4	9
Current use	9	10	4	9	5	11
Missing	8	9	3	7	5	11

time points throughout the year of the study period. The standard-dose patients were found to have taken 96.5% of their AI pills, and the high-dose patients took 98.1% of their pills. Because of the low numbers of patients in this analysis, we did not perform statistical tests for this endpoint.

Grip strength

The mean grip strength decreased by 1.3 mm Hg in the patients who did develop AIA, and it decreased by 3.5 mm Hg in those patients who did not develop AIA. There was no significant difference between these two groups ($p=0.37$). Thus,

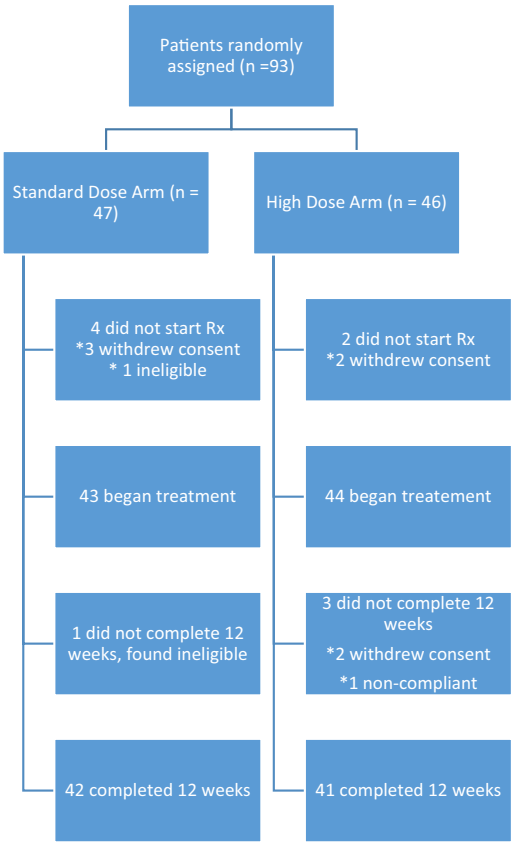

Fig. 2 CONSORT diagram

grip strength is not a good surrogate for AIA measurement; it cannot take the place of a questionnaire such as the HAQ-II.

Adverse effects

High-dose and standard-dose vitamin D were well tolerated. There were no grade 4 or grade 5 adverse events. One patient on the standard-dose arm developed grade 1 hypercalcemia, and one patient on the high-dose arm developed renal stones. There were 12 grade 3 adverse events, 8 of these occurring in the high-dose arm, and 4 occurring in the standard-dose arm. All grade 3 AEs were deemed to be unrelated to the study drugs. Grade 3 adverse events included arthralgia, peripheral sensory neuropathy, hypertension, hyperglycemia, and skin infection. All adverse events which occurred in two or more patients are summarized in Table 2.

Discussion

This multi-center, randomized controlled trial of high-dose versus standard-dose vitamin D was terminated early for futility after 93 patients were enrolled. There was no signal for improvement of AIA with high-dose vitamin D supplementation, though vitamin D levels were significantly increased in this arm.

These results add to a field of somewhat complex data in the arena of vitamin D treatment for AIA. For example, Khan

