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ORIGINAL PAPER

Treatment with *Ruta graveolens* 5CH and *Rhus toxicodendron* 9CH may reduce joint pain and stiffness linked to aromatase inhibitors in women with early breast cancer: results of a pilot observational study

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Objective: **To determine the possible effect of two homeopathic medicines, *Ruta graveolens* 5CH and *Rhus toxicodendron* 9CH, in the prevention of aromatase inhibitor (AI) associated joint pain and/or stiffness in women with early, hormone-receptor positive, breast cancer.**

Methods: **This prospective, unrandomized observational study was carried out between April and October 2014. Women were recruited in two groups, according to which of the two study centres they attended: one receiving homeopathy in addition to standard treatment (group H) and a control group, receiving standard treatment (group C). All women were treated with an AI. In addition, women in group H also took *Ruta graveolens* 5CH and *Rhus toxicodendron* 9CH (5 granules, twice a day) up to 7 days before starting AI treatment. The homeopathic medicines were continued for 3 months. Demographic and clinical data were recorded using a self-assessment questionnaire at inclusion (T0) and 3 months (T3). Primary evaluation criteria were the evolution of scores for joint pain and stiffness, the impact of pain on sleep and analgesic consumption in the two groups after 3 months of treatment.**

Results: **Forty patients (mean age 64.9 ± 8.1 years) were recruited, 20 in each group. Two-thirds of the patients had joint pain before starting AI treatment. There was a significant difference in the evolution of mean composite pain score between T0 and T3 in the two groups (−1.3 in group H vs. +3.4 in group C; p = 0.0001). The individual components of the pain score (frequency, intensity and number of sites of pain) also decreased significantly in group H. Nine patients in group C (45%) vs. 1 (5%) in group H increased their analgesic consumption between T0 and T3 (p = 0.0076). After 3 months of treatment, joint pain had a worse impact on sleep in patients in group C (35% vs. 0% of patients; p = 0.0083). The differences observed in the evolution of morning and daytime stiffness between the two groups were smaller (p = 0.053 and p = 0.33, respectively), with the exception of time necessary for the disappearance of morning stiffness which was greater in group C (37.7 ± 23.0 vs. 17.9 ± 20.1 min; p = 0.0173).**

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Conclusion: **These preliminary results suggest that treatment with *Ruta graveolens* 5CH and *Rhus toxicodendron* 9CH may decrease joint pain/stiffness in breast cancer patients treated with AIs. A larger-scale randomized study is required to confirm these results.** *Homeopathy* (2016) **105**, 299–308.

Keywords: Aromatase inhibitor; Breast cancer; Homeopathy; Joint pain; Joint stiffness

Introduction

Breast cancer is the most frequently diagnosed cancer in women with 464,000 new cases diagnosed in Europe in 2012 and 131,000 deaths.[1] In the same year in the USA, Siegel et al. calculated an estimated prevalence of breast cancer in women of more than 200,000 new cases and nearly 40,000 deaths from the disease.[2] Most breast cancers are diagnosed in post-menopausal women at an early treatable stage and are hormone-receptor positive. Most women with tumours of this type will receive standard adjuvant treatment with an aromatase inhibitor (AI) to reduce the risk of breast cancer recurrence.[3,4] However, this hormone treatment is associated with a number of important side-effects, particularly joint pain and stiffness,[5–7] most likely due to oestrogen deprivation.[6,8] In a recent study of AI treatment discontinuations, Moscetti et al. reported that 52.4% of patients who discontinued treatment did so because of grade 2/3 arthralgia.[9] In other studies, the frequency of appearance or worsening of joint pain in breast cancer patients treated with AIs is between 20 and 50%.[10–13]

A number of risk factors for the development of AI-associated arthralgia and/or joint stiffness have been identified including excess weight, previous chemotherapy, prior hormone replacement therapy[5] and time since last menstrual period.[14]

Current treatment options for AI-associated arthralgia, mainly non-steroidal anti-inflammatory drugs (NSAIDs), are inadequate and many patients report persistent pain despite taking medication.[6] Furthermore, the long-term use of NSAIDs is associated with a number of side-effects, particularly gastrointestinal and cardiovascular morbidity.[15–17] Other therapies such as increased physical activity or yoga[18–20] and a treatment algorithm for AI-induced arthralgia have been investigated,[21] but despite this, arthralgia remains the most common reason for the premature discontinuation of AI therapy, compromising the outcome of treatment.[21,22] New medicines or treatment approaches are therefore required to limit the appearance or decrease the intensity of AI-associated musculoskeletal pain.

