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Assessment of early therapy discontinuation and health-related quality of life in breast cancer patients treated with aromatase inhibitors: B-ABLE cohort study

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Abstract

Purpose

The most frequent adverse effects of aromatase inhibitors (AI) are arthralgia and bone loss induction. These reduce the quality of life of patients and their adherence to the treatment. This study evaluates the early AI cessation caused by AI intolerance, and the evolution of joint pain and health-related quality of life (HRQoL) during AI treatment until 1-year after AI completion.

Methods

Data of 910 women diagnosed with early breast cancer and candidates for AI were recruited in B-ABLE cohort. AI discontinuation was analyzed by survival analysis, including Kaplan–Meier estimation and Cox regression. Patients were distributed in three groups of the study according to previous tamoxifen (TAM) exposure and length of AI treatment: TAM-2yAI, TAM-3yAI, and 5yAI. Evolution of joint pain and HRQoL in osteoporosis was evaluated using Visual Analog Scale (VAS) and ECOS-16 tests, respectively, from baseline to 1-year after AI completion through repeated-measures ANOVA.

Results

Risk of AI discontinuation was increased in patients previously exposed to tamoxifen compared to non-exposed (adjusted HR 5.30 [95% CI 2.23 to 12.57]). VAS and ECOS-16 scores of TAM-2yAI and TAM-3yAI groups increased during AI treatment, mainly during the first 3–12 months. After 1-year from AI completion, values tend to decrease to baseline levels. In

5yAI group, VAS and ECOS-16 levels increased at three months, and VAS remained significantly higher at 1-year post-treatment.

Conclusions

AI therapy increased joint pain and reduced HRQoL, mainly during the first year of treatment. Patients previously treated with tamoxifen experienced greater pain when they switched to AI therapy and had an excess risk of discontinuation during the first 12 months.

Trial registration

ClinicalTrials.gov: NCT03811509. Registered 28 January 2018-
Retrospectively registered, <https://clinicaltrials.gov/ct2/show/NCT03811509>.

Keywords

Aromatase inhibitors

Tamoxifen

Breast cancer

Joint pain

Arthralgia

Health-related quality of life

B-ABLE cohort

Introduction

Aromatase inhibitors (AI) are the recommended therapy for early estrogen-receptor-positive breast cancer [1]. The introduction of AIs has improved the overall survival to 80% [2, 3]. However, this therapy has been related to several side effects that reduce the quality of life of these patients and their adherence to AI treatment [4]. The most frequent adverse effects are arthralgia—defined as joint pain—and bone loss induction [5, 6, 7].

Joint pain etiology due to AIs remains unknown, but has been related to estrogen depletion [8]. Additionally, decreased estrogen production induces bone loss, and therefore increases the risk of fragility fracture [9], morbidity, and mortality [10]. Validated tools for pain and health impairment assessment

include Visual Analog Scale (VAS) and health-related quality of life (HRQoL) in osteoporosis (ECOS-16) [11, 12, 13]. The VAS has also been widely used in breast cancer patients, including the Barcelona–Aromatase induced Bone Loss in Early breast cancer (B-ABLE) cohort [14, 15], whereas ECOS-16 has not been validated in these patients.

The B-ABLE cohort is a prospective, clinical cohort study of women diagnosed with early breast cancer and candidates for AI treatment that aims to improve the quality of life in patients with breast cancer (ClinicalTrials.gov Identifier: NCT03811509) [16]. Previous findings in the B-ABLE cohort have described a worsening of joint pain in 50% of patients at 3 and 12 months after starting AI treatment, and an increased bone loss in up to 45% of patients after 2 years of AI treatment [15, 17].

The main objective of this study was to evaluate early cessation of AI due to patient intolerance in the B-ABLE cohort. Additionally, evolution of joint pain and HRQoL during AI treatment, and up to 1-year post-treatment, was assessed.

Materials and methods

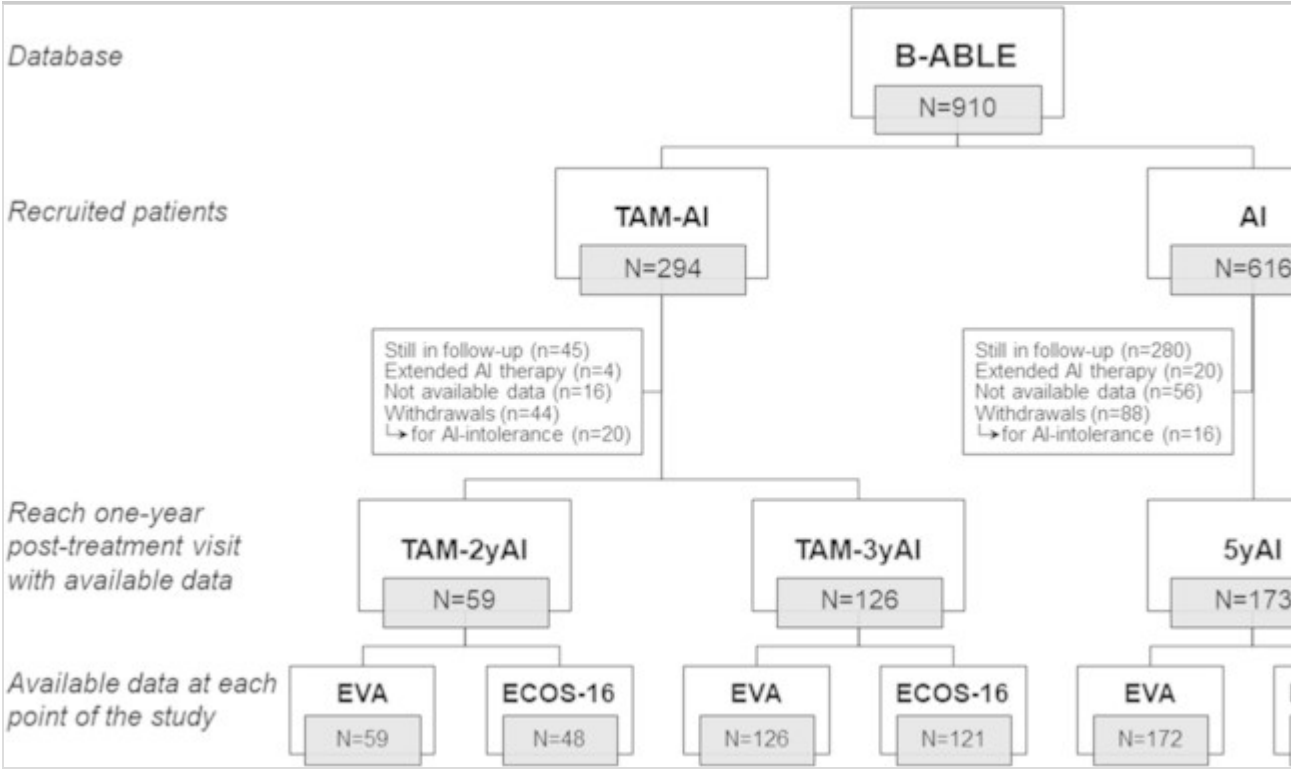
Study design

The B-ABLE cohort is a prospective, interventional, clinical cohort study of postmenopausal women diagnosed with early estrogen-receptor-positive breast cancer and candidates for AI (letrozole or exemestane) [16, 18]. Patients were recruited from January 2006 to June 2018 in Hospital del Mar (Barcelona, Spain). End of treatment was considered a total of 5 years of hormonal adjuvant therapy, according to American Society of Clinical Oncology recommendations [19].

Participants

Participants were included upon starting AI therapy, either 6 weeks post-surgery or 1 month after the last cycle of chemotherapy (AI patients) for a 5-year treatment program (5yAI group); or alternatively, after taking tamoxifen (TAM-AI-patients) for 2–3 years and initiating AI to complete 5 years of anti-estrogen therapy (TAM-2yAI and TAM-3yAI groups) (Fig. 1). Postmenopausal status was defined as patients > 55 years old with amenorrhea for > 12 months, or those ≤ 55 with luteinizing hormone levels > 30 mIU/mL or follicle-stimulating hormone values > 40 mIU/mL.

Fig. 1
Flowchart of patients from B-ABLE cohort included in the study. 2y 2 years, 3y 3 years, 5y 5 years, *AI* aromatase inhibitor, *ECOS-16* health-related quality of life questionnaire in osteoporosis, *TAM* tamoxifen, *VAS* visual analogic scale



AQ1

Data for a number of demographic and clinical variables were collected, including age at recruitment, body mass index (BMI), and bone mineral density (BMD) among others. Exclusion criteria included previous history of any metabolic, endocrine, or bone diseases, as well as alcoholism, rheumatoid arthritis, and concurrent or prior treatment with bisphosphonates (BP), oral corticosteroids, or any other bone-active drug except tamoxifen. Those who developed osteoporosis during the treatment were immediately prescribed oral BP treatment and censored from the study.

Additionally, all participants received supplements of calcium and 25(OH)vitD3 tablets (1000 mg and 800 IU daily, respectively), and those with baseline 25-hydroxyvitamin D deficiency (< 30 ng/mL) received an additional dose of 16,000 IU of oral calcifediol (HIDROFEROL® FAES FARMA) every 2 weeks.

Study outcomes

Treatment discontinuation due to AI intolerance

Participants who decided to discontinue AI treatment due to an intolerable increase in joint pain were designated as AI-intolerant.

VAS

Visual analogic scale (VAS) was used to score the intensity of self-reported joint pain at baseline (before starting AI therapy), at 3 months and every 12 months until 1 year after concluding AI therapy. Score ranged from 0 (no pain) to 10 (maximum pain). The question associated to the VAS reads as follows (translated from Catalan and Spanish by the authors): “please, score the intensity of the pain you feel in your peripheral joints (knee, wrist, fingers/toes, elbow, shoulder, etc.), excluding spine/back pain and pain at the operated area” [14].

ECOS-16

The ECOS-16 questionnaire is a short version of the combination of the Osteoporosis Quality Of Life Questionnaire and the Quality of Life Questionnaire of the European Foundation for Osteoporosis [12].

ECOS-16 was used to score the assessment of health-related quality of life (HRQoL) in osteoporosis at baseline (before starting AI therapy), 3 months and every 12 months until 1 year after concluding AI therapy. Score ranged from 12 (best possible health status) to 75 (worst possible health status).

Statistical methods

Cumulative hazard plots and Cox proportional hazards models by Kaplan–Meier estimation were carried out. Hazard ratios (HR) are reported with 95% confidence intervals [95% CI], using patients non-exposed to tamoxifen (AI patients) as reference group. Additionally, proportionality assumption was tested. Survival analysis was adjusted by age, body mass index, BP use, and baseline VAS and ECOS-16 scores. Survival analysis of AI-intolerants according to previous tamoxifen exposure was analyzed in all B-ABLE participants.

Baseline differences between groups of participants who completed AI treatment were assessed by one-way ANOVA. VAS and ECOS-16 changes in each group were analyzed by repeated-measures ANOVA from baseline to each appointment, until 1 year after AI therapy conclusion. Interaction of BP

with study outcomes was tested.

Statistical analysis was carried out using R for Windows version 3.3.3 (foreign, compare Groups, plyr, and ggplot2 packages) and SPSS Statistics version 22.0. *P* values lower than 0.05 were considered significant, and all statistical contrasts were corrected by Bonferroni test for multiple comparisons.

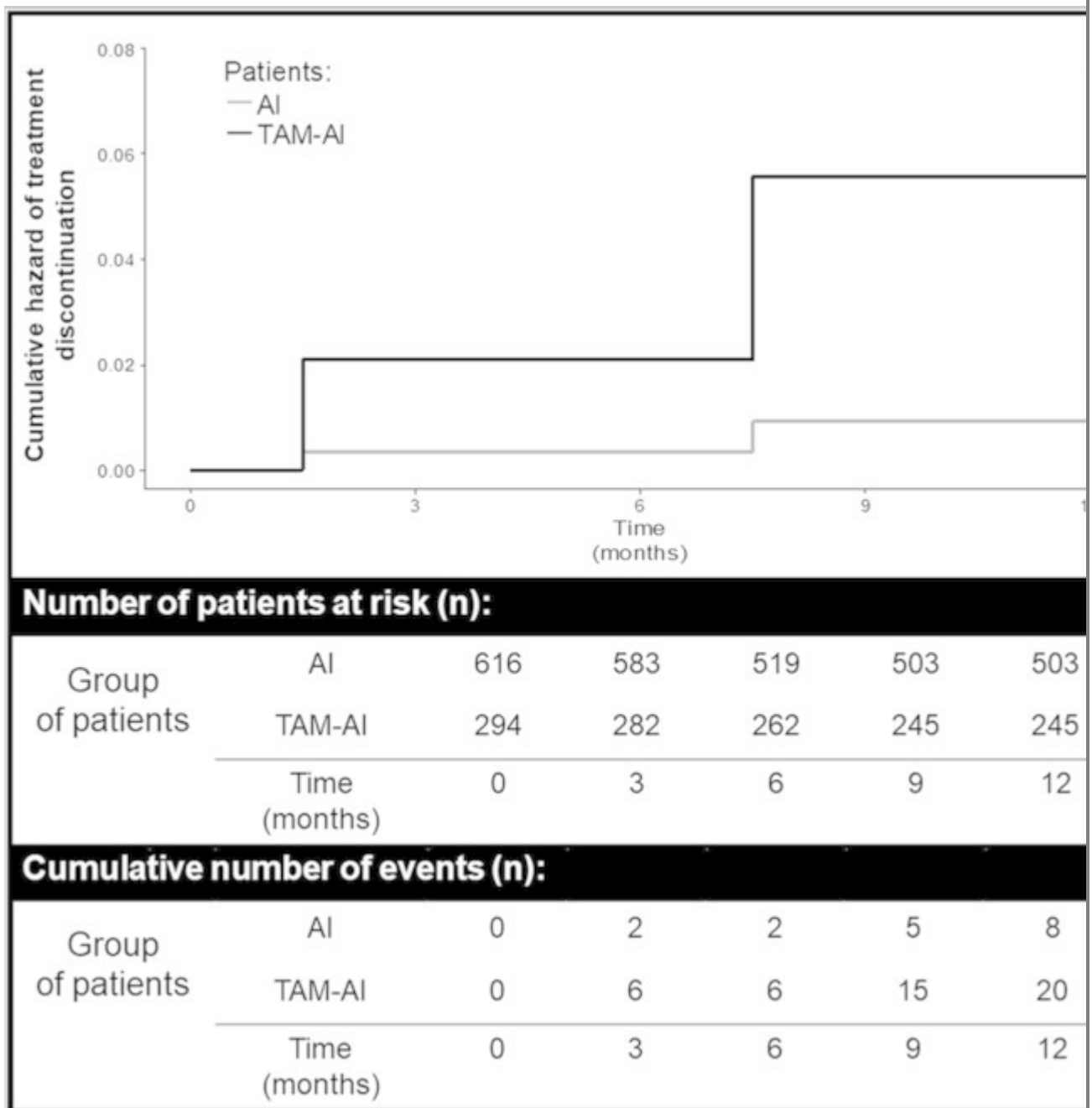
Results

AI discontinuation

Of 910 patients recruited in the B-ABLE cohort, 36 interrupted their treatment due to AI intolerance, of which 20 patients (55.6%) had previous tamoxifen exposure (TAM-AI patients) and 16 (44.4%) were not exposed (AI patients). In survival analysis, proportionality assumption was significant ($p < 0.05$). For this reason, data were censored at 12 months of follow-up (Fig. 2). Unadjusted Cox analysis estimated a discontinuation HR of 5.10 [95% CI 2.25 to 11.58] in the TAM-AI group, compared with AI patients. After adjustment, HR was 5.30 [95% CI 2.23 to 12.57] ($p < 0.01$). Moreover, in the adjustment, higher baseline VAS levels were associated with AI intolerance (HR; 1.26 [95% CI 1.06 to 1.49], $p < 0.05$).

Fig. 2

Cumulative hazard plot of treatment discontinuation due to AI intolerance. Kaplan–Meier curve shows early AI cessation due to extreme pain, in terms of cumulative hazards. *AI* patients treated with aromatase inhibitors, *TAM-AI* patients previously treated with tamoxifen who switched to AI therapy



Pain evolution during AI treatment

Currently, 358 participants had completed AI treatment and VAS and/or ECOS-16 values recorded for all appointments, including the post-treatment visit at 1-year follow-up. Baseline characteristics of patients are detailed in Table 1. The TAM-3yAI group was younger and had lower BMI, compared to the 5yAI group ($p < 0.001$ and $p < 0.05$, respectively). The groups did not differ in baseline VAS and ECOS-16 scores nor in the proportion of patients treated with BP.

Table 1

Baseline characteristics of selected participants

	TAM-2yAI (<i>n</i> = 59)	TAM-3yAI (<i>n</i> = 126)	5yAI (<i>n</i> = 173)	<i>p</i> value
Age (mean ± SD)	60.3 ± 9.81	58.1 ± 8.71 ^a	62.8 ± 6.99	< 0.001
BMI (mean ± SD)	28.4 ± 5.73	27.9 ± 5.14 ^b	29.7 ± 4.85	0.013
BP [<i>n</i> (%)]	19 (32.2%)	27 (21.4%)	35 (20.2%)	0.152
VAS (mean ± SD)	2.45 ± 2.31	2.39 ± 2.46	2.19 ± 2.28	0.681
ECOS-16 (mean ± SD)	27.4 ± 10.9	26.2 ± 13.6	24.3 ± 10.7	0.160
2y 2 years, 3y 3 years, 5y 5 years, <i>AI</i> aromatase inhibitor, <i>BMI</i> body mass index, <i>BP</i> bisphosphonates, <i>VAS</i> visual analogic scale, <i>ECOS-16</i> evaluation of health-related quality of life in osteoporosis, <i>TAM</i> tamoxifen				
In one-way ANOVA, differences in post hoc comparisons are annotated as ^a (<i>p</i> value < 0.001) and ^b (<i>p</i> value < 0.05), compared with 5yAI group				

VAS score

Absolute VAS values during follow-up are reported in Table 2. Mean values of absolute changes in VAS from baseline to post-treatment are summarized in Fig. 3. Repeated-measures ANOVA in each group showed significant differences in VAS progression during follow-up ($p < 0.001$). No significant interaction effect was found between VAS and BP ($p > 0.05$).

Table 2

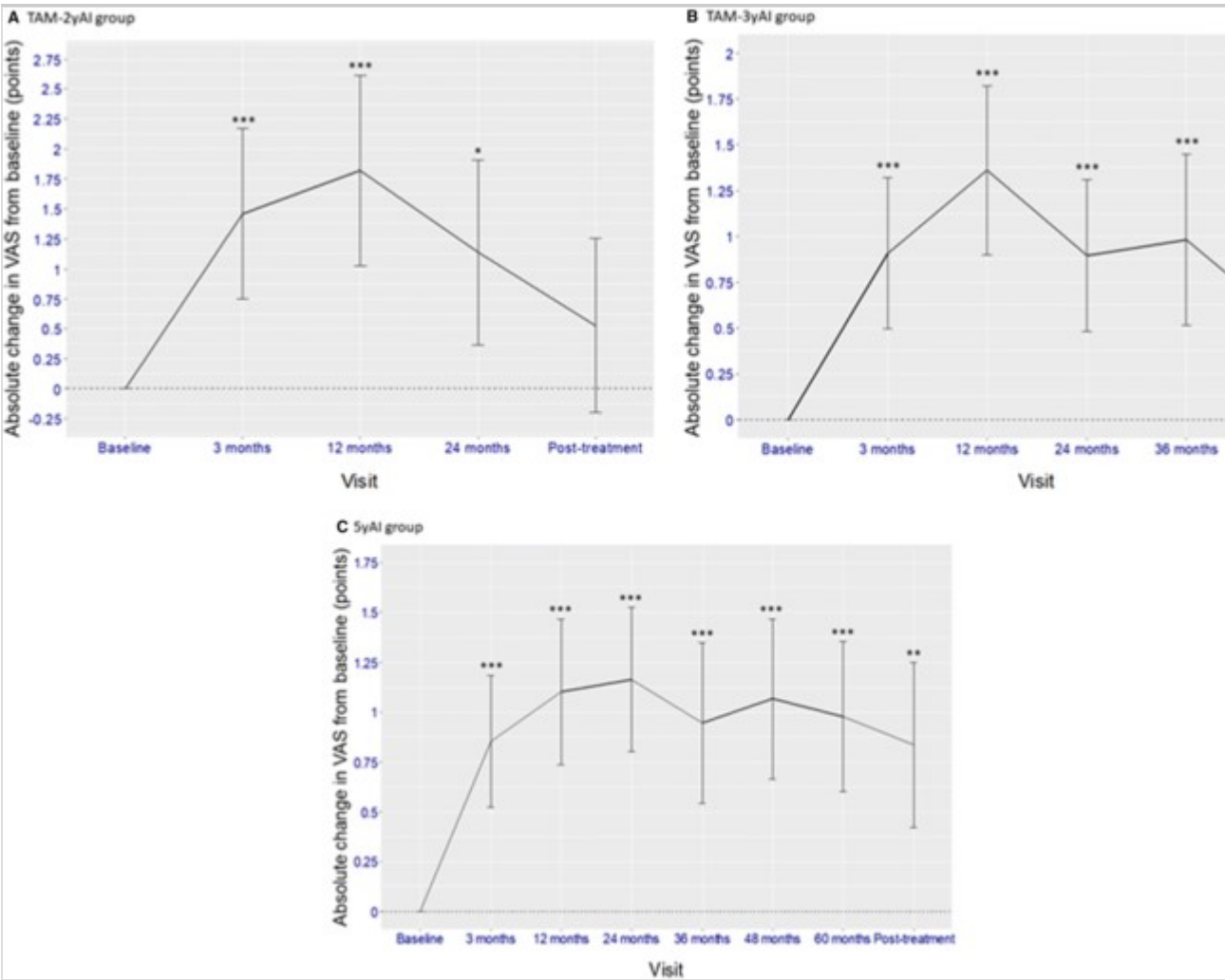
Absolute VAS values at each appointment, from baseline to one-year post-treatment, in each group

	TAM-2yAI (<i>n</i> = 59) Mean ± SD	TAM-3yAI (<i>n</i> = 126) Mean ± SD	5yAI (<i>n</i> = 172) Mean ± SD
Baseline	2.45 ± 2.31	2.39 ± 2.46	2.16 ± 2.24
3 months	3.91 ± 2.84	3.29 ± 2.83	3.01 ± 2.68
12 months	4.27 ± 2.96	3.75 ± 2.65	3.26 ± 2.76
24 months	3.58 ± 2.97	3.28 ± 2.65	3.32 ± 2.68
2y 2 years, 3y 3 years, 5y 5 years, <i>AI</i> aromatase inhibitor, <i>n/a</i> non-applicable, <i>SD</i> standard deviation, <i>TAM</i> tamoxifen			

	TAM-2yAI (<i>n</i> = 59) Mean ± SD	TAM-3yAI (<i>n</i> = 126) Mean ± SD	5yAI (<i>n</i> = 172) Mean ± SD
36 months	n/a	3.37 ± 2.86	3.10 ± 2.79
48 months	n/a	n/a	3.22 ± 2.77
60 months	n/a	n/a	3.14 ± 2.88
Post-treatment	2.97 ± 2.58	2.92 ± 3.22	2.99 ± 2.89

2y 2 years, 3y 3 years, 5y 5 years, AI aromatase inhibitor, n/a non-applicable, SD standard deviation, TAM tamoxifen

Fig. 3
Individual absolute change in VAS score during follow-up in each group of patients. **a** TAM-2yAI, **b** TAM-3yAI, and **c** 5yAI. Mean ± 95% CI is reported. Post hoc comparisons from baseline in repeated-measures ANOVA: **p* < 0.05, ***p* < 0.01, ****p* < 0.001. 2y 2 years, 3y 3 years, 5y 5 years, AI aromatase inhibitor, TAM tamoxifen



TAM-2yAI patients

In Fig. 3a, a significant increase of joint pain was observed at 3 months (1.46 [95% CI 0.74 to 2.17], $p < 0.01$), 12 months (1.82 [95% CI 1.03 to 2.61], $p < 0.001$), and 24 months (1.14 [95% CI 0.37 to 1.91], $p < 0.05$), compared to baseline. At 1-year post-treatment, VAS levels were comparable to baseline values (0.53 [95% CI -0.20 to 1.25], $p = 1.00$).

TAM-3yAI patients

Likewise, TAM-3yAI patients (Fig. 3b) reported a significant increase of joint pain at 3 months (0.91 [95% CI 0.50 to 1.32], $p < 0.001$), 12 months (1.36 [95% CI 0.90 to 1.82], $p < 0.001$), 24 months (0.88 [95% CI 0.48 to 1.31], $p < 0.001$), and 36 months (0.98 [95% CI 0.51 to 1.44], $p < 0.001$), compared to baseline values. At 1-year post-treatment, joint pain was comparable to baseline VAS values (0.53 [95% CI 0.05 to 1.01], $p = 0.46$).

5yAI patients

As shown in Fig. 3c, joint pain was significantly increased at each appointment during AI treatment ($p < 0.001$ for all), compared to baseline VAS values (3 months: 0.85 [95% CI 0.52 to 1.18; 12 months: 1.10 [95% CI 0.74 to 1.47]; 24 months: 1.16 [95% CI 0.80 to 1.52]; 36 months 0.95 [95% CI 0.54 to 1.35]; 48 months: 1.07 [95% CI 0.66 to 1.47]; 60 months 0.98 [95% CI 0.60 to 1.35]) and also at 1 year post-treatment ($p < 0.01$): VAS 0.83 [95% CI 0.42 to 1.25].

A sub-analysis of patients reporting a clinically relevant change during the follow-up (VAS change ≥ 2 points from baseline) showed the greatest increases in joint pain during the first 3–12 months: 36 patients (61.02%) in the TAM-2yAI group had a mean VAS change of 2.81 [95% CI 1.98 to 5.26] at 3 months and 3.48 [95% CI 2.58 to 6.11] at 12 months; in the TAM-3yAI group, 81 patients (64.29%) had a mean change of 1.73 [95% CI 1.23 to 4.02] at 3 months and 2.57 [95% CI 2.06 to 4.88] at 12 months; and 117 patients (68.02%) in the 5yAI group had a mean change of 1.37 [95% CI 0.93 to 3.73] at 3 months and 1.92 [95% CI 1.48 to 4.37] 12 months.

ECOS-16 score

Absolute ECOS-16 values during follow-up are reported in Table 3 and the mean values of absolute changes from baseline to post-treatment are summarized in Fig. 4. Repeated-measures ANOVA showed significant

differences in ECOS-16 during follow-up in each group (TAM-2yAI: $p < 0.05$; TAM-3yAI: $p < 0.05$; and 5yAI: $p < 0.001$). No significant interaction effect was found between ECOS-16 and BP ($p > 0.05$).

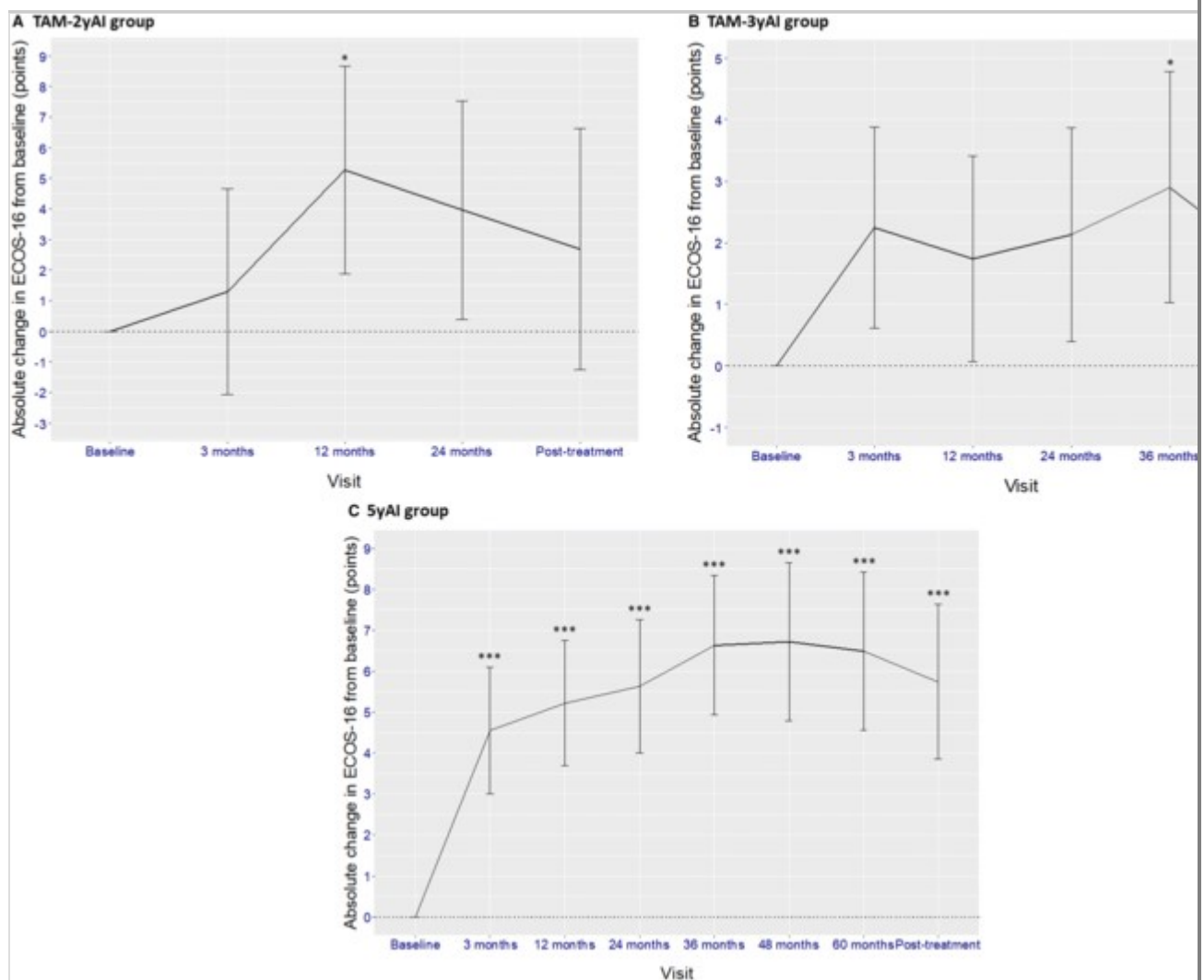
Table 3

Absolute ECOS-16 values at each appointment, from baseline to one-year post-treatment, in each group

	TAM-2yAI (<i>n</i> = 48) Mean ± SD	TAM-3yAI (<i>n</i> = 121) Mean ± SD	5yAI (<i>n</i> = 169) Mean ± SD
Baseline	26.79 ± 11.45	25.55 ± 13.39	24.28 ± 10.63
3 months	28.08 ± 12.95	27.80 ± 13.60	28.85 ± 14.33
12 months	32.06 ± 15.64	27.29 ± 13.33	29.50 ± 13.79
24 months	30.75 ± 14.01	27.69 ± 14.94	29.92 ± 14.33
36 months	n/a	28.45 ± 15.20	30.91 ± 15.20
48 months	n/a	n/a	31.01 ± 15.83
60 months	n/a	n/a	30.78 ± 14.98
Post-treatment	29.48 ± 15.07	27.24 ± 15.45	30.03 ± 14.86
2y 2 years, 3y 3 years, 5y 5 years, AI aromatase inhibitor, n/a non-applicable, SD standard deviation, TAM tamoxifen			

Fig. 4

Individual absolute change in ECOS-16 score during follow-up in each group of patients. **a** TAM-2yAI, **b** TAM-3yAI, and **c** 5yAI. Mean ± 95% CI is reported. Post hoc comparisons from baseline in repeated-measures ANOVA: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. 2y 2 years, 3y 3 years, 5y 5 years, AI aromatase inhibitor, TAM tamoxifen



TAM-2yAI patients

ECOS-16 score (Fig. 4a) was increased after starting AI treatment with the worst values detected after 12 months of treatment (5.27 [95% CI 1.87 to 16.97], $p < 0.05$).

TAM-3yAI patients

Similarly, in TAM-3yAI patients (Fig. 4b), ECOS-16 increased from baseline, with the greatest increase at 36 months (2.90 [95% CI 1.02 to 13.33], $p < 0.05$).

5yAI patients

Significant increases ($p < 0.001$) of ECOS-16 were observed at each follow-up visit, compared to baseline values (3 months: 4.56 [95% CI 3.02 to 14.73]; 12 months: 5.22 [95% CI 3.69 to 15.31]; 24 months: 5.64 [95% CI 4.01 to 16.35]; 36 months: 6.34 [95% CI 4.93 to 17.88]; 48 months: 6.72 [95% CI

4.79 to 19.43]; 60 months: 6.49 [95% CI 4.56 to 19.20]; and 1-year post-treatment: 5.75 [95% CI 3.85 to 18.20]).

Discussion

In this prospective study, a 3.96% of breast cancer patients treated with AI and recruited in the B-ABLE cohort discontinued treatment due to AI intolerance. Patients with previous exposure to tamoxifen therapy had a 430% increased risk of discontinuation during the first 12 months, compared to AI monotherapy. VAS and ECOS-16 scores increased rapidly in the first 3–12 months of treatment, and then stabilized. About 65% of all participants experienced arthralgia, according to VAS scores.

According to clinical trials and other published studies, up to 30% of patients discontinued AI due to its toxic effects [4], and 24.3% of patients discontinued due to musculoskeletal symptoms during the first 2 years, with a median of 6.1 months [20]. In contrast, discontinuation for AI intolerance was lower (3.96%) in the B-ABLE cohort, with an overall discontinuation during the treatment period of 14.51%. This difference might be explained by the vitamin D supplements prescribed, which diminished arthralgia levels [14], and the close monitoring of patients in the B-ABLE cohort, compared to usual care.

Furthermore, the present study considered previous tamoxifen therapy in evaluating pain reported by AI-treated patients. Hence, patients were distributed in three groups according to length of AI treatment, based on tamoxifen exposure: TAM-2yAI, TAM-3yAI, and 5yAI. VAS and ECOS-16 scores were recorded from baseline until 1-year post-treatment.

In TAM-2yAI and TAM-3yAI patients, VAS and ECOS-16 scores increased during AI treatment, mainly during the first 3–12 months. These levels were maintained and even slightly reduced until the end of AI treatment. At 1-year post-completion, values tended to decrease to baseline levels.

The 5yAI patients showed a rapid increase in VAS and ECOS-16 levels at 3 months of AI therapy; from this point on, values stabilized or increased slightly until end of treatment. In contrast to patients exposed to tamoxifen, joint pain in 5yAI patients decreased slightly after completing AI treatment but remained significantly higher at 1-year post-treatment.

Despite increased joint pain and the worsening of HRQoL that persisted after

AI completion in 5yAI patients, their absolute VAS levels were lower than patients previously treated with tamoxifen. These results are in accordance with Kadakia et al., who reported that previous tamoxifen users have a greater worsening in musculoskeletal symptoms and a significantly worse VAS score at 3 months of treatment, compared to non-users [4]. These higher joint pain levels observed in previous tamoxifen users might be associated with the early therapy discontinuation due to AI intolerance detected in TAM-AI patients of B-ABLE.

Other researchers have observed a decline in self-reported pain during the first year of treatment in patients using zoledronic acid [21]. However, oral BP therapy was not associated with AI intolerance, VAS, or ECOS-16 values in the B-ABLE cohort. Further research is needed to confirm or discard a potential role of BP in modulating joint pain in AI-treated patients.

A limitation of the study is that our cohort, recruited from the population served by our hospital, is likely more closely monitored than patients not included in a study cohort. Moreover, all patients in the B-ABLE received vitamin D supplements which may have contributed to decrease pain scores and the incidence of AI discontinuation in our study, compared to general clinical practice. Another limitation is the potential subjectivity of VAS and ECOS-16 outcomes, as pain is essentially a subjective perception influenced by a complex interaction of behavioral, environmental, biological, and social factors. However, the daily experience of toxic effects produced by therapies is comprehensively captured by self-reported pain assessment [22]. Likewise, pain has a high concordance with HRQoL [23, 24].

In conclusion, AI therapy increased joint pain and reduced HRQoL, measured by VAS and ECOS-16 scores, respectively, mainly during the first year of treatment. At 1-year post-treatment, both values returned to baseline levels in patients previously treated with tamoxifen, while patients treated with AI monotherapy for 5 years maintained higher levels of joint pain, compared to baseline. On the other hand, breast cancer patients previously treated with tamoxifen experienced greater pain when they switched to AI therapy and therefore had an excess risk of discontinuation during the first 12 months, compared to patients not exposed to tamoxifen. Strictly monitoring AI patients, especially previous tamoxifen users, might reduce the incidence of AI-treatment discontinuation.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval The ethics committee of Parc de Salut Mar (2016/6803/I) approved the study protocol, which was carried out in accordance with the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study after they had read the study information sheet and any questions had been answered. The privacy rights of human subjects are carefully protected in our institution.

References

1. Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KA, Giordano SH, Hudis CA, Solky AJ, Stearns V, Winer EP, Griggs JJ (2018) Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. <https://doi.org/10.1200/JCO.18.01160>
2. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, Forbes JF, Investigators AL (2010) Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol* 11(12):1135–1141. [https://doi.org/10.1016/S1470-2045\(10\)70257-6](https://doi.org/10.1016/S1470-2045(10)70257-6)

3. Regan MM, Neven P, Giobbie-Hurder A, Goldhirsch A, Ejlertsen B, Mauriac L, Forbes JF, Smith I, Lang I, Wardley A, Rabaglio M, Price KN, Gelber RD, Coates AS, Thurlimann B, Group BIGC, International Breast Cancer Study G (2011) Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol* 12(12):1101–1108. [https://doi.org/10.1016/S1470-2045\(11\)70270-4](https://doi.org/10.1016/S1470-2045(11)70270-4)
4. Kadakia KC, Snyder CF, Kidwell KM, Seewald NJ, Flockhart DA, Skaar TC, Desta Z, Rae JM, Otte JL, Carpenter JS, Storniolo AM, Hayes DF, Stearns V, Henry NL (2016) Patient-reported outcomes and early discontinuation in aromatase inhibitor-treated postmenopausal women with early stage breast cancer. *Oncologist* 21(5):539–546. <https://doi.org/10.1634/theoncologist.2015-0349>
5. Eastell R, Adams JE, Coleman RE, Howell A, Hannon RA, Cuzick J, Mackey JR, Beckmann MW, Clack G (2008) Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol* 26(7):1051–1057. <https://doi.org/10.1200/JCO.2007.11.0726>
6. Laroche F, Coste J, Medkour T, Cottu PH, Pierga JY, Lotz JP, Beerblock K, Tournigand C, Decleves X, de Cremoux P, Bouhassira D, Perrot S (2014) Classification of and risk factors for estrogen deprivation pain syndromes related to aromatase inhibitor treatments in women with breast cancer: a prospective multicenter cohort study. *J Pain* 15(3):293–303. <https://doi.org/10.1016/j.jpain.2013.11.004>
7. Pineda-Moncusi M, Servitja S, Casamayor G, Cos ML, Rial A, Rodriguez-Morera J, Tusquets I, Diez-Perez A, Garcia-Giralt N, Nogues X (2018) Bone health evaluation one year after aromatase inhibitors completion. *Bone* 117:54–59. <https://doi.org/10.1016/j.bone.2018.09.010>
8. Niravath P (2013) Aromatase inhibitor-induced arthralgia: a review. *Ann Oncol* 24(6):1443–1449. <https://doi.org/10.1093/annonc/mdt037>
9. Goldvaser H, Barnes TA, Seruga B, Cescon DW, Ocana A, Ribnikar D, Amir E (2018) Toxicity of extended adjuvant therapy with aromatase inhibitors in early breast cancer: a systematic review and meta-analysis. *J*

Natl Cancer Inst. <https://doi.org/10.1093/jnci/djx141>

10. Rizzoli R (2018) Postmenopausal osteoporosis: assessment and management. *Best Pract Res Clin Endocrinol Metab* 32(5):739–757. <https://doi.org/10.1016/j.beem.2018.09.005>

11. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP (2011) Validity of four pain intensity rating scales. *Pain* 152(10):2399–2404. <https://doi.org/10.1016/j.pain.2011.07.005>

12. Badia X, Diez-Perez A, Lahoz R, Lizan L, Nogues X, Iborra J (2004) The ECOS-16 questionnaire for the evaluation of health related quality of life in post-menopausal women with osteoporosis. *Health Qual Life Outcomes* 2:41. <https://doi.org/10.1186/1477-7525-2-41>

13. Hawker GA, Mian S, Kendzerska T, French M (2011) Measures of adult pain: visual analog scale for pain (VAS Pain), numeric rating scale for pain (NRS Pain), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-MPQ), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). *Arthritis Care Res (Hoboken)* 63(Suppl 11):S240–252. <https://doi.org/10.1002/acr.20543>

14. Prieto-Alhambra D, Javaid MK, Servitja S, Arden NK, Martinez-Garcia M, Diez-Perez A, Albanell J, Tusquets I, Nogues X (2011) Vitamin D threshold to prevent aromatase inhibitor-induced arthralgia: a prospective cohort study. *Breast Cancer Res Treat* 125(3):869–878. <https://doi.org/10.1007/s10549-010-1075-9>

15. Garcia-Giralt N, Rodriguez-Sanz M, Prieto-Alhambra D, Servitja S, Torres-Del Pliego E, Balcells S, Albanell J, Grinberg D, Diez-Perez A, Tusquets I, Nogues X (2013) Genetic determinants of aromatase inhibitor-related arthralgia: the B-ABLE cohort study. *Breast Cancer Res Treat* 140(2):385–395. <https://doi.org/10.1007/s10549-013-2638-3>

16. ClinicalTrials.gov (2019) Study for improving life quality in breast cancer women treated with aromatase inhibitors: cohort B-ABLE. Parc de Salut Mar, Instituto de Salud Carlos III, Hospital del Mar, Barcelona

17. Rodriguez-Sanz M, Prieto-Alhambra D, Servitja S, Garcia-Giralt N,

Garrigos L, Rodriguez-Morera J, Albanell J, Martinez-Garcia M, Gonzalez I, Diez-Perez A, Tusquets I, Nogues X (2016) AI-related BMD variation in actual practice conditions: a prospective cohort study. *Endocr Relat Cancer* 23(4):303–312. <https://doi.org/10.1530/ERC-16-0025>

18. Servitja S, Nogues X, Prieto-Alhambra D, Martinez-Garcia M, Garrigos L, Pena MJ, de Ramon M, Diez-Perez A, Albanell J, Tusquets I (2012) Bone health in a prospective cohort of postmenopausal women receiving aromatase inhibitors for early breast cancer. *Breast* 21(1):95–101. <https://doi.org/10.1016/j.breast.2011.09.001>

19. Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, Chlebowski RT, Gelber R, Edge SB, Gralow J, Cobleigh MA, Mamounas EP, Goldstein LJ, Whelan TJ, Powles TJ, Bryant J, Perkins C, Perotti J, Braun S, Langer AS, Browman GP, Somerfield MR (2005) American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol* 23(3):619–629. <https://doi.org/10.1200/JCO.2005.09.121>

20. Henry NL, Azzouz F, Desta Z, Li L, Nguyen AT, Lemler S, Hayden J, Tarpinian K, Yakim E, Flockhart DA, Stearns V, Hayes DF, Storniolo AM (2012) Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. *J Clin Oncol* 30(9):936–942. <https://doi.org/10.1200/JCO.2011.38.0261>

21. Santa-Maria CA, Bardia A, Blackford AL, Snyder C, Connolly RM, Fetting JH, Hayes DF, Jeter SC, Miller RS, Nguyen A, Quinlan K, Rosner GL, Slater S, Storniolo AM, Wolff AC, Zorzi J, Henry NL, Stearns V (2018) A phase II study evaluating the efficacy of zoledronic acid in prevention of aromatase inhibitor-associated musculoskeletal symptoms: the ZAP trial. *Breast Cancer Res Treat.* <https://doi.org/10.1007/s10549-018-4811-1>

22. Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, Appawu M, Iasonos A, Atkinson T, Goldfarb S, Culkin A, Kris MG, Schrag D (2009) Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. *J Natl Cancer Inst* 101(23):1624–1632. <https://doi.org/10.1093/jnci/djp386>

23. Wang J, Tang X, Shen Y, Shang G, Fang L, Wang R, Xu Y (2015) The correlations between health-related quality of life changes and pain and anxiety in orthodontic patients in the initial stage of treatment. *Biomed Res Int* 2015:725913. <https://doi.org/10.1155/2015/725913>
24. Kawai K, Kawai AT, Wollan P, Yawn BP (2017) Adverse impacts of chronic pain on health-related quality of life, work productivity, depression and anxiety in a community-based study. *Fam Pract* 34(6):656–661. <https://doi.org/10.1093/fampra/cmz034>