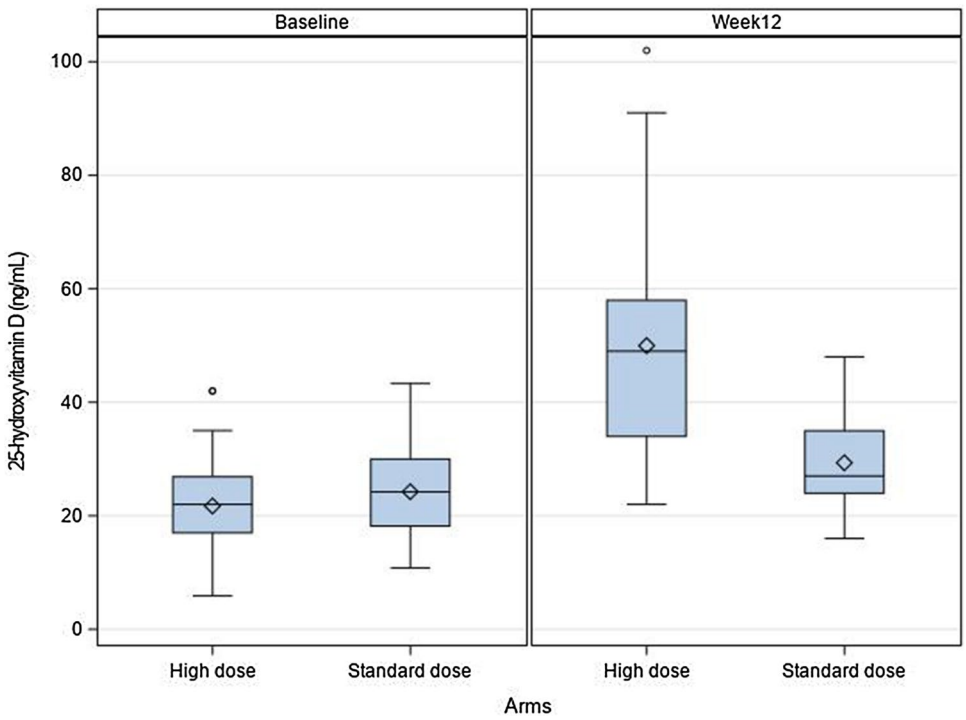

Fig. 3 Baseline and week 12 vitamin D levels

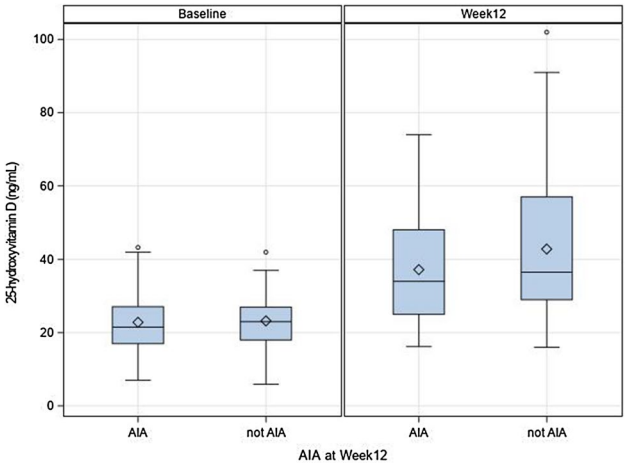

Fig. 4 Correlation between vitamin D level and AIA

et al. enrolled sixty women who were beginning adjuvant AI therapy in a small study which supplemented women with low-baseline Vitamin D levels (≤40 ng/mL) with increased doses of vitamin D at 50,000 IU per week for 12 weeks. They found that that the supplementation was effective in raising women's Vitamin D levels, and higher Vitamin D level (25OHD > 66 ng/mL) correlated with less joint pain and disability from joint pain [9]. Similarly, other studies [10, 14] have also shown some benefit to high-dose vitamin D replacement.

In contrast, Shapiro et al. conducted a single-center phase III RCT comparing two different doses of Vitamin D3 replacement (4000 IU/daily vs 600 IU/daily) for 6 months. In this trial, 113 patients were randomized onto one of these two arms for 6 months. They found no difference between the two groups in terms of AIA incidence, as measured by the BCPT-MS (Breast Cancer Prevention Trial Symptom Scale-Musculoskeletal) [11]. Similarly, the VITAL-D trial