Ruta graveolens (common rue) and *Rhus toxicodendron* (poison ivy) have traditionally been used to treat soreness in the bones, joints, tendons and cartilage, lower back pain and rheumatic pain. *In vitro* and *in vivo* studies have demonstrated anti-inflammatory and anti-arthritic activity of homeopathic *Rhus toxicodendron* treatment.[23–25] Moreover, *Rhus toxicodendron* 6C was effective at reducing tenderness and improving pain in patients with primary fibromyalgia.[26] To our knowledge, no previous studies have been published on the interest of these two medicines to prevent or decrease the intensity of arthralgia and/or joint stiffness in women with early hormone-receptor sensitive breast cancer treated with AIs.

As a result of observations made previously by a physician during the use of the homeopathic medicines *Ruta graveolens* and *Rhus toxicodendron* in a hospital, we carried out a preliminary study to investigate the interest of *Ruta graveolens* 5CH and *Rhus toxicodendron* 9CH in preventing or decreasing the intensity of arthralgia and/or joint stiffness in women with early hormone-receptor positive breast cancer treated with AIs.

Materials and methods

Study design

This unrandomized, prospective, open, controlled, comparative, observational study was carried out at two centres, the Centre Hospitalier, Troyes, and Institut Godinot, Reims, France, between 1 April and 30 October 2014. The study was initiated by a homeopathic physician who wanted to evaluate the contribution of homeopathic therapy during consultation at an oncology service at Troyes hospital as supportive care. This oncology department works in multidisciplinary collaboration with other hospitals such as the Institut Godinot, which does not include homeopathic consultations. Thus, patients attending the Institut Godinot only received AIs and constituted the control group.

The study was carried out by healthcare professionals in the two hospitals who assured the follow-up of the women as part of their usual medical care. As the study was strictly observational and the patients did not require any supplementary diagnostic or therapeutic investigations, ethical approval was not required.

Women were recruited during consultation with a homeopathic clinician at the Troyes hospital or during consultation with an oncologist at the Institut Godinot, before starting treatment with AIs. The study design and treatment schedules are summarized in Figure 1.

The study duration for each patient was 3 months.

Study population

Patients were recruited at each centre if they fulfilled the following inclusion criteria: post-menopausal; with histologically-confirmed, non-metastatic (early), hormone-receptor positive breast cancer; starting adjuvant anti-hormonal treatment with an AI.

Exclusion criteria included: breast cancer overexpressing HER2; patient receiving chemotherapy or radiotherapy

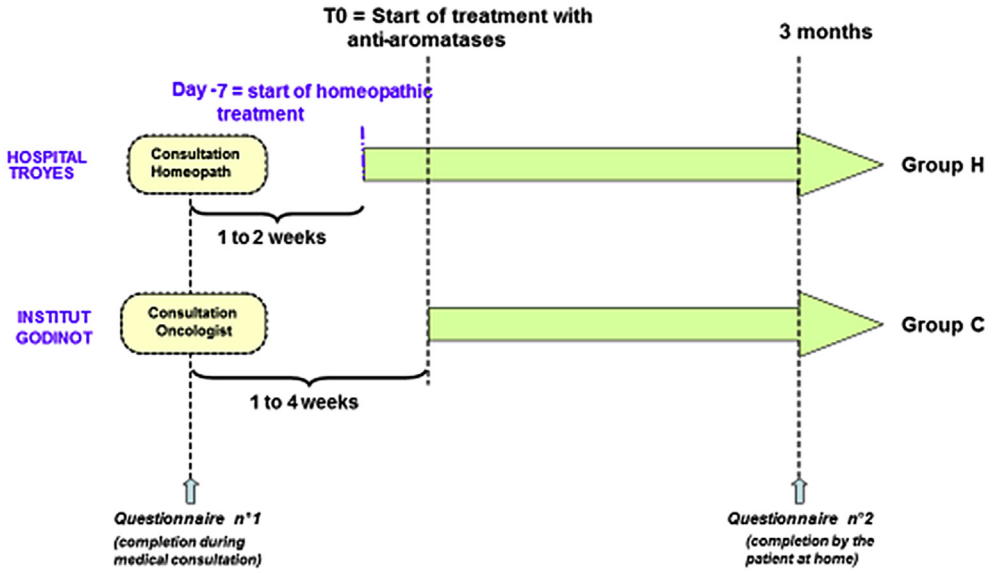

Figure 1 Summary of the study protocol.

or scheduled to receive these treatments during the study period. The patients included consisted of the first 20 women who consulted a homeopathic clinician and the first 20 who consulted an oncologist.

All patients gave their informed consent before taking part in the study.

Treatment groups

The patients were divided into two groups according to the treatments they received. Patients at the Centre Hospitalier, Troyes, received treatment with two homeopathic medicines: *Ruta graveolens* 5CH and *Rhus toxicodendron* 9CH, prescribed during a consultation with a homeopathic clinician in the week preceding the start of AI treatment. The dose of each homeopathic medicine was 5 granules, twice a day. The granules were dissolved in the mouth at least 15 min before or after taking food. Homeopathic treatment was started in the week before starting AIs and was continued for 3 months (homeopathy group H).

