Breast Cancer Res Treat (2017) 166:491–500
DOI 10.1007/s10549-017-4429-8

CLINICAL TRIAL

Randomized trial of vitamin D3 to prevent worsening of musculoskeletal symptoms in women with breast cancer receiving adjuvant letrozole. The VITAL trial

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Received: 25 July 2017 / Accepted: 28 July 2017 / Published online: 2 August 2017
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Abstract
Purpose Aromatase inhibitor-associated musculoskeletal symptoms (AIMSS) frequently occur in women being treated for breast cancer. Prior studies suggest high prevalence of vitamin D deficiency in breast cancer patients with musculoskeletal (MS) pain. We conducted a randomized, placebo-controlled trial to determine if 30,000 IU vitamin D3 per week (VitD3) would prevent worsening of AIMSS in women starting adjuvant letrozole for breast cancer.
Methods Women with stage I–III breast cancer starting adjuvant letrozole and 25(OH)D level $\leq$40 ng/ml were eligible. All subjects received standard daily supplement of 1200 mg calcium and 600 IU vitamin D3 and were randomized to 30,000 IU oral VitD3/week or placebo. Pain, disability, fatigue, quality of life, 25(OH)D levels, and hand grip strength were assessed at baseline, 12, and 24 weeks. The primary endpoint was incidence of an AIMSS event.
Results Median age of the 160 subjects (80/arm) was 61. Median 25OHD (ng/ml) was 25 at baseline, 32 at 12 weeks, and 31 at 24 weeks in the placebo arm and 22, 53, and 57 in the VitD3 arm. There were no serious adverse events. At week 24, 51% of women assigned to placebo had a protocol defined AIMSS event (worsening of joint pain using a categorical pain intensity scale (CPIS), disability from joint pain using HAQ-II, or discontinuation of letrozole due to MS symptoms) vs. 37% of women assigned to VitD3 ($p = 0.069$). When the brief pain inventory (BPI) was used instead of CPIS, the difference was statistically significant: 56 vs. 39% ($p = 0.024$).
Conclusions Although 30,000 IU/week of oral vitamin D3 is safe and effective in achieving adequate vitamin D levels, it was not associated with a decrease in AIMSS events based on the primary endpoint. Post-hoc analysis using a different tool suggests potential benefit of vitamin D3 in reducing AIMSS.

Keywords AIMSS · Aromatase inhibitor · Arthralgia · Musculoskeletal · Pain · Vitamin D

Abbreviations

AIMSS	Aromatase Inhibitor-Associated Musculoskeletal Symptoms
AIST	Aromatase Inhibitor Symptom Tool
AIs	Aromatase Inhibitors
BFI	Brief Fatigue Inventory
BPI	Brief Pain Inventory
CPIS	Categorical Pain Intensity Scale
FACT-B	Functional Assessment of Cancer Therapy-Breast
HAQ-II	Health Assessment Questionnaire II
MENQOL	Menopause-specific Quality of Life
VITAL	VITamin D treatment to prevent Arthralgia in women starting Letrozole
VitD3	30,000 IU vitamin D3 per week

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Introduction

Musculoskeletal (MS) pain is a frequent side effect among women taking adjuvant aromatase inhibitors (AIs) for hormone receptor positive early breast cancer [1–3]. Cross-sectional studies show that about half of the women receiving adjuvant AIs report new or worsening MS symptoms, with a quarter reporting severe symptoms [4]. As a result, considerable research activity has focused on preventing or treating the spectrum of side effects referred to collectively as aromatase inhibitor-associated musculoskeletal symptoms (AIMSS) [5].

Vitamin D deficiency is prevalent in women with breast cancer who also have MS symptoms and among women receiving adjuvant chemotherapy for breast cancer [6–8]. A pain syndrome similar to AIMSS has been described in subjects with extreme vitamin D deficiency and treatment with vitamin D results in rapid resolution of these symptoms [6, 9]. Estrogen can upregulate both the 1-α-hydroxylase enzyme required for conversion of 1,25(OH)2D from 25(OH)D and increase levels of vitamin D receptor [10, 11]. Thus, AI induced estrogen deprivation may unmask subclinical vitamin D deficiency, which also may increase the severity of AIMSS. Replacement with vitamin D3 may correct that subclinical deficiency.