Table 2 Adverse events

	All ($n=87$)		High dose ($n=44$)		Standard dose ($n=43$)	
	n	%	*n*	%	*n*	%
Hot flashes	43	49.4	23	52.3	20	46.5
Arthralgia	39	44.8	20	45.5	19	44.2
Fatigue	10	11.5	6	13.6	4	9.3
Peripheral sensory neuropathy	10	11.5	9	20.5	1	2.3
Pain in extremity	9	10.3	2	4.5	7	16.3
Vaginal dryness	8	9.2	5	11.4	3	7.0
Depression	7	8.0	4	9.1	3	7.0
Hypertension	5	5.7	4	9.1	1	2.3
Constipation	4	4.6	3	6.8	1	2.3
Insomnia	4	4.6	1	2.3	3	7.0
Gastroesophageal reflux disease	3	3.4	1	2.3	2	4.7
Pain	3	3.4	2	4.5	1	2.3
Arthritis	3	3.4	2	4.5	1	2.3
Myalgia	3	3.4			3	7.0
Headache	3	3.4	2	4.5	1	2.3
Anxiety	3	3.4			3	7.0
Vertigo	2	2.3	1	2.3	1	2.3
Hypothyroidism	2	2.3	2	4.5		
Diarrhea	2	2.3	2	4.5		
Nausea	2	2.3	1	2.3	1	2.3
Hyperkalemia	2	2.3	1	2.3	1	2.3
Bone pain	2	2.3	1	2.3	1	2.3
Neck pain	2	2.3	2	4.5		
Dizziness	2	2.3	1	2.3	1	2.3
Breast pain	2	2.3	1	2.3	1	2.3
Cough	2	2.3	2	4.5		

failed to meet its primary endpoint after randomizing 160 women to high-dose vitamin D versus placebo [12].

Considering the disparate results of the existing trials which examine vitamin D as a treatment for AIA, more work needs to be done to understand the optimal dosing and goal levels of vitamin D. Though there are some promising results in literature, many more trials need to be done to further clarify the role which vitamin D may play in AIA.

There were several limitations to our study. Firstly, per the protocol, many patients had to be counted as failures because they did not complete the 12-week or 52-week questionnaires. Also, there were ten patients on the trial who did not complete 12 weeks of study treatment for various reasons. These patients also were counted as failures. Secondly, the trial was not blinded. Because the patients and the physicians knew which study treatment each subject was receiving, there could have been some bias in assessing arthralgia, as per the questionnaire. Thirdly, some controversy remains as to which questionnaire is the best tool to capture the symptoms and severity of AIA. Some trials have found that the HAQ-II is adequately sensitive to pick up the sometimes subtle signs of AIA. However, other trials have used the brief pain inventory (BPI), Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index, or other pain scales to measure AIA. There is no consensus on which tool is the most effective in detecting the syndrome of AIA.

While our trial adds to the negative data for vitamin D in the treatment of AIA, more nuanced questions remain in this field. It is unclear why some trials show benefit of vitamin D, and others do not. Host factors may play a role in the heterogeneity of patients' responses to Vitamin D. For example, there are some data to indicate that single-nucleotide polymorphisms (SNPs) may play a role in modulating an individual's response to vitamin D replacement [19]. Further research is necessary to better understand the etiology and treatment of AIA, as this remains an important cause of non-compliance with AI therapy for breast cancer survivors.

Compliance with ethical standards

Conflict of interest Dr. Nangia has had a consultant/advisory role with Puma, and she has received funding from Paxman Coolers. Dr. Ademuyiwa has had a consultant/advisory role with Immunomedics, AstraZeneca, Jounce, Eisai, and Best Doctors; she has received funding from Pfizer, Abbvie, Seattle Genetics, Immunomedics, and Polyphor. Dr. Ellis has had a consultant/advisory role with NanoString, Novartis, AstraZeneca, Pfizer, Abbvie, Sermonix, and Puma; he has stock ownership in Bioclassifier with Royalty income from Prosigna/NanoString. Dr. Osborne has had a consultant/advisory role with Puma, AstraZeneca, and Genentech; stock ownership in GENETEX; and funding from Puma. Dr. Rimawi has had a consultant/advisory role in MacroGenics, Daiichi, and Novartis; he has received funding from Novartis and Pfizer. Dr. Ma has had a consultant/advisory role with Pfizer, Novaris, and Lilly; she has received funding from Eisai, Puma, and Pfizer.

Ethical approval All procedures and processes in this clinical trial comply with all regulatory laws in the United States, where the study was conducted. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Baylor College of Medicine Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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