The second group, consisting of patients who attended the Institut Godinot, Reims, received only AIs (control group C).

Data collected

At inclusion, patients completed a self-assessment questionnaire during the medical consultation (with an oncologist in group C and homeopath in group H) recording the following demographic and clinical data: age, height, weight, smoking history, participation in sport, age at last menstrual cycle, previous treatments for breast cancer (chemotherapy, radiotherapy, tamoxifen), other symptoms of the menopause, date of starting homeopathy, type of AI used, joint pain/stiffness before starting AI (absent/present). If joint pain/stiffness was present, additional descriptive data were sought: joint pain during the previous week (site(s), frequency (rare, occasional, frequent, permanent), severity (absent, mild, moderate, severe)), consumption of analgesics (never, rare, occasional, every day), impact of pain on sleep (never, sometimes, often, all the time), joint stiffness during the previous week (absent, mild, moderate, severe), severity of joint stiffness in the morning (absent, mild, moderate, severe), severity of joint stiffness during the daytime (absent, mild, moderate, severe), time necessary for stiffness to disappear.

A second self-assessment questionnaire was completed by the patients and sent by post to the physician after 3 months recording: weight, participation in sport, compliance with AI and homeopathic treatment, joint pain/stiffness (absent/present), association with AI treatment, time between AI treatment and appearance or worsening of pain, joint pain during the previous week (site, frequency, analgesic treatments, severity, impact on sleep), joint stiffness during the previous week (severity in the morning, severity during the daytime, time required for stiffness to disappear).

A composite score for joint pain was calculated at inclusion and at 3 months as follows: number of sites of pain (1 point per site), frequency of pain (permanent = 3, frequent = 2, occasional = 1, rare = 0), treatment of pain (every day = 3, occasionally = 2, rare = 1, never = 0), intensity of pain (severe = 3, moderate = 2, mild = 1, absent = 0). Overall score ranged from 0 to 15.

A composite score for joint stiffness was also calculated at inclusion and at 3 months as follows: severity of morning stiffness (severe = 3, moderate = 2, mild = 1, absent = 0), severity of stiffness during the daytime (severe = 3, moderate = 2, mild = 1, absent = 0), time necessary for the stiffness to disappear (≥60 min = 3, 30–60 min = 2, <30 min = 1, or no time = 0). Overall score ranged from 0 to 9.

Compliance was evaluated by asking the question: "*Did you ever forget to take your AI treatment and/or homeopathic treatment*"? The possible responses were: no, yes sometimes, yes often, yes never took the medication.

Evaluation criteria

The evaluation criteria were the frequency, intensity and number of site(s) of joint pain, the use of analgesics, the impact of pain on the quality and quantity of sleep, the morning and daytime intensity and the time to disappearance of joint stiffness at 3 months compared to inclusion. Patients with an improvement (decrease in composite scores), stability (no change in scores) or aggravation (increase in scores) of their joint pain/stiffness were identified from the evolution of each parameter between inclusion and 3 months.

Statistical analysis

According to previous studies,[10–13] the frequency of appearance or aggravation of joint pain/stiffness in patients taking AIs is between 20 and 50%. The study therefore required a target population of approximately 20 patients per group to allow comparisons between the two groups.

Quantitative variables are described as number, mean, standard deviation (SD), median, minimum and maximum (range), and number of missing data. Qualitative variables are described as frequency, percentage and number of missing data (percentages were calculated from the number without missing data).

Quantitative variables in the two groups were compared using the Student's t test for independent data or Wilcoxon Mann–Whitney test for non-normality of data. The two groups were compared using the Chi^2 test or Fischer's exact test if one group contained less than 5 observations. The level of significance was set at 5%.

All statistical analyses were carried out using SAS Enterprise Guide 6.1.

Results

Study population

Forty patients were included in this study, 20 in each centre/group. Mean age (±SD) was 64.9 ± 8.1 years (range: 52.0–83.0), mean BMI was 27.9 ± 6.1 (range: 18.2–43.6), mean age at last menstrual period was 49.1 ± 5.0 years (range: 34.0–57.0), six patients (15%) smoked and seven (17.5%) were physically active (Table 1). Twelve patients (30%) had previously been treated with chemotherapy and one (2.5%) had received tamoxifen. More patients in group C had received prior chemotherapy than in group H (40% vs. 20%, respectively). At inclusion, more patients participated in sport in group H than in group C (25% vs. 10%, respectively).

The AI prescribed was anastrozole (Arimidex®, AstraZeneca) in 25 (62.5%) patients and letrozole (Femara®, Novartis Pharmaceuticals) in 15 (37.5%). No patient received exemestane (Aromasine®, Pfizer). Mean time between inclusion and the first dose of AI was 11.4 ± 13.5 days (range: −1.0–48.0). Mean time between the first

Table 1 Characteristics of the study population at inclusion

Characteristic	*Homeopathy group (n = 20)*	*Control group (n = 20)*	*Total (n = 40)*
Age (years)			
Mean ± SD	67.8 ± 8.2	62.0 ± 7.1	64.9 ± 8.1
Median (range)	66.0 (57.0–83.0)	60.5 (52.0–76.0)	64.0 (52.0–83.0)
Body mass index			
Mean ± SD	26.7 ± 6.3	29.0 ± 5.9	27.9 ± 6.1
Median (range)	26.1 (18.5–43.0)	29.5 (18.2–43.6)	27.8 (18.2–43.6)
Age at last menstrual cycle	(n = 18)	(n = 18)	(n = 36)
Mean ± SD	50.4 ± 5.2	47.9 ± 4.7	49.1 ± 5.0
Median (range)	51.5 (34.0–57.0)	49.0 (37.0–55.0)	50.0 (34.0–57.0)
Smoker, yes	1 (5)	5 (25)	6 (15)
Sports activity, yes	5 (25)	2 (10)	7 (17.5)
Previous treatment			
Chemotherapy, yes	4 (20)	8 (40)	12 (30)
Tamoxifen, yes	0 (0)	1 (5)	1 (2.5)
Aromatase inhibitor prescribed			
Anastrozole	6 (30)	19 (95)	25 (62.5)
Letrozole	14 (70)	1 (5)	15 (37.5)
Time between inclusion and first dose of aromatase inhibitor (days) (n = 38)			
Mean ± SD			11.4 ± 13.5
Median (range)			8.0 (−1.0–48.0)
Time between aromatase inhibitor and first dose of homeopathy (days) (n = 20)			
Mean ± SD			−7.2 ± 5.6
Median (range)			−5.5 (−19.0–0.0)

All values shown are mean ± SD or n (%). Group sizes are given when less than 20 (i.e. there are missing data).

Table 2 Clinical characteristics of the study population at inclusion

Clinical characteristic	*Homeopathy group (n = 20)*	*Control group (n = 20)*	*Total (n = 40)*
Joint pain at inclusion, yes	13 (65)	16 (80)	29 (72.5)
Site of pain			
Knees	10 (27.8)	8 (20.5)	18 (24.0)
Hands/wrists	10 (27.8)	7 (18.0)	17 (22.7)
Spine	5 (13.9)	8 (20.5)	13 (17.3)
Feet/ankles	5 (13.9)	5 (12.8)	10 (13.3)
Hips	4 (11.1)	6 (15.4)	10 (13.3)
Shoulders	2 (5.6)	5 (12.8)	7 (9.3)
Number of sites of pain			
0	0 (0)	0 (0)	0 (0)
1	2 (15.4)	6 (37.5)	8 (27.6)
≥2	11 (84.6)	10 (62.5)	21 (72.4)
Frequency of pain			
Rare	0 (0)	0 (0)	0 (0)
Occasional	2 (15.4)	7 (43.8)	9 (31.0)
Frequent	9 (69.2)	8 (50.0)	17 (58.6)
Permanent	2 (15.4)	1 (6.25)	3 (10.3)
Previous treatment for pain, yes	10 (76.9)	10 (62.5)	20 (69.0)
Frequency of treatment for pain			
Rare	1 (10)	1 (10)	2 (10)
Occasional	6 (60)	4 (40)	10 (50)
Every day	3 (30)	5 (50)	8 (40)
Intensity of pain during the previous week			
Absent	0 (0)	0 (0)	0 (0)
Mild	0 (0)	6 (37.5)	6 (20.7)
Moderate	10 (76.9)	8 (50)	18 (62.1)
Severe	3 (23.1)	2 (12.5)	5 (17.2)
How often does pain disturb sleep?			
Never	3 (23.1)	3 (18.8)	6 (20.7)
Sometimes	8 (61.5)	8 (50)	16 (55.2)
Often	2 (15.4)	4 (25)	6 (20.7)
All the time	0 (0)	1 (6.25)	1 (3.5)
Joint stiffness in the morning			
Absent	0 (0)	2 (12.5)	2 (6.9)
Mild	5 (38.5)	6 (37.5)	11 (37.9)
Moderate	6 (46.2)	4 (25)	10 (34.5)
Severe	2 (15.4)	4 (25)	6 (20.7)
Joint stiffness during the daytime			
Absent	0 (0)	2 (12.5)	2 (6.9)
Mild	6 (46.2)	3 (18.8)	9 (31)
Moderate	5 (38.5)	10 (62.5)	15 (51.7)
Severe	2 (15.4)	1 (6.25)	3 (10.3)
Time to disappearance of morning stiffness (min)			
Mean ± SD	19.9 ± 20.5	32.9 ± 30.0	26.6 ± 26.2
Median (range)	10.0 (3.0–60.0)	30.0 (0.0–120.0)	15.0 (0.0–120.0)

All values shown are n (%) unless indicated otherwise.

dose of homeopathic medicine and first dose of AI was −7.2 ± 5.6 days (range: −19.0–0.0) (Table 1).

Frequency and severity of joint pain/stiffness at inclusion

Overall, 29 patients (72.5%) complained of joint pain at inclusion, before taking the AI, 80% of group C vs. 65% of group H (Table 2). Of these, 14 patients attributed their pain to arthritis. The most common sites of pain were the knee (24.0%), hands and wrists (22.7%) and spine (17.3%). The majority of patients (72.4%) had two or more sites of pain (Table 2). The most painful site was the knee (37.9%). Over half of the patients (58.6%) complained of frequent pain and 20 patients (69.0%) had taken treatment for their pain in the week preceding inclusion, 76.9% of group H vs. 62.5% of group C. Eighteen patients (62.1%) complained of moderate pain and five (17.2%) complained of severe pain in the week preceding the study. Moderate/severe pain in the week prior to inclusion in the study was reported by 100% of patients in group H vs. 62.5% of group C. Over half (55.2%) stated that the pain occasionally affected their sleep, 61.5% of group H vs. 50% of group C (Table 2).

Joint/muscle stiffness in the morning was moderate in 10 patients (34.5%) and severe in six (20.7%). Joint stiffness during the daytime was moderate in 15 patients (51.7%) and severe in three (10.3%). The mean time to the disappearance of morning stiffness was 26.6 ± 26.2 min (range: 0.0–120.0). This was higher in group C than in group H (32.9 ± 30.0 vs. 19.9 ± 20.5 min, respectively) (Table 2).

Evolution of joint pain between inclusion and 3 months

After 3 months of treatment, 30 patients (12 (60%) in group H and 18 (90%) in group C) complained of joint/muscle pain. In comparison with T0, new joint pain had appeared in three patients (7.5%) (1 in group H vs. 2 in group C) and disappeared in two (5.0%) (both in group H).

The main sites of pain at 3 months were similar to those at inclusion. Six patients (50%) in group H complained of

Table 3 Evolution of composite scores for joint pain and joint stiffness between inclusion (T0) and 3 months (T3) in the two treatment groups

	Homeopathy group			*Control group*			*Total*		
	T0 (n = 20)	*T3 (n = 20)*	*T3-T0 (n = 20)*	*T0 (n = 20)*	*T3 (n = 20)*	*T3-T0 (n = 20)*	*T0 (n = 40)*	*T3 (n = 40)*	*T3-T0 (n = 40)*
Pain score*									
Mean ± SD	5.7 ± 4.6	4.4 ± 4.1	−1.3 ± 3.2	5.9 ± 4.2	9.2 ± 4.3	3.4 ± 3.7	5.8 ± 4.3	6.8 ± 4.8	1.1 ± 4.1
Median (range)	7.0 (0.0–13.0)	5.0 (0.0–13.0)	−0.5 (−9.0–7.0)	5.5 (0.0–13.0)	9.5 (0.0–15.0)	3.0 (−2.0–13.0)	6.5 (0.0–13.0)	7.0 (0.0–15.0)	0.0 (−9.0–13.0)
	T0 (n = 13)	*T3 (n = 12)*	*T3-T0 (n = 11)*	*T0 (n = 16)*	*T3 (n = 18)*	*T3-T0 (n = 16)*	*T0 (n = 29)*	*T3 (n = 30)*	*T3-T0 (n = 27)*
Stiffness score†									
Mean ± SD	4.9 ± 1.7	4.1 ± 2.1	−1.0 ± 1.4	4.7 ± 2.4	5.4 ± 3.0	0.8 ± 2.7	4.8 ± 2.1	4.9 ± 2.7	0.04 ± 2.4
Median (range)	5.0 (3.0–9.0)	4.5 (0.0–8.0)	−1.0 (−3.0–2.0)	4.5 (0.0–8.0)	5.5 (0.0–9.0)	0.5 (−4.0–8.0)	5.0 (0.0–9.0)	5.0 (0.0–9.0)	0.0 (−4.0–8.0)

* Homeopathy vs. control group, p = 0.0001, Wilcoxon test.
† Homeopathy vs. control group, p = 0.0567, Student's t test.

moderate pain vs. 7 in group C (38.9%). Conversely, eight patients (44.4%) in group C complained of severe pain vs. 0 patients in group H. Thirteen patients (43.3%) complained of permanent pain (3 (25%) in group H vs. 10 (55.6%) in group C). The majority (90%) had taken some type of medication for their pain in the week preceding the 3-month analysis (10 (83.3%) in group H vs. 17 (94.4%) in group C) (data not shown). Nearly half of the patients (47.1%) in group C took analgesic medication daily whereas only 20% of patients in group H took analgesic medication daily.

There was a significant difference in the evolution of composite pain scores between T3 and T0 in group H compared to group C (Table 3). After 3 months, the pain score was significantly worse in 70% of patients in group C compared to 5% of patients in group H ($p < 0.0001$). Overall, the composite score for pain decreased in group H (−1.3) while it increased in group C (+3.4) ($p = 0.0001$) (Table 3).

The evolution of the individual components of pain between inclusion and 3 months is shown for the two groups in Figure 2.

There was a significant difference between the two groups ($p = 0.0315$) in the evolution of number of sites of pain between inclusion (V1) and 3 months (V2) with a decrease in mean score in group H (−0.2) and an increase in group C (+1.0) (Figure 2A).

There was also a significant difference in evolution of the frequency of pain. This decreased in group H (−0.25) and increased in group C (+0.85) ($p = 0.0004$) (Figure 2B). The frequency of pain improved in 40% of patients in group H vs. 5% in group C. Conversely, the frequency of pain worsened in 70% of patients in group C vs. 15% in group H.

There was also a significant difference in the evolution of intensity of pain which decreased in group H (−0.60) and increased in group C (+0.65) ($p = 0.0004$) (Figure 2C). The intensity of pain improved in 45% of patients in group H vs. 5% in group C. Conversely, the intensity of pain became worse in 50% of patients in group C vs. 5% in group H.

Finally, there was a significant difference ($p = 0.0034$) in the evolution of the frequency of taking analgesic medication. This decreased in group H (−0.20) and increased in group C (+0.85) (Figure 2D). Nine patients in group C (45%) vs. 1 (5%) in group H increased their consumption of analgesics between T0 and T3 ($p = 0.0076$).

Evolution of joint stiffness between inclusion and 3 months

After 3 months of treatment, 10 patients (50%) in group H and 15 (75%) in group C had joint stiffness in the morning or during the daytime. The mean time to the disappearance of morning stiffness was 29.2 ± 23.6 min (17.9 ± 20.1 min in group H vs. 37.7 ± 23.0 min in group C; $p = 0.0173$).

When the composite scores for joint stiffness were compared, 1/11 patients (9.1%) in group H vs. 8/16 patients (50%) in group C had an aggravation of their

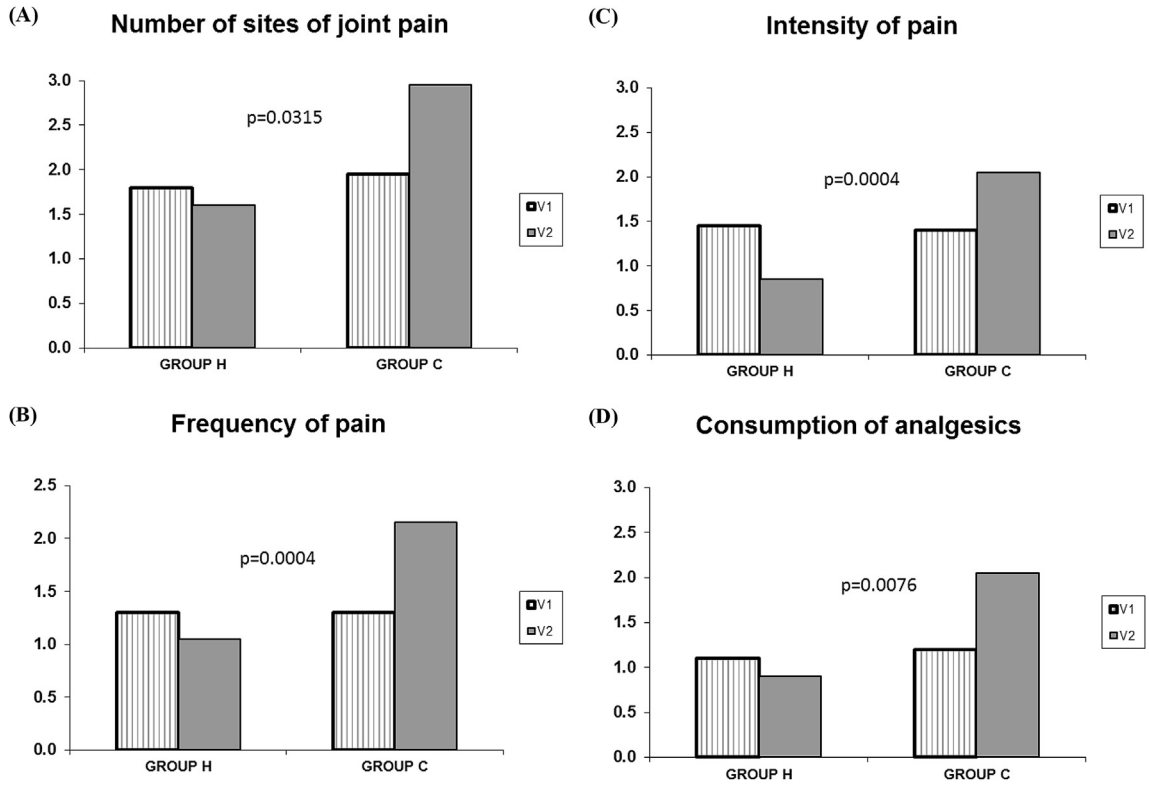

Figure 2 Changes in pain parameters and analgesic use in the two treatment groups between inclusion (V1) and 3 months (V2). All values shown are mean values.

stiffness (p = 0.0141). When the overall scores for joint stiffness were compared there was a non-significant difference (p = 0.0567) between group H and group C. Group H had an overall decrease in score (−1.0) whereas the score for group C increased (+0.75) between T3 and T0 (Table 3).

When the individual components of the composite score were compared between the two groups (data not shown) there was a significant difference (p = 0.0198) in the evolution of intensity of morning stiffness with a decrease in score in group H (−0.55) and an increase in group C (+0.25). Conversely, the differences observed in the evolution of daytime stiffness between the two groups were not significant (p = 0.179). Finally, there was a significant difference in the time necessary for the disappearance of morning stiffness with a ≈2 min decrease in group H but a ≈5 min increase in group C (changes in score: −0.18 vs. +0.46, respectively, p = 0.022).

Evolution of the impact of joint pain on sleep

At 3 months, 66.7% of patients in group H vs. 16.7% in group C stated that pain never disturbed their sleep. This compares to 23.1% and 18.8% of patients, respectively, who stated that pain never disturbed their sleep at T0. The evolution of the impact of joint pain on sleep is summarized in Table 4. After 3 months of treatment, joint pain had a worse impact on sleep in 7 patients (35%) in group C vs. 0 patients in group H. This difference was statistically significant (p = 0.0083, Fisher's exact test).

Table 4 Evolution of the impact of joint pain on sleep

	Evolution of the impact of pain on sleep		
	Worsened	*Stabilized*	*Improved*
Homeopathy group (n = 20)	0 (0)	2 (10)	18 (90)
Control group (n = 20)	7 (35)	1 (5)	12 (60)
Total (n = 40)	7 (17.5)	3 (7.5)	30 (75)

Values shown are n (%).

Compliance

Compliance with the AIs and homeopathic medicines was excellent throughout the study (100% for both types of treatment in both patient groups).

Discussion

In our study, which followed two groups of women with hormone-receptor positive breast cancer treated with AIs, we observed that women who received additional treatment with two homeopathic medicines, *Ruta graveolens* 5CH and *Rhus toxicodendron* 9CH, appeared to experience a more favourable evolution of joint pain and joint stiffness after 3 months of treatment. The composite scores for these two variables both decreased in group H patients compared to group C which did not use homeopathic medicines (median values: −0.5, −1.0 vs. +3.0, +0.5, respectively) as did the individual scores for number of sites of pain, frequency of pain, intensity of pain, morning stiffness, time to disappearance of stiffness and impact of pain on sleep. Use of

analgesic medication for pain also decreased in group H at T3. Compliance with homeopathic and AI treatment was excellent (100% for both treatments in both groups) and no side-effects of homeopathic treatment were noted. Although these results are encouraging they need to be confirmed in a larger placebo-controlled clinical study.

Breast cancer is the most common form of cancer in women[1,2] and is a disease of ageing with an average age at diagnosis of 61 years.[27] Treatment of breast cancer depends on the type, grade and stage of the tumour and previous medical history of the patient. Older women with early-stage breast cancer should be treated initially with surgery, but hormone therapy should be considered for patients who have hormone-receptor positive tumours and a short life-expectancy, those with an acute illness that delays surgery and those with larger tumours that need to be reduced in size before surgery.[27] The majority of older women with stage I and II breast cancer have hormone-receptor positive, HER2-negative tumours and hormone therapy provides optimal systemic treatment.[27] One of the main concerns of studies in breast cancer is the support of patients undergoing treatment, including ways to reduce the side-effects of AI treatment such as musculoskeletal symptoms.[28]

In studies reported in the literature, musculoskeletal pain is experienced by 20−50% of breast cancer patients treated with AIs[10−13,22,29] with an average time of 2 months between starting AI treatment and the appearance of symptoms. The event rate for joint symptoms reaches a peak within 6 months of starting AI therapy and declines thereafter.[29] The sites most commonly affected are the hands/wrists, followed by the knees, spine, shoulders and more rarely the feet and ankles.[29] Our study confirms these findings. In group C, 70% of patients had new or aggravated joint pain, in most cases 1 month after the initiation of AI treatment. The most commonly affected sites were the knees, followed by the hands/wrists, spine, feet and ankles. The mean intensity of the pain was severe. In contrast, only 5% of patients given the homeopathic medicines (group H) complained of new or aggravated joint pain, mostly 1 month or 2 months after starting AI combined with homeopathic treatment. The most commonly affected sites were the knees followed by the spine, hips, hands/wrists and finally the feet and ankles. The mean intensity of this pain was mild to moderate with no severe intensity at T3 for group H. This difference between the two groups was statistically significant ($p < 0.0001$).

Spontaneous resolution of AI-associated arthralgia occurs slowly during therapy and joint pain may still be present after 1−2 years of AI treatment.[22] Resolution of joint pain is common after AI treatment has been stopped. Steps to manage AI-related pain are therefore important so that AI treatment is not discontinued prematurely.[22]

In a survey on the use of different types of alternative or complementary therapy in 2022 breast cancer survivors diagnosed between 1998 and 2003, treatment with tamoxifen or anastrozole was often associated with the use of homeopathy [OR = 0.5; 95% CI: 0.3−0.9].[30] However, to our knowledge, no study has evaluated the efficacy of homeopathic medicines for the treatment of pain associated with AIs in patients with breast cancer.

On the other hand, several studies have been published in rheumatology demonstrating the efficacy of homeopathic treatments for the relief of pain. In a double-blind study on the treatment of rheumatoid arthritis carried out by two homeopathic physicians,[31] 23 patients using NSAIDs plus homeopathy were compared with a similar group of 23 patients using NSAIDs plus placebo. There was a significant improvement in subjective pain, joint pain index, stiffness and grip strength in patients who received homoeopathic medicines whereas there was no significant change in patients who received placebo.[31] *Rhus toxicodendron* 6 CH was also shown to be more effective than placebo at reducing tenderness and improving pain and sleep in patients with primary fibromyalgia.[32] In another randomized, double-blind, placebo-controlled trial of a selection of homeopathic medicines in patients with fibromyalgia, Bell et al. showed that individualized homeopathy was significantly better than placebo at lessening tender point pain and improving the quality of life and global health of patients.[32] Finally, in a recent meta-analysis of case reports, observational studies, randomized and non-randomized clinical trials of homeopathy in the treatment of fibromyalgia, an effect of homeopathic treatment was shown on tender point count, pain intensity and fatigue compared to placebo.[33]

In France, complementary and alternatives medicines, particularly homeopathy, are commonly used as supportive care by patients with early-stage breast cancer and other malignancies.[34−36] Consultations in supportive care, including the use of homeopathy to reduce the side-effects of treatment and improve host defences, are expanding in French oncology departments.[36] In a recent face-to-face and online survey of oncologists working in different fields of cancer, complementary therapies were seen as an essential part of supportive care. These therapies allow the treatment of patients as a whole, treating the adverse effects of cancer treatments and addressing the quality of life and psychological wellbeing of the patients. However, this latter idea has not yet been developed. The expectations of oncologists towards homeopathic medicines in the context of cancer are to treat the adverse effects of cancer treatments for which there is no satisfactory therapeutic solution including musculoskeletal pain, peripheral neuropathies, hot flushes, sleep problems, anxiety, fatigue and dry eyes (unpublished data).

Limitations

Our study has a number of limitations. The recruitment of patients was carried out on two different sites and it was not possible to change the practices of the two hospital departments. Thus, all patients consulting at the Troyes hospital underwent a homeopathic consultation. It has been suggested that the clinical benefits of homeopathy can be attributed to the homeopathic consultation itself rather than to the homeopathic medicine.[37] Further studies should therefore aim to give all patients a similar consultation experience, irrespective of what type of treatment they

receive. Furthermore, no randomization was applied in this study so the patients were not closely matched, particularly as regards to the type of AI that was used (i.e. 70% letrozole in group H vs. 95% anastrozole in group C) even if in practice it does not make much difference to the side-effects. Joint pain was worse in group H at inclusion but was better in group H treated with the two homeopathic medicines at 3 months. Other confounding factors that could have influenced the results such as participation in sport, smoking and previous chemotherapy were not controlled for. Twenty percent of patients in group H vs. 40% of patients in group C had been treated with chemotherapy prior to inclusion and previous chemotherapy has been identified as a risk factor for developing AI-associated arthralgia.[5] The group sizes were also small and it was not possible to carry out a statistical analysis on the risk factors linked to the appearance or worsening of joint pain and/or stiffness or the characteristics of the patients at inclusion that could help identify those in whom pain will appear or worsen.

Conclusion

This preliminary observational study suggests that joint pain linked to the treatment of hormone-receptor positive breast cancer with AIs can be prevented or improved by concomitant homