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Randomized Multicenter Placebo-Controlled Trial of Omega-3 Fatty Acids for the Control of Aromatase Inhibitor–Induced Musculoskeletal Pain: SWOG S0927

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See accompanying editorial on page 1870; listen to the podcast by Dr Loprinzi at www.jco.org/podcasts

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A B S T R A C T

Purpose
Musculoskeletal symptoms are the most common adverse effects of aromatase inhibitors (AIs) and can result in decreased quality of life and discontinuation of therapy. Omega-3 fatty acids (O3-FAs) can be effective in decreasing arthralgia resulting from rheumatologic conditions and reducing serum triglycerides.

Patients and Methods
Women with early-stage breast cancer receiving an AI who had a worst joint pain/stiffness score ≥ 5 of 10 using the Brief Pain Inventory–Short Form (BPI-SF) were randomly assigned to receive either O3-FAs 3.3 g or placebo (soybean/corn oil) daily for 24 weeks. Clinically significant change was defined as ≥ 2-point drop from baseline. Patients also completed quality-of-life (Functional Assessment of Cancer Therapy–Endocrine Symptoms) and additional pain/stiffness assessments at baseline and weeks 6, 12, and 24. Serial fasting blood was collected for lipid analysis.

Results
Among 262 patients registered, 249 were evaluable, with 122 women in the O3-FA arm and 127 in the placebo arm. Compared with baseline, the mean observed BPI-SF score decreased by 1.74 points at 12 weeks and 2.22 points at 24 weeks with O3-FAs and by 1.49 and 1.81 points, respectively, with placebo. In a linear regression adjusting for the baseline score, osteoarthritis, and taxane use, adjusted 12-week BPI-SF scores did not differ by arm ($P = .58$). Triglyceride levels decreased in patients receiving O3-FA treatment and remained the same for those receiving placebo ($P = .01$). No between-group differences were seen for HDL, LDL, or C-reactive protein.

Conclusion
We found a substantial (> 50%) and sustained improvement in AI arthralgia for both O3-FAs and placebo but found no meaningful difference between the groups.

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INTRODUCTION

Despite the well-proven efficacy of aromatase inhibitors (AIs) for the treatment of hormone-sensitive breast cancer,[1] some patients experience—and may even stop treatment early because of—undesirable adverse effects.[2] Observational studies have shown that AI-related arthralgia is more prevalent than originally reported.[3,4] In a cross-sectional survey of 200 consecutive postmenopausal women receiving adjuvant AI therapy for breast cancer, 94 (47%) reported AI-related joint pain, and 88 (44%) reported joint stiffness, with the bulk of the symptoms reported in the hands and knees.[3] Risk factors include time since cessation of menstrual function, previous taxane chemotherapy, and prior hormone-replacement therapy.[3,5,6] Of concern, only approximately 50% of women receive adjuvant hormonal therapy for the full duration at the optimal schedule.[7]

The use of omega-3 fatty acids (O3-FAs) for rheumatoid arthritis as well as other inflammatory conditions has been studied for more than 20 years. In a mouse model, fish oil, which is a rich source of O3-FAs—particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—decreased the

incidence as well as severity of joint pain and inflammation.[8] EPA and DHA inhibit the conversion of arachidonic acid to prostaglandin and leukotrienes, which results in reduced inflammation.[9,10] Several randomized controlled trials have suggested that patients receiving O3-FAs or eating diets rich in O3-FAs have fewer symptoms of rheumatoid arthritis.[11-15] A meta-analysis in 2007 found significant changes in patient-assessed pain, morning stiffness, number of painful and/or tender joints, and nonsteroidal anti-inflammatory drug consumption.[16] O3-FAs have also been found to be equivalent to nonsteroidal anti-inflammatory drugs in patients with acute and chronic back pain.[17] Finally, O3-FAs have been evaluated for the prevention of cardiovascular disease and have been shown to reduce serum triglyceride levels, which also may be increased in women receiving AIs.[18-21]

There are currently no proven treatments for AI-related arthralgia. We conducted a multicenter randomized double-blind placebo-controlled clinical trial to test the hypothesis that O3-FAs reduce pain and stiffness in women undergoing adjuvant AI therapy for early-stage breast cancer.

PATIENTS AND METHODS

The study was activated in February 2012 and closed to accrual in February 2013. Patients were informed of the investigational nature of the study and signed informed consent. The study was conducted after appropriate approval by individual institutional review boards at 52 sites, in compliance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

Patient Characteristics

Postmenopausal women with a history of stage I to III hormone-sensitive breast cancer receiving adjuvant AI therapy for ≥ 90 days were screened. Those with a score of ≥ 5 of 10 on the Brief Pain Inventory–Short Form (BPI-SF) worst pain/stiffness measure (item 2) who reported that the symptoms started or worsened after initiation of AI therapy were eligible. Patients were required to have a Zubrod performance status of 0 to 2. Those who had received O3-FA supplements within 3 months before enrollment

were excluded, as were those with a history of fracture or surgery involving the affected joint within the prior 6 months. Patients receiving oral narcotics or topical analgesics within the prior 14 days were excluded, and those receiving oral steroids or who received intra-articular steroid injections within the prior 28 days were excluded.

Study Design

A randomized double-blind multicenter trial comparing OA-FAs 3.3 g per day (six capsules; Ocean Nutrition, Dartmouth, Nova Scotia, Canada) versus matching placebo daily for 24 weeks was conducted. Each active capsule contained 560 mg of EPA plus DHA in a 40-to-20 ratio. Each placebo capsule contained a blend of soybean and corn oil. Both the active and placebo capsules were colored with carob and flavored with natural lemon-lime. Patient random assignment was stratified by prior history of arthritis (yes v no) and prior taxane use (yes v no). Fasting serum was collected at baseline and weeks 12 and 24, stored at −80°C, and tested centrally for total cholesterol, HDL, LDL, triglycerides, and C-reactive protein (CRP).

Patient-Reported Outcome Measures

Because there are no well-validated measures specifically for AI-induced arthralgia, we selected a general pain scale used in patients with cancer—the BPI-SF—to assess the primary end point.[20] Numeric rating scales such as the BPI are among the most common, valid, and reliable measures used to assess cancer pain.[22] The BPI-SF is a 14-item questionnaire that asks patients to rate pain over the prior week and the degree to which it interfered with activities on a 0-to-10 scale, where higher scores indicate more pain. We used the worst pain (item 2) as the primary end point measure. This form was modified to include stiffness.

We also used scales to assess joint pain, stiffness, and functional status in the knees and hands as secondary end points. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; version 3.1) is a validated measure for assessing osteoarthritis of the knees and/or hips and consists of 24 questions related to three subscales: pain (0 to 500), stiffness (0 to 200), and physical function (0 to 1,700).[23] The Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) consists of three domains assessing pain, stiffness, and functional status in those with hand osteoarthritis and rheumatoid arthritis, using 100-mm visual analog scales.[24] For both instruments, higher scores represent higher symptom burden. The Functional Assessment of Cancer Therapy–
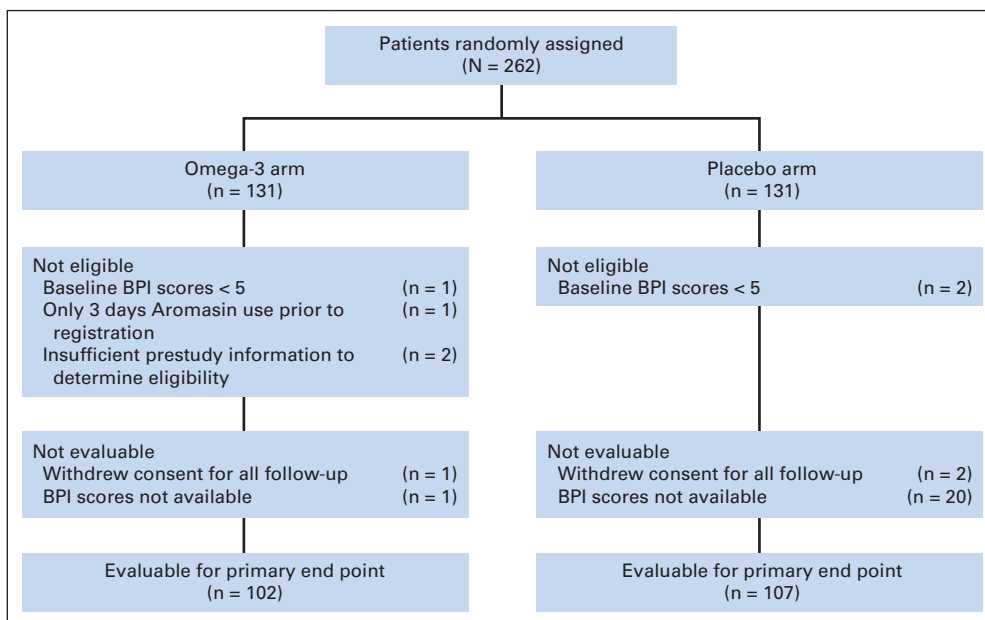

Fig 1. CONSORT diagram. BPI, Brief Pain Inventory.

Endocrine Symptoms (FACT-ES) measures physical, social and family, emotional, and functional well-being and endocrine symptoms.[25] The FACT scales have five response levels ("not at all" to "very much"), where higher scores reflect better well-being and fewer symptoms. This scale provided a measure of the broader impact of join pain and stiffness symptoms. Two single-item 7-point global rating of change scales for joint pain and stiffness were used to evaluate patients' perception of change in symptoms.[26]

Fasting Serum Analyses

Lipids and CRP were measured using the Cobas Integra 400 plus automated analyzer (Roche, Basel, Switzerland). Total cholesterol, HDL, and triglycerides were measured using individual enzymatic colorimetric methods. For cholesterol, interassay precision is 1.90%, intra-assay precision is 0.51%, and the quantification limit is 0.116 mg/dL. For HDL, interassay precision is 1.00%, intra-assay precision is 1.13%, and the quantification limit is 3 mg/dL. For triglycerides, interassay precision is 1.90%, intra-assay precision is 1.60%, and the quantification limit is 8.85 mg/dL. LDL is calculated from these measurements using the Friedewald equation. CRP (high sensitivity) was measured with an immunoturbimetric assay; interassay precision is 3.1%, intra-assay precision is 1.30%, and the quantification limit is 0.1 mg/L.

Statistical Considerations

The primary hypothesis of the study was that O3-FAs would decrease joint pain and/or stiffness associated with the use of AIs in patients with breast cancer compared with placebo at 12 weeks, as measured by the BPI worst pain and/or stiffness item. The study stipulated a two-sided $\alpha = 0.05$, with an estimated 5% nonadherence (reducing nominal effect size) and 20% dropout rate (increasing total required sample size) at the primary end point evaluation time of 12 weeks after random assignment. For a 2-point difference and 3.5-point standard deviation at 12 weeks, with other parameters as specified, 222 eligible patients were required for 90% power under a two-arm normal design.

Secondary analyses examined BPI worst pain scores at weeks 6 and 24. Also, outcomes for the M-SACRAH, WOMAC, FACT-ES, and global rating of change scales were assessed at weeks 6, 12, and 24. These secondary end points were examined using multiple linear regression, adjusting for the baseline score and prespecified stratification factors. We also analyzed adverse events by intervention arm.

Cholesterol, LDL, HDL, triglycerides, and CRP were measured at baseline and weeks 12 and 24. Raw means at each time point and means of the difference from baseline to week 12 were calculated by treatment arm. Paired t tests were used to calculate unadjusted P values comparing week 12 with baseline measures within treatment arm, and two-sample t tests were used to calculate unadjusted P values comparing differences in serum measures, from baseline to week 12, between treatment arms. Counts of patients at each time point with elevated levels of each serum measure were calculated, and χ^2 tests were used to calculate unadjusted P values comparing the proportions of patients with elevated levels between treatment arms.

RESULTS

Accrual, Eligibility, and Evaluability

Accrual to this study was rapid, with a total of 262 patients registered from 52 sites between February 2012 and February 2013. Six patients were ineligible (one because of 3 days of exemestane use before registration, three because of low baseline BPI score, and two because of insufficient prestudy information; Fig 1). In addition, seven patients withdrew consent for all study follow-up and were considered not analyzable, leaving 249 evaluable patients (O3-FA arm, n = 122; placebo arm, n = 127). Nine of these patients were considered major deviations because they received only 0 to 1 week of intervention.

Patient Characteristics

Patient characteristics by intervention assignment are listed in Table 1. No notable imbalances by arm were observed by age, ethnicity, prior osteoarthritis, or prior taxane use, although fewer black women were randomly assigned to the O3-FA arm (4% v 12%).

Table 1. Patient Demographic and Clinical Characteristics						
	Total (N = 249)		O3-FA Arm (n = 122)		Placebo Arm (n = 127)	
Characteristic	No.	%	No.	%	No.	%
Age, years						
Median	59.2		59.5		59.1	
Hispanic ethnicity						
Yes	16	6	7	6	9	7
No	225	90	112	92	113	89
Unknown	8	3	3	2	5	4
Race						
White	217	87	113	93	104	82
Black*	20	8	5	4	15	12
Asian	4	2	1	1	3	2
Native American	1	< 1	0	0	1	1
Multiracial	2	1	1	1	1	1
Unknown	5	2	2	2	3	2
Osteoarthritis						
Yes	57	23	28	23	29	23
No	192	77	94	77	98	77
Prior taxane						
Yes	144	58	71	58	73	57
No	105	42	51	42	54	43
Location of joint pain*†						
Knee	178	71	87	69	91	75
Hand	169	68	90	71	79	65
Ankle	91	37	34	27	57	47
Wrist	84	34	38	30	46	38
Shoulder	97	39	51	40	46	38
Other	130	52	65	51	65	53
Self-reported comorbid conditions						
Diabetes	32	13	19	15	13	11
Hypertension	101	41	48	38	53	43
High cholesterol	77	31	45	35	32	26
Heart disease	13	5	9	7	4	3
AI						
Anastrozole	146	59	73	57	73	60
Exemestane	29	12	14	11	15	12
Letrozole	74	30	40	31	34	28
Years since starting AI therapy						
Median	1.2		1.1		1.3	
Years since last menstrual period						
Median	9.4		9.9		8.8	
Weight, kg						
Median	79.0		79.8		77.3	
Fish consumption						
Mean total servings per week						
Baseline	1.6		1.7		1.5	
Week 6	1.7		1.9		1.4	
Week 12	2.1		2.0		2.2	
Week 24	1.7		2.0		1.5	

Abbreviations: AI, aromatase inhibitor; O3-FA, omega-3 fatty acid.
*Patient characteristics were well balanced by arm for all factors shown except location of joint pain and black race.
†Percent columns sum to > 100% because patients could report > one location of joint pain.

Table 2. Mean BPI Worst Pain/Stiffness Score, Pain Interference, and Global Rating of Change

Analysis	No. of Patients	Observed Results								Adjusted Results[a]				
		Baseline[b]		Follow-Up		Within Group		Between Group		Follow-Up				
		Mean	95% CI	Mean	95% CI	Difference	P[e]	Difference[f]	P[g]	Mean	95% CI	Difference[c]	95% CI	P[d]
BPI worst pain score														
Week 6								−0.33	.32			−0.27	−0.88 to 0.34	.38
O3-FAs	108	7.09	6.80 to 7.39	5.41	4.94 to 5.87	−1.69	< .001			5.38	4.77 to 5.99			
Placebo	115	6.98	6.71 to 7.25	5.63	5.17 to 6.08	−1.36	< .001			5.65	5.04 to 6.26			
Week 12								−0.24	.38			−0.17	−0.79 to 0.44	.58
O3-FAs	102	7.08	6.77 to 7.39	5.34	4.85 to 5.84	−1.74	< .001			5.30	4.68 to 5.91			
Placebo	107	6.92	6.65 to 7.20	5.43	4.97 to 5.89	−1.50	< .001			5.47	4.86 to 6.09			
Week 24								−0.43	.52			−0.36	−1.08 to 0.38	.34
O3-FAs	94	7.06	6.75 to 7.38	4.83	4.28 to 5.38	−2.23	< .001			4.77	4.04 to 5.50			
Placebo	98	6.88	6.59 to 7.16	5.07	4.53 to 5.61	−1.81	< .001			5.13	4.40 to 5.86			
BPI pain interference														
Week 6								−0.06	.82			−0.05	−0.57 to 0.47	.84
O3-FAs	108	4.14	3.73 to 4.55	3.22	2.74 to 3.69	−0.92	< .001			3.22	2.84 to 3.59			
Placebo	115	4.13	3.72 to 4.54	3.27	2.82 to 3.72	−0.86	< .001			3.27	2.91 to 3.63			
Week 12								0.10	.74			0.11	−0.44 to 0.66	.70
O3-FAs	102	4.17	3.74 to 4.60	3.14	2.64 to 3.64	−1.03	< .001			3.12	2.73 to 3.51			
Placebo	107	4.12	3.70 to 4.55	2.99	2.55 to 3.44	−1.13	< .001			3.01	2.63 to 3.40			
Week 24								−0.14	.65			−0.15	−0.39 to 0.70	.58
O3-FAs	94	4.05	3.62 to 4.48	2.57	2.10 to 3.05	−1.48	< .001			2.58	2.19 to 3.00			
Placebo	98	4.09	3.64 to 4.54	2.75	2.28 to 3.21	−1.34	< .001			2.74	2.35 to 3.13			
Global rating of change in joint pain from baseline[h]														
Week 6								0.10	.56			0.10	−0.24 to 0.44	.57
O3-FAs	109			0.72	0.47 to 0.96	—	< .001			0.72	0.47 to 0.96			
Placebo	112			0.62	0.39 to 0.85	—	< .001			0.62	0.38 to 0.86			
Week 12								0.27	.16			0.26	−0.10 to 0.63	.16
O3-FAs	98			0.76	0.47 to 1.04	—	< .001			0.75	0.49 to 1.02			
Placebo	104			0.49	0.25 to 0.73	—	< .001			0.49	0.24 to 0.75			
Week 24								0.08	.74			0.07	−0.35 to 0.49	.74
O3-FAs	90			0.77	0.46 to 1.08	—	< .001			0.77	0.46 to 1.07			
Placebo	95			0.69	0.40 to 0.99	—	< .001			0.70	0.40 to 0.99			
Global rating of change in joint stiffness from baseline[h]														
Week 6								0.13	.43			0.13	−0.20 to 0.46	.44
O3-FAs	109			0.59	0.35 to 0.82	—	< .001			0.59	0.35 to 0.82			
Placebo	114			0.46	0.23 to 0.69	—	< .001			0.46	0.23 to 0.69			
Week 12								0.27	.12			0.28	−0.07 to 0.62	.12
O3-FAs	98			0.68	0.41 to 0.95	—	< .001			0.68	0.43 to 0.93			
Placebo	103			0.41	0.18 to 0.63	—	< .001			0.41	0.16 to 0.65			
Week 24								0.00	1.00			−0.003	−0.41 to 0.41	.99
O3-FAs	91			0.65	0.35 to 0.94	—	< .001			0.65	0.35 to 0.94			
Placebo	97			0.65	0.36 to 0.94	—	< .001			0.65	0.36 to 0.94			

Abbreviations: BPI, Brief Pain Inventory; O3-FA, omega-3 fatty acid.
[a]From linear regression adjusting for baseline BPI score and stratification factors.
[b]Among patients with week-6, -12, or -24 BPI worst pain score, respectively.
[c]Difference derived from O3-FAs minus placebo.
[d]Between-group P values.
[e]P value for paired t tests for difference between baseline and week-12 measures within treatment arm.
[f]Difference from change between follow-up and baseline score for O3-FAs minus change between baseline and follow-up for placebo (ie, difference in differences).
[g]P value for unpaired t tests for difference in change measures between treatment arms.
[h]Questionnaire evaluates changes in symptoms since last visit, so no baseline scores were collected.

Dropout and Nonadherence

The study design assumed a dropout rate of 20% and nonadherence rate of 5% (or total noncompliance rate of 25%) for the primary end point assessment time of 12 weeks after registration. BPI worst pain scores were not available for 20 (16%) of the 122 evaluable patients in the O3-FA arm (dropout, n = 18; nonadherence, n = 2); in the placebo arm, scores were not available for 20 (16%) of 127 eligible patients (dropout, n = 19; nonadherence, n = 1). Therefore, dropout and nonadherence were lower than anticipated and did not differ by arm.

Primary End Point: BPI Worst Pain/Stiffness at Week 12

In total, 84% (102 of 122) of patients in the O3-FA arm and 84% (107 of 127) in the placebo arm had week-12 BPI worst pain scores available for analysis. The mean observed BPI worst pain score was 1.74 points lower (reduced pain) at 12 weeks compared with baseline in the O3-FA arm and 1.49 points lower in the placebo arm (Table 2). In multivariable analysis, adjusted week-12 BPI worst pain scores were 0.17 points lower on average (implying slightly less pain) in the O3-FA arm versus the placebo arm (95%

CI, −0.79 to 0.44; $P = .58$; Table 2). The effect of intervention on BPI worst pain did not differ according to stratification factors or baseline BPI score (data not shown). Results were similar at weeks 6 and 24 (Fig 2). A 2-point change from baseline was achieved in 61% of women receiving O3-FAs and 57% of women receiving placebo. Similar results were seen with regard to pain interference and the global rating of change scales (Table 2).

Secondary End Points

The mean observed change in the M-SACRAH, WOMAC, and FACT-ES measures reflected somewhat reduced symptoms in the O3-FA arm compared with the placebo arm at each of the assessment times using the M-SACRAH and WOMAC measures and somewhat increased symptoms in the O3-FA arm compared with the placebo arm at each assessment time using the FACT-ES measure (Appendix Table A1, online only). There was no evidence that any of these differences were statistically significant in multivariable regression analyses. There were no differences by arm in analgesic use over time.

Serum Analysis

Most of the serum measures remained at the same level over time or changed consistently between treatment arms (Table 3). However, triglycerides decreased in patients receiving O3-FA treatment (difference, −22.1 mg/dL) and stayed the same for those receiving placebo (difference, 0.1 mg/dL). The differences over time by arm were statistically significant ($P = .01$). At 12 weeks, HDL increased by 2.9 mg/dL in the O3-FA arm ($P = .007$); however, there was no statistically significant difference over time by arm ($P = .25$). At baseline, > 70% of women had LDL levels > 100 mg/dL, and approximately 50% had total cholesterol levels > 200 mg/dL (Table 4).

Adverse Events

Among the 249 evaluable patients, 10 were not evaluable for adverse events because of either receiving no intervention[7] or lack of adverse event reporting.[3] Among the 239 patients for whom adverse events were assessed, there was one case each of grade 3 diarrhea, dyspepsia, and pain in the extremity in the O3-FA arm and one case

each of grade 3 arthralgia, pain, peripheral motor neuropathy, and rash maculo-papular toxicity in the placebo arm (Appendix Table A2, online only).

Adverse events potentially related to AI joint pain/stiffness included arthralgia, range of motion decrease, and pain. There were 27 cases of grade ≥ 1 of these adverse events among patients receiving O3-FAs (23%) and 33 cases among those receiving placebo (27%; $P = .68$); there were 13 cases of grade ≥ 2 of these adverse events among those receiving O3-FAs (11%) and 25 cases among those receiving placebo (20%; $P = .09$). However, baseline symptoms were eligibility criteria, and the change in these adverse events from baseline is not known.

DISCUSSION

In this multicenter placebo-controlled trial, we found a substantial (approximately 50%) and sustained improvement in AI-associated arthralgia with both O3-FAs and placebo, but we found no meaningful difference between the groups. Surprisingly, the absolute reduction in both arms was similar to the effects seen in the intervention arms of other randomized studies.[27-30] Women receiving O3-FAs had a significant lowering of triglyceride levels compared with those receiving placebo, which is a known benefit of O3-FAs. This observation reassures us that patients were compliant, and the supplement was active. In addition, we found an increase in serum HDL from baseline in the O3-FA group; however, the difference in HDL at 12 weeks was not different than with placebo.

The improvement in symptoms in both the treatment and placebo groups was unexpected. The magnitude of the expected placebo effect reported in the literature can vary from 6% to 59%[31-33] and can be higher in symptom-management studies. We found an effect of > 50%. This larger-than-expected placebo effect may have been a result of the natural history of arthralgia, which can improve over time. It is also possible that the placebo contained ingredients (soy/corn oil) that were active in reducing arthralgia. It is also possible there was some contamination in the placebo arm, although the lower triglyceride levels in the O3-FA arm suggests that any contamination was limited.

With regard to the placebo effect, two randomized trials have been completed reporting no placebo effect. The first is a randomized sham-controlled blinded trial to assess the effect of a 6-week intervention of acupuncture in 38 women with AI-associated joint symptoms. The study reported that the true acupuncture group had a 50% decrease in pain compared with no change in the sham acupuncture group.[27] Similarly, a randomized trial of an exercise intervention in 121 women with AI arthralgia reported that pain scores had decreased by 24% at 12 months among women randomly assigned to exercise versus no change among women randomly assigned to usual care.[30] Similar to our study, both the acupuncture and exercise intervention trials used BPI score of 3 to 4 as an inclusion criterion, used the BPI as an outcome measure, and showed a decrease in mean pain score in the therapeutic arms similar to that in the O3-FA arm in our trial. The exercise trial was not blinded, and the acupuncture trial used sham acupuncture as the placebo.

Although several studies have been conducted to evaluate interventions to treat AI arthralgia, no clear treatment has emerged. The
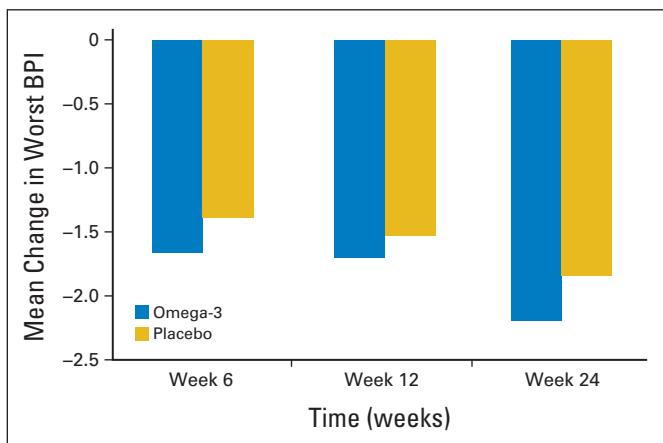
Fig 2. Adjusted change in mean Brief Pain Inventory (BPI) worst pain/stiffness score from baseline based on linear regression adjusting for taxane use, prior history of osteoarthritis, and baseline BPI score. Significant reduction in pain from baseline for both omega-3 fatty acid and placebo groups at 6, 12, and 24 weeks ($P < .01$). No significant between-group differences.

Table 3. Between- and Within-Group Differences in Cholesterol and CRP in Women Receiving O3-FAs Versus Placebo

Treatment	Baseline			Week 12			Week 24			Difference (week 12 − baseline)				
	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	P*	P†
Cholesterol, mg/dL														
All	175	201.7	38.7	172	201.3	40.3	146	201.3	38.0	169	−1.0	27.8		.66
O3-FAs	85	201.6	37.5	80	200.9	39.2	74	202.9	34.9	79	−2.0	31.2	.56	
Placebo	90	201.9	40.0	92	201.7	41.5	72	199.7	41.2	90	−0.1	24.5	.97	
CRP, mg/L														
All	175	4.1	5.5	172	5.2	8.9	146	4.1	5.5	169	1.1	8.2		.71
O3-FAs	85	4.1	4.4	80	5.5	9.3	74	4.0	5.5	79	1.3	7.8	.13	
Placebo	90	4.2	6.3	92	5.0	8.6	72	4.3	5.6	90	0.9	8.6	.34	
HDL, mg/dL														
All	175	55.5	16.9	172	57.4	17.8	146	57.3	18.7	169	1.9	8.9		.25
O3-FAs	85	56.2	16.6	80	59.1	18.5	74	59.6	19.3	79	2.7	8.8	.007	
Placebo	90	54.8	17.2	92	55.8	17.1	72	55.1	18.0	90	1.1	9.0	.23	
LDL, mg/dL														
All	172	117.0	31.7	169	116.6	33.3	143	116.1	30.8	165	−0.7	23.4		.60
O3-FAs	85	117.7	32.9	79	118.8	35.1	73	118.4	30.3	78	0.3	27.5	.93	
Placebo	87	116.4	30.6	90	114.6	31.7	70	113.7	31.3	87	−1.7	19.2	.42	
Triglycerides, mg/dL														
All	175	144.6	88.3	172	134.4	84.1	146	134.0	79.1	169	−10.3	56.8		.01
O3-FAs	85	138.4	69.3	80	115.9	61.4	74	122.5	62.7	79	−22.1	52.1	< .001	
Placebo	90	150.5	103.2	92	150.5	97.2	72	145.7	92.1	90	0.0	59.0	1.00	

Abbreviations: CRP, C-reactive protein; O3-FA, omega-3 fatty acid; SD, standard deviation.
*P value for paired *t* tests for difference between baseline and week-12 measures within treatment arm.
†P value for unpaired *t* tests for difference in change measures between treatment arms.

studies have been limited by small sample size, inconsistent definitions, and lack of objective outcome measures. A randomized trial evaluating vitamin D for the prevention of AI arthralgia reported that 61% of controls and 38% of those receiving vitamin D had an increase in pain after initiation of treatment.[34] In addition, duloxetine,[35] glucosamine chondroitin,[36] testosterone,[37] prednisolone,[38] and switching therapies[39] have all been evaluated in uncontrolled trials. Prospective double-blind studies are currently evaluating duloxetine

and transdermal testosterone. Future studies may consider evaluating the effect of soy.

The mechanism of AI-associated arthralgia is unknown; however, preliminary evidence suggests there is an inflammatory component, which was a factor influencing the evaluation of O3-FAs. In a study conducted by Dizdar et al,[40] women receiving AIs had increased tendon thickness and higher rates of effusions in hand joints/tendons on musculoskeletal sonography, compared with women who never

Table 4. Proportion of Patients With Abnormal* Lipid Profiles at Baseline and 12 and 24 Weeks by Treatment Arm

Assay	Baseline			Week 12			Week 24		
	No.	%	P	No.	%	P	No.	%	P
Cholesterol ≥ 200 mg/dL			.72			.74			.41
O3-FAs	43	50.6		42	52.5		41	55.4	
Placebo	48	53.3		46	50.0		35	48.6	
CRP ≥ 5 mg/L			.46			.35			.37
O3-FAs	24	28.2		27	33.8		14	18.9	
Placebo	21	23.3		25	27.2		18	25.0	
HDL ≤ 40 mg/dL			.33			.48			.32
O3-FAs	9	10.6		10	12.5		9	12.2	
Placebo	14	15.6		15	16.3		13	18.1	
LDL ≥ 100 mg/dL			.92			.49			.86
O3-FAs	61	71.8		54	68.4		49	67.1	
Placebo	63	72.4		57	63.3		46	65.7	
Triglycerides ≥ 150 mg/dL			.66			.11			.31
O3-FAs	32	37.6		19	23.8		20	27.0	
Placebo	31	34.4		32	34.8		25	34.7	

Abbreviations: CRP, C-reactive protein; O3-FA, omega-3 fatty acid.
*As defined by National Institute of Health, National Heart Lung and Blood, guidelines.

received AIs.[40-42] There may also be an autoimmune component to the syndrome; in mouse models where aromatase was knocked out, the mice manifested symptoms similar to Sjögren's syndrome.[43] A better understanding of the mechanism of action may assist in the identification of interventions to control or prevent this common adverse effect that can result in decreased adherence and diminished quality of life.

Anastrozole results in significantly fewer thromboembolic and cerebrovascular events compared with tamoxifen and a similar incidence of ischemic cardiovascular events.[2] However, in 2008, the US Food and Drug Administration issued a black-box warning for anastrozole as a result of data from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial suggesting that women with pre-existing ischemic heart disease were at increased risk of ischemic cardiovascular events with anastrozole compared with tamoxifen (17% v 10%).[2,44] In comparison with placebo after tamoxifen in the MA.17 adjuvant trial, patients receiving letrozole experienced significant increases from baseline in total cholesterol, LDL cholesterol, and lipoprotein A.[21] In our study, we found a surprisingly high baseline rate of unfavorable lipid levels in those receiving an AI. Although it was encouraging that the group randomly assigned to O3-FAs had significant lowering of triglyceride levels and a suggestion of an increase in HDL levels, further research is necessary to determine optimal monitoring and treatment of hypercholesterolemia in this population of cancer survivors.

In summary, we found no evidence that O3-FAs improved joint pain or stiffness associated with AIs any more than placebo; however, we did find a large reduction in symptoms in both the treatment and placebo groups. Currently, there are no proven therapies for the treatment or prevention of AI-induced arthralgia; therefore, determination of optimal approaches to define, treat, and prevent this adverse effect is necessary. The high prevalence of unfavorable lipid profiles in this cohort suggests that more efforts are needed to manage long-term comorbidities in cancer survivors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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1917

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Multicenter Placebo-Controlled Trial of Omega-3 Fatty Acids for the Control of Aromatase Inhibitor–Induced Musculoskeletal Pain: SWOG S0927

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Appendix

Table A1. Mean M-SACRAH, WOMAC, and FACT-ES Scores at 6, 12, and 24 Weeks											
		Observed Results						Adjusted Results*			
		Baseline†		Follow-Up			Follow-Up				
Analysis	No. of Patients	Mean	95% CI	Mean	95% CI	Difference‡	Mean	95% CI	Difference‡	95% CI	P
M-SACRAH											
Week 6						−3.5			−1.77	−6.16 to 2.63	.43
O3-FAs	107	35.6	31.1 to 40.1	28.7	24.4 to 33.0		29.6	25.2 to 34.0			
Placebo	115	38.3	34.4 to 42.3	32.2	28.3 to 36.2		31.4	27.0 to 35.8			
Week 12						−0.6			0.72	−4.17 to 5.60	.77
O3-FAs	100	34.9	30.3 to 39.6	28.1	23.2 to 33.0		28.8	23.9 to 33.7			
Placebo	107	37.3	33.2 to 41.4	28.7	24.9 to 32.6		28.1	23.2 to 33.0			
Week 24						−2.3			−0.99	−6.32 to 4.34	.72
O3-FAs	92	35.2	30.4 to 39.9	24.2	19.3 to 29.1		24.8	19.5 to 30.2			
Placebo	97	37.8	33.4 to 42.2	26.5	22.4 to 30.5		25.8	20.5 to 31.2			
WOMAC											
Week 6						−0.4			−1.19	−5.74 to 3.37	.61
O3-FAs	108	49.1	45.2 to 53.0	38.2	33.7 to 42.8		37.8	33.2 to 42.3			
Placebo	115	47.9	43.9 to 51.9	38.6	34.2 to 42.9		39.0	34.4 to 43.5			
Week 12						−0.7			−2.13	−7.30 to 3.04	.42
O3-FAs	100	49.5	45.4 to 53.6	35.3	30.4 to 40.2		34.5	29.4 to 39.7			
Placebo	107	47.4	43.3 to 51.6	36.0	31.6 to 40.4		36.7	31.5 to 41.8			
Week 24						−1.3			−2.41	−8.13 to 3.31	.41
O3-FAs	93	49.0	44.7 to 53.3	31.4	26.4 to 36.4		30.8	25.1 to 36.6			
Placebo	97	47.3	43.0 to 51.6	32.7	28.1 to 37.4		33.2	27.5 to 39.0			
FACT-ES											
Week 6						−1.1			1.37	−1.47 to 4.21	.35
O3-FAs	108	87.4	84.2 to 90.5	92.5	89.2 to 95.8		93.8	91.0 to 96.7			
Placebo	115	90.6	87.6 to 93.7	93.6	90.7 to 96.6		92.4	89.6 to 95.3			
Week 12						−0.2			2.14	−1.16 to 5.44	.21
O3-FAs	100	87.8	84.5 to 91.1	93.8	90.4 to 97.2		95.0	91.7 to 98.3			
Placebo	107	90.9	87.8 to 94.0	94.0	90.7 to 97.2		92.8	89.5 to 96.1			
Week 24						−0.3			1.44	−2.07 to 4.95	.42
O3-FAs	93	88.4	84.9 to 91.8	96.9	93.3 to 100.4		97.8	94.3 to 101.3			
Placebo	97	90.8	87.4 to 94.3	97.2	93.8 to 100.6		96.3	92.8 to 99.8			
Analgesic use§											
Week 6						−0.13			−0.09	−0.81 to 0.63	.80
O3-FAs	68	5.49	4.79 to 6.18	4.82	4.13 to 5.52		4.84	4.30 to 5.38			
Placebo	82	5.54	4.78 to 6.30	4.95	4.14 to 5.77		4.93	4.44 to 5.43			
Week 12						−0.42			−0.53	−1.39 to 0.33	.23
O3-FAs	64	5.70	5.00 to 6.40	4.84	4.08 to 5.60		4.79	4.16 to 5.41			
Placebo	69	5.55	4.78 to 6.32	5.26	4.43 to 6.10		5.31	4.71 to 5.92			
Week 24						−0.004			0.10	−0.83 to 1.03	.84
O3-FAs	62	4.52	4.68 to 6.16	4.92	4.12 to 5.72		4.97	4.30 to 5.65			
Placebo	65	5.65	4.84 to 6.45	4.92	4.21 to 5.63		4.87	4.21 to 5.53			

Abbreviations: BPI, Brief Pain Inventory; FACT-ES, Functional Assessment of Cancer Therapy–Endocrine Symptoms; M-SACRAH, Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands; O3-FA, omega-3 fatty acid; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
*From linear regression adjusting for baseline BPI score and stratification factors (osteoarthritis, prior taxane exposure).
†Among patients with week-6, -12, or -24 worst pain scores, respectively.
‡Difference derived from O3-FAs minus placebo. (for M-SACRAH and WOMAC).
§Frequency of analgesic use, where 1 = ≤ one pill per week, 2 = two to three pills per week, 3 = four to six pills per week, 4 = one pill/ per day, and 5 = ≥ one pill per day. Value is sum of frequencies of use of acetaminophen, ibuprofen, other nonsteroidal anti-inflammatory drugs, narcotics, other pain medication, and aspirin. At each time point, < 5% of participants took narcotics.

	O3-FA Arm (n = 115)						Placebo (n = 124)					
Adverse Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Abdominal pain	114	1	0	0	0	0	124	0	0	0	0	0
ALP increased	115	0	0	0	0	0	123	1	0	0	0	0
Allergic reaction	115	0	0	0	0	0	123	0	1	0	0	0
Arthralgia	96	7	12	0	0	0	102	5	16	1	0	0
Back pain	114	0	1	0	0	0	122	2	0	0	0	0
Bloating	110	3	2	0	0	0	122	2	0	0	0	0
Blood or lymph disorder—other	114	1	0	0	0	0	124	0	0	0	0	0
Bone pain	114	1	0	0	0	0	124	0	0	0	0	0
Breast pain	115	0	0	0	0	0	123	1	0	0	0	0
Chest pain—cardiac	115	0	0	0	0	0	123	0	1	0	0	0
Constipation	113	2	0	0	0	0	123	1	0	0	0	0
Cough	114	1	0	0	0	0	123	1	0	0	0	0
Diarrhea	100	10	4	1	0	0	118	5	1	0	0	0
Dizziness	114	1	0	0	0	0	124	0	0	0	0	0
Dry mouth	115	0	0	0	0	0	122	2	0	0	0	0
Dry skin	115	0	0	0	0	0	123	0	1	0	0	0
Dysgeusia	112	3	0	0	0	0	124	0	0	0	0	0
Dyspepsia	95	11	8	1	0	0	112	7	5	0	0	0
Dysphagia	115	0	0	0	0	0	122	2	0	0	0	0
Epistaxis	115	0	0	0	0	0	123	1	0	0	0	0
Esophagitis	115	0	0	0	0	0	123	0	1	0	0	0
Fatigue	113	1	1	0	0	0	124	0	0	0	0	0
Fever	115	0	0	0	0	0	123	0	1	0	0	0
Flatulence	113	1	1	0	0	0	123	1	0	0	0	0
Flu-like symptoms	114	1	0	0	0	0	123	1	0	0	0	0
GERD	114	1	0	0	0	0	123	0	1	0	0	0
GI disorders—other (specify)	114	1	0	0	0	0	124	0	0	0	0	0
Headache	114	1	0	0	0	0	124	0	0	0	0	0
Hot flashes	115	0	0	0	0	0	123	1	0	0	0	0
Insomnia	115	0	0	0	0	0	123	1	0	0	0	0
Mucositis oral	115	0	0	0	0	0	123	0	1	0	0	0
Nausea	106	9	0	0	0	0	110	12	2	0	0	0
Pain	115	0	0	0	0	0	122	0	1	1	0	0
Pain in extremity	113	1	0	1	0	0	122	1	1	0	0	0
Paresthesia	114	1	0	0	0	0	124	0	0	0	0	0
Peripheral motor neuropathy	115	0	0	0	0	0	123	0	0	1	0	0
Pruritus	115	0	0	0	0	0	122	0	2	0	0	0
Purpura	114	1	0	0	0	0	124	0	0	0	0	0
ROM decreased	109	6	0	0	0	0	117	2	5	0	0	0
Rash acneiform	115	0	0	0	0	0	123	0	1	0	0	0
Rash maculopapular	114	1	0	0	0	0	123	0	0	1	0	0
Respiratory, thoracic, or mediastinal disorder	115	0	0	0	0	0	123	0	1	0	0	0
Sore throat	115	0	0	0	0	0	123	1	0	0	0	0
Weight gain	112	3	0	0	0	0	119	4	1	0	0	0
Maximum-grade any adverse event	57	30	25	3	0	0	74	19	27	4	0	0

Table A2. Adverse Events

NOTE. Investigators were instructed to document only those adverse events related to blinded protocol treatment (O3-FAs or placebo) and joint pain/stiffness resulting from aromatase inhibitor treatment.

Abbreviations: ALP, alkaline phosphatase; GERD, gastroesophageal reflux disease; O3-FA, omega-3 fatty acid; ROM, range of motion.