Optimal serum 25-hydroxyvitaminD [25(OH)D] level, the best indicator of vitamin D stores in the body, is unknown. Levels less than 20 ng/ml are considered deficient for bone health; but higher levels may be necessary for optimal MS function. A level of more than 150 ng/ml is considered toxic [12, 13].

In a pilot study, we observed that 50,000 IU VitD3/week in women taking letrozole was associated with reduced disability from joint pain but that three women had 25(OH)D levels of >100 ng/ml [14]. Subsequently, we initiated the placebo-controlled VITAL trial (VITamin D treatment to prevent Arthralgia in women starting Letrozole) at the lower dose of 30,000 IU VitD3 weekly. With this dose of VitD3 we hypothesized that most participants with a starting 25(OH)D level of ≤40 ng/ml should experience an increase to 50–80 ng/ml but nobody should approach the toxic level of 150 ng/ml. Goals of the study were to examine the efficacy of VitD3 for preventing the worsening of AIMSS and to determine the efficacy of 30,000 IU VitD3 in achieving 25OHD levels of >40 ng/ml compared to placebo, and its safety.

Methods

Cohort

The study was conducted at the University of Kansas Medical Center (Kansas City) and the Cancer Center of Kansas (Wichita), under a protocol approved by local IRBs (NCT00867217). Subjects were postmenopausal women with stage I–III hormone receptor positive breast cancer scheduled to start treatment with an adjuvant AI and with a 25(OH)D level ≤40 ng/ml. Subjects were excluded if they had history of renal stones, hypercalcemia, or hyperparathyroidism. Informed consent was obtained from each participant. Upon study entry, participants were asked to stop any vitamin D and calcium supplements and were provided with a standard supplement.

Study schedule

Baseline assessments

Baseline assessments included history, physical exam, CBC, calcium and phosphorus, liver/renal functions, serum estradiol and 25(OH)D, handgrip test, and completion of various questionnaires (below). 25(OH)D levels using LC/MS/MS were performed at Quest Laboratories. Hand grip strength was measured using a Jamar dynamometer.

Questionnaires

- Health assessment questionnaire II (HAQ-II) is commonly used in rheumatology. It consists of categorical (integer) values from 0 to 3 for ten separate functions; an increase of 0.25 in the mean score is considered clinically relevant worsening of symptoms (disability).
- Categorical pain intensity scale (CPIS)—five descriptors (none, mild, moderate, severe, disabling) as reported by subject. Any step increase is considered relevant.
- Brief pain inventory (BPI); consists of two separate scales, intensity and interference, with two sets of questions (integer values from 0 to 10) focused on intensity of pain and on Interference with a variety of normal activities, with an average score provided for both. A 1 point change is considered relevant.
- Brief fatigue inventory (BFI); usual level of fatigue during the past 24 h is considered the most informative;

integer values from 0 to 10. Any increase is considered as evidence of worsening.
- Functional assessment of cancer therapy-breast (FACT-B) and menopause-specific quality of life (MENQOL).

Stratification, randomization, and treatment Participants were stratified by site and use of adjuvant chemotherapy and randomized 1:1 to either 30,000 IU VitD3 (VitD3) or placebo weekly for 24 weeks (three capsules of 10,000 IU VitD3 or three capsules of matched placebo weekly). Only the study biostatistician and investigational pharmacists were aware of drug assignments. All subjects received 1200 mg of calcium plus 600 IU of vitamin D daily ("standard supplementation") and Letrozole 2.5 mg PO daily. All study related drugs including standard supplements were provided without charge to participants. There were no dose adjustments.

Follow-up assessments

All baseline assessments were repeated at weeks 12 and 24. Since 25(OH)D measurement had the potential to reveal the study agent assignment, a serum specimen was sent to Quest Laboratories for assessment of 25(OH)D, and the results sent to a designated individual not involved with the study. If levels >100 ng/ml had been reported, the individual would have contacted the PI who would have taken the subject off-study. This did not occur. Once all study assessments had been completed, data audited, and the trial database locked, all 25(OH)D results were sent to the study biostatistician.

Statistical considerations

The planned accrual of 160 subjects was intended to provide at least 144 evaluable subjects (72/arm) if the drop-out rate was no greater than 10%. This would provide 88% power to detect a statistically significant reduction using 1-sided Fisher's exact test at 5% type I error rate if the proportions of worsening AIMSS were 25% and 50% for women randomized to high dose vitamin D and placebo, respectively. These proportional reductions were estimated from our pilot study that compared women receiving VitD3 (50,000 IU/week) versus only standard supplementation [14]. All subjects that received study agent were considered evaluable for safety and for efficacy.

The protocol defined primary outcome was a worsening of AIMSS from baseline to 24 weeks, evidenced by any of the following three events: (1) an increase in the HAQ-II score of 0.25 or more; (2) an increase in CPIS score; or (3) discontinuation of letrozole specifically due to AIMSS. Secondary endpoints were changes in hand grip strength using a Jamar dynamometer; and increases in fatigue and menopause symptoms using BFI, FACT-B, and MENQOL.

For the primary endpoint, the difference in the incidence of worsening of AIMSS between individuals randomized to VitD3 vs. placebo was first examined by a 1-sided Fisher's exact test. Multiple logistic regression analysis was then used to investigate whether changes in AIMSS from baseline to 24 weeks were due to variables other than assigned treatment.

For secondary categorical variables, Fisher's exact test was used. For continuous variables, the Mann–Whitney test or Kruskal–Wallis test was used for comparison between groups; the Wilcoxon's signed rank test was used for within-subject changes over time. Given the exploratory nature of the analyses dealing with AIMSS, no corrections were made for multiple comparisons and the two-sided type I error rate was maintained at 0.05.

Results

Characteristics of subjects

Accrual of 160 subjects was achieved between April 2009 and July 2010; with an exact 1:1 (80:80) randomization (Fig. 1). Distribution of demographics, stage, and adjuvant therapy was balanced between the two arms, as shown in Table 1.

Baseline serum 25(OH)D levels, AIMSS and quality of life assessments

Prior to enrollment, 49 of 160 subjects were taking vitamin D supplements. Baseline median 25(OH)D levels were 25.1 and 22.5 ng/ml for women randomized to placebo and VitD3, respectively (Table 1). As shown in Table 2, median baseline values for various quality of life assessments were similar for the two groups, except for several specific activities (mood, walking, relations, and enjoyment) in the brief fatigue inventory.

Study completion and evaluability

Of the 160 subjects enrolled and randomized (Fig. 1), one subject was determined to be not eligible because she consumed high dose VitD between screening assay and baseline visit. An additional 12 subjects did not complete the study for reasons unrelated to study agents and/or AIMSS (withdrawal of consent, never started study agent, personal decision, etc.). Additionally, all quality of life assessments were not available for all participants at all visits. Specifically, 72 and 70 complete sets of assessments were available for the vitD and placebo arms at week 12,

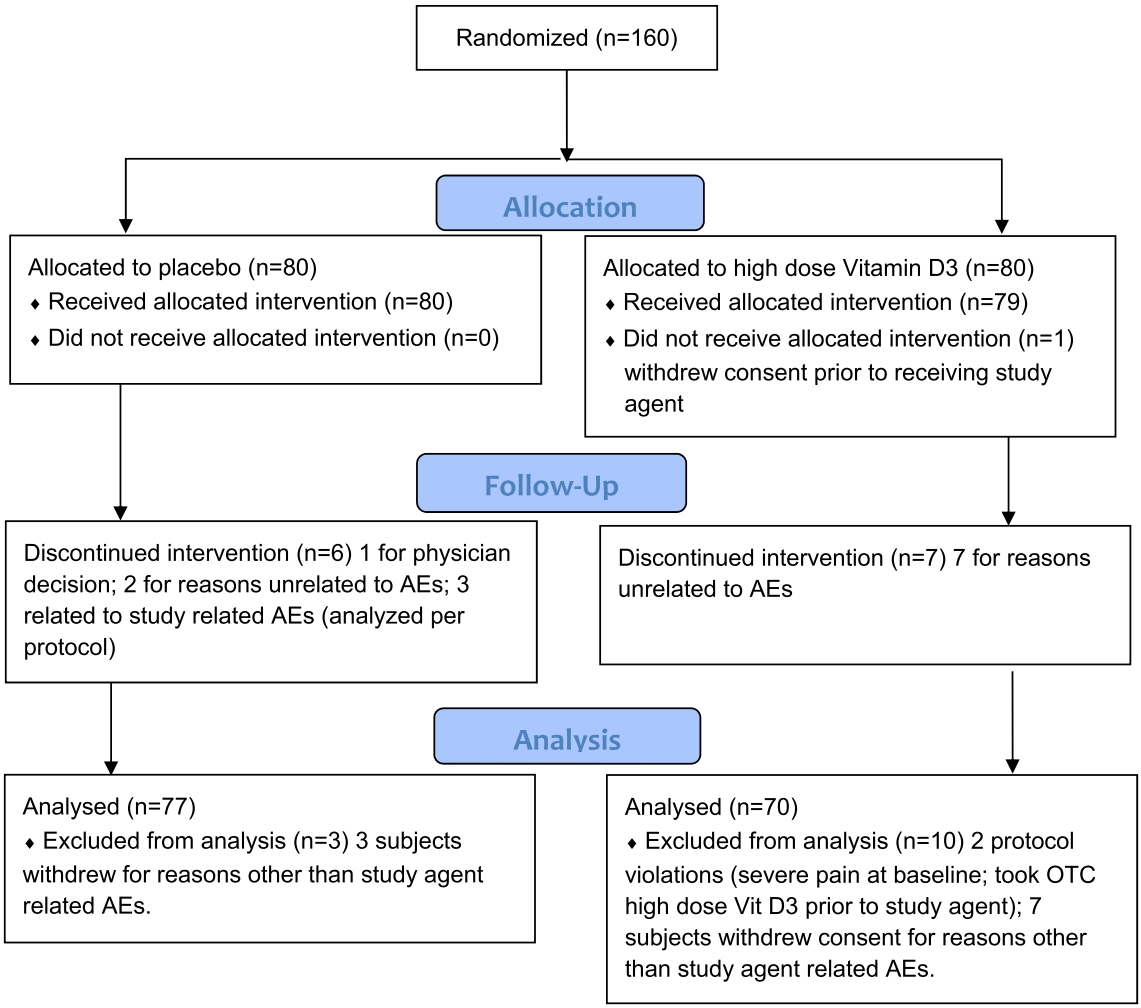

Fig. 1 Diagram of subject allocation, follow-up, and basis for analysis

and 73 and 65 at week 24. The number of missing values was not significantly different between arms at week 12 or 24 (2-sided $p = 0.80$ and 0.11 by Fisher's exact test). Overall, sufficient information was available to allow assessment of protocol defined worsening of AIMSS for 147 evaluable subjects, with 77 in the placebo group and 70 in the VitD3 group. This formed the basis for all assessments of efficacy.

Effect of VitD3 on serum 25(OH)D levels

For women randomized to placebo (Table 3), median increase in 25(OH)D was 7.1 ng/ml between week 0 and 12, and then no further increase from 12 to 24 weeks. Only nine subjects achieved a level >40 ng/ml. In contrast, VitD3 (30,000 IU per week) increased 25(OH)D levels by a median of 32 ng/ml between week 0 and 12 (Table 3), with a slight further increase between weeks 12 and 24 (median 3.0 ng/ml). 91% achieved a level >40 ng/ml by 24 weeks; maximum value measured was 87 ng/ml. The differential effect of VitD3 is graphically displayed in Fig. 2.

Adverse events

Excluding the adverse events related to letrozole, there were no adverse events attributed to vitamin D3. One subject in placebo group had mild hypercalcemia at 12 week assessment. She was taking a thiazide diuretic and had serum 25(OH)D level of 20 ng/ml at the time. There were no differences between the groups for off-study levels of urinary calcium, creatinine, or calcium:creatinine ratio.

Efficacy of vitamin D3 supplementation in preventing AIMSS

Frequency of subjects classified as exhibiting a worsening of AIMSS by each of the three individual measures that contribute to the protocol defined primary outcome is shown in Table 4. While for each there are numerical

Table 1 Demographic, tumor, and treatment characteristics for 160 enrolled subjects

Characteristic	Placebo $N = 80$	High dose VitD3 $N = 80$
Age at diagnosis, years	62 (54–69)	60.5 (55–71)
Weight, Kg	80.4 (70.7–91.7)	80.3 (68.6–90.9)
Height, m	1.64 (1.59–1.69)	1.63 (1.59–1.68)
BMI, Kg/m^2	29.6 (26.8–33.6)	29.9 (25.6–34.4)
25(OH)D at baseline, ng/ml	25.1 (18.0–30.5)	22.5 (15.9–29.7)
Race (self-reported)		
Caucasian	75 (94%)	77 (96%)
Other than caucasian	5 (6%)	3 (4%)
Ethnicity (self-reported)		
Not hispanic	77 (96%)	78 (98%)
Hispanic	3 (4%)	2 (2%)
Educational Level		
High school/GED	24 (30%)	21 (26%)
Vocational/technical	4 (5%)	4 (5%)
Some college	25 (31%)	33 (41%)
College degree	10(13%)	12 (15%)
Graduate/professional	13 (17%)	8 (10%)
Other or missing	4 (5%)	2 (3%)
Taking vitamin D at baseline	29	20
Stage		
I	28 (35%)	33 (41%)
II	38 (48%)	25 (31%)
III	6 (8%)	6(8%)
No data	8 (10%)	16 (20%)
Surgery type		
Lumpectomy	44 (56%)	42 (55%)
Mastectomy	35 (44%)	35 (45%)
Adjuvant chemotherapy scheduled	45 (56%)	41 (51%)
Radiation therapy received	49 (65%)	48 (62%)

For continuous variables, median and interquartile ranges are provided; for frequencies, the number and percent are given

differences in favor of the VitD3 arm, none reached significance. For the protocol defined primary endpoint using the composite of HAQ-II, CPIS, and letrozole discontinuation due to AIMSS side effects, 51% of the women randomized to placebo vs. 37% of those randomized to VitD3 experienced onset or worsening of AIMSS ($p = 0.069$). Four other measures including hand grip strength showed a similar lack of difference between groups (Table 4), as did quality of life assessments using FACT-B and MENQOL (data not shown).

BPI-Intensity index, with greater dynamic range than the five category CPIS, did identify nine additional subjects exhibiting an increase in pain intensity. As an exploratory post hoc analysis when this was used instead of the CPIS in the composite, the difference between groups was statistically significant, with 56% (43/77) of women randomized to placebo vs. 39% (27/70) of those randomized to VitD3 classified as having worsening of AIMSS ($p = 0.024$).

Discussion

AIMSS is a symptom complex with variable phenotype consisting of varying degrees of joint and muscle pain, stiffness, and disability which may be difficult for a patient to describe and is not optimally defined with tools used in adjuvant trials. Trials of adjuvant AIs may therefore be underestimating the frequency of AIMSS due to a lack of tools specific for their assessment [15–17].

Estrogen deprivation is thought to be one of the underlying reasons for AIMSS. Joint stiffness and arthralgia are common after menopause [18], and especially among

Table 2 Baseline values for quality of life and musculoskeletal symptom assessments

Characteristic	Placebo $N = 80$	High dose VitD3 $N = 80$
Median HAQ-II score (mean of 10 items)	0.6 (0.2–0.9)	0.5 (0.3–0.9)
Median brief fatigue inventory (BFI)[a]		
Median value, mean of 9 items	2.75 (1.0–4.7)	3.7 (1.4–5.4)
Median for usual	3 (2–5)	4 (2–6)
Median for general activity	3 (0–5)	3 (0.75–6)
Median for mood	1 (0–4)	3 (0.75–5)
Median for walking	1 (0–4)	3.0 (0–5)
Median for relations	1 (0–3)	2.5 (0–5)
Median for enjoyment	1 (0–5)	3 (0–6)
MENQOL		
Summary	0.9 (0.4–2.0)	1.1 (0.5–2.0)
Vasomotor	0.7 (0.0–2.0)	0.7 (0.0–1.3)
Psychosocial	0.9 (0.4–1.9)	1.1 (0.4–3.0)
Physical	1.3 (0.6–2.1)	1.3 (0.8–2.0)
Sexual	0.0 (0.0–1.3)	0.0 (0.0–2.4)
Categorical pain (past 24 h)		
None	29 (36%)	40 (50%)
Mild	24 (30%)	16(20%)
Moderate	24 (30%)	21 (26%)
Severe (ineligible per criterion)	0 (0%)	1 (1%)
Unknown	3 (4%)	2 (3%)
Hand grip strength, Kg		
Right	39.4 (25.3–52.0)	45.2 (31.6–53.0)
Left	36.8 (21.0–49.7)	43.1 (31.0–49.9)
Dominant	42.6 (25.3–53.7)	47.1 (34.5–53.8)
Non-dominant	36.0 (20.5–47.2)	40.9 (30.0–48.2)
Maximum strength	42.6 (25.3–53.7)	47.0 (34–53.4)
Brief pain inventory (BPI)		
Median value—intensity, mean of 4 items	1.3 (0.3–3.4)	1.5 (0.3–2.4)
Median value—interference, mean of 7 items	0.95 (0.0–2.9)	1.1 (0.0–3.0)

For continuous variables, median and interquartile ranges are provided; for frequencies, the number and percent are given

[a] Individual elements of BFI (mood, walking, relations) were different, but not the summary mean value

premenopausal women receiving gonadotropin-releasing hormone analogs such as luperolide. Estrogen has tissue specific effects on inflammatory cytokines and lack of estrogen may result in augmentation of inflammation and enhanced nociception from inflammation [19, 20]. An indirect evidence of this phenomenon comes from the observation that women on AIs complaining of joint pain have MRI findings of tenosynovitis suggesting local inflammation in the joints [21, 22]. A pain syndrome similar to AIMSS has been described in subjects with extreme vitamin D deficiency. More importantly, treatment with vitamin D results in rapid resolution of these symptoms [6, 9]. Vitamin D deficiency is prevalent in breast cancer patients who also have MS symptoms and among women receiving adjuvant chemotherapy [6, 7, 23].

The exact mechanism of a Vitamin D effect ameliorating AIMSS is not known but may be related to its anti-inflammatory properties [8]. The active hormone calcitriol is locally produced from vitamin D3 in macrophages and may have a role in limiting joint inflammation. Estrogen increases calcitriol, and estrogen deprivation from AIs is therefore expected to be pro-inflammatory by decrease in this active form of vitamin D [24, 25]. Higher doses of vitamin D3 would provide a substrate for increased local production of calcitriol serving to limit joint inflammation and pain resulting from AIs.

Table 3 Changes in 25(OH)D levels (ng/ml) over time for Placebo and vitamin D3 arms

Placebo group							
25(OH)D values	0 wk $N = 77$	12 wk $N = 72$	24 wk $N = 73$	P value (Wilcoxon signed rank)	0–12 wk $N = 72$	12–24 wk $N = 69$	0–24 wk $N = 73$
Minimum value	4.6	6.0	13.0	0–12 wk	−21.0	−24.0	−16.3
Maximum value	40.0	57.0	55.0	$p < 0.001$	27.8	24.0	34.8
Range interval	35.4	51.0	42.0	12–24 wk	48.8	48.0	51.1
Median	25.1	32.0	31.0	$p = 0.66$	7.1	0.0	6.2
Mean	23.9	31.9	31.2	0–24 wk	8.3	−0.6	7.1
Standard Deviation	9.1	9.1	7.7	$p < 0.001$	9.8	7.7	11.5
Number < 40 ng/ml	77	63	75				
Number > 40 ng/ml	0	9	8				
High dose vitamin D3 group							
25(OH)D values	0 wk $N = 70$	12 wk $N = 70$	24 wk $N = 65$	P value (Wilcoxon signed rank)	0–12 wk $N = 65$	12–24 wk $N = 65$	0–24 wk $N = 70$
Minimum value	4.3	25.4	23.0	0–12 wk	3.0	−23.0	−6.0
Maximum value	39.5	81.0	87.0	$p < 0.001$	56.5	39.0	69.1
Range interval	35.2	55.6	64.0	12–24 wk	53.5	62.0	75.1
Median	22.4	53.0	57.0	$p = 0.005$	32.0	3.0	34.2
Mean	21.9	53.2	57.1	0–24 wk	30.9	4.3	35.2
Standard Deviation	9.1	12.4	13.9	$p < 0.001$	13.9	11.3	14.9
Number < 40 ng/ml	70	11	6				
Number > 40 ng/ml	0	59	59				

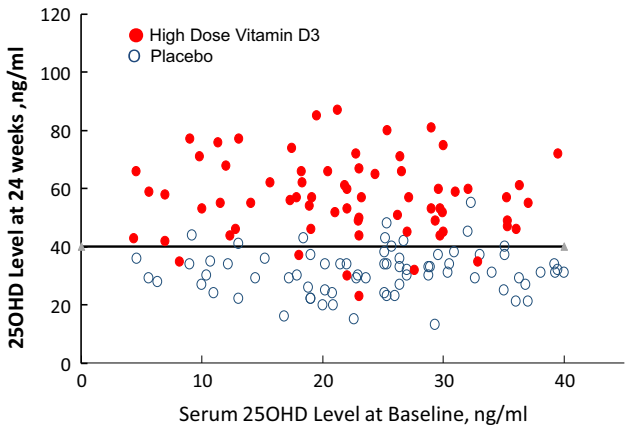

Fig. 2 Comparison of final (24 week) levels of 25(OH)D, plotted as a function of the baseline levels. There was no statistically significant difference between the two groups at baseline ($p = 0.25$); but there was for 12-week levels, 24-week levels, and change from baseline to 24-weeks ($p < 0.001$, Mann–Whitney test)

In our trial, supplementation with 30,000 IU of vitamin D3 weekly in women with early breast cancer who were receiving letrozole, was safe and extremely effective in replenishing vitamin D stores. No subject's 25(OH)D level exceeded 87 ng/ml; yet the target level of >40 ng/ml was achieved in 91% of women. This extends our pilot trial experience [14] where 50,000 IU of vitamin D3 weekly for up to 24 weeks was quite tolerable and safe. Conversely, <10% of women had a level more than 40 ng/ml with standard supplementation of 600 IU vitamin D3 per day in the placebo group. The steep increase in 25(OH)D levels during the first 3 months followed by plateau suggests that 30,000 IU of vitamin D may be safely continued beyond 6 months if needed with minimal additional monitoring.

During the design of the trial, based on our phase II experience, our assumption was that no single measure of AIMSS worsening would be sufficient to detect a clinically meaningful change in AIMSS. This is particularly problematic in a trial designed to prevent development of AIMSS (rather than treat existing symptoms) since one does not know a priori what problems or complaints a woman might experience. For this reason, the protocol defined criteria for AIMSS worsening was any of three events (increase in HAQ-II score, increase in CPIS score, or discontinuation due to AI-related AEs). In general, these three measures tended to identify different women suffering different problems, as anticipated. However, the CPIS measure, which we had selected on the basis of our pilot study results, did not perform as well in this regard as it had

Table 4 Comparison of measures of worsening of musculoskeletal symptoms between randomization arms at 24 weeks (end of study agent intervention)

Criterion for assessment	Incidence of worsening number (%)		*P* value Fisher's exact test (1-sided)	
	Placebo	High Dose VitD3		
HAQ-II increase by 0.25	23 (32%)	18 (27%)	0.34	Protocol defined
Categorical pain intensity	24 (33%)	18 (29%)	0.36	
Discontinuation due to AEs	3 (4%)	0 (0%)	0.14	
Any of the three measures	39 (51%)	26 (37%)	0.069	
Pain increase by BPI-Intensity	29 (42%)	22 (33%)	0.38	Post hoc analysis
BPI—interference	25 (36%)	17 (26%)	0.26	
BFI—usual fatigue	28 (38%)	19 (29%)	0.26	
Hand grip strength (−6.2 kg)	6 (9%)	6 (9%)	0.98	

in the pilot study. Despite achieving desired levels of 25(OH)D with supplementation, and observing a numerical decrease in worsening of AIMSS events (our primary, protocol defined endpoint) from 51 to 37%, the difference was not statistically significant. Thus, the trial was negative based on failure to meet its primary endpoint.

In contrast to CPIS, the BPI-Intensity index increased the number of subjects identified as having a worsening of AIMSS. The BPI provides four questions regarding severity of pain, with a broader range of possible responses (10 point scale) and is a more sensitive tool for pain assessment. Justification for use of the BPI comes from a phase II trial of women on anastrozole for at least 8 weeks who had existing AIMSS as well as serum 25(OH)D levels of 10–29 ng/ml, and were randomized to receive 50,000 IU weekly of vitamin D2 or placebo for 2–4 months in an attempt to reduce AIMSS [26]. At 2 months, scores for several measures of pain intensity in the BPI were more favorable in women randomized to vitamin D2 compared to placebo [26]. As an exploratory, post hoc analysis, when we replaced CPIS with BPI-Intensity in our composite index (i.e., HAQ-II + BPI-Intensity + letrozole discontinuation) to define an AIMSS event, the difference between groups was statistically significant ($p = 0.024$).

Based on the above encouraging result from an admittedly post hoc analysis, we proceeded to a further post hoc effort to develop a cumulative index (AIST—aromatase inhibitor symptom tool) from the VITAL trial that would capture as many AIMSS side effects as possible and would serve as a sensitive tool for future trials, designed specifically for AIMSS. For this purpose, all assessments were scored as change over the 24-week period of study agent intervention. For exploratory purposes, 2-sided statistical approaches were used. Of the seven measures in Table 4, no single assessment revealed statistically significant differences between the two randomized arms. However, the different tests did identify different subjects as having evidence of increasing discomfort/disability. Therefore, a stepwise approach was used to determine the utility of adding tests sequentially to provide evidence of "worsening" (Table 5). The first endpoint employed was discontinuation of AI therapy due to AEs. Even though this only contributed three subjects, it is obviously the most clinically relevant endpoint. It also avoided the need to censor subjects that dropped out prior to providing any of the 6-month objective assessments. Next, tests were added in order of the largest number of events that would be gained. BFI-Usual Activity (1 point increase) resulted in an additional 47 subjects with symptoms, followed by HAQ-II (0.25 increase) which identified 20 more subjects with symptoms and improved the discriminant ability to marginal statistical significance. When BPI-Interference was added, identifying 13 more subjects, the distinction between the two groups was definitely statistically significant. By this post hoc derived metric, evidence for worsening of AIMSS was observed in 71% of subjects randomized to placebo (plus the standard supplement of 600 IU of D3/day) versus only 40% of subjects randomized to high dose vitamin D3 plus the standard supplemental dose ($p < 0.001$). This indicates that a multi-component assessment may provide a robust means of demonstrating the beneficial effects of an intervention such as vitamin D3 on preventing the development or worsening of AIMSS. However, this new assessment tool needs to be validated in a prospective trial.

Our results indicate that six months of oral vitamin D3 at 30,000 IU weekly is safe in women starting an AI for adjuvant treatment of breast cancer and is very effective in increasing serum 25(OH)D levels. Although this intervention failed to show a benefit in preventing new or worsening AIMSS events in women starting adjuvant AIs based on the protocol defined primary endpoint, post hoc analysis

Table 5 Stepwise addition of individual tests to develop an alternate index of musculoskeletal symptom worsening between randomization arms

Step	Assessments utilized	Total events (of 147)	Events "added"	Incidence of worsening number (percent)		*P* value (Pearson Chi square (2-sided)
				Placebo $N = 77$	VitD3 $N = 70$	
1	AE due to AI	3 (2%)	3	3 (4%)	0 (0%)	0.095
2	AE + BFI-Usual	50 (34%)	47	31 (40%	18 (27%)	0.094
3	AE + BFI + HAQ-II	70 (48%)	20	44 (57%)	26 (37%)	0.015
4	AE + BFI + HAQ-II + BPI-IF	83 (57%)	13	55 (71%)	28 (40%)	<0.001

using a more sensitive tool suggests benefit of vitamin D supplementation to prevent AIMSS. A new arthralgia assessment tool (AIST), specific for measuring AIMSS, needs to be validated in larger AI symptom intervention trials.

Acknowledgements Letrozole and funding for this study were provided by Novartis Pharmaceutical Corporation (East Hanover, NJ). Vitamin D3 (10,000 IU capsules) and matched, blinded placebo were provided by BTR Group, Inc. (Pittsfield, IL). Neither company was the sponsor for the trial; nor were they involved in any aspect of design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Compliance with ethical standards

Conflict of interest The following authors are without financial interests or conflicts of interest related to this trial: Kimler, Reddy, Klemp, Nydegger, and Yeh. Within the past three years, Dr. Khan has served as a consultant to Novartis Pharmaceutical Company, Inc. and Pfizer. Drs. Khan and Sharma have received during the past three years, via their institution, funding for support of research and clinical trials from the following companies: AstraZeneca; Bristol-Myers Squibb; Celgene, Inc.; Novartis Pharmaceutical Company, Inc.; Genentech-Roche, GlaxoSmithKline, and Pfizer. Study agent but no funding has been provided by DSM and Pfizer for trials conducted by Dr. Fabian.

Ethical standards The conduct of the trial complies with the current laws of the United States of America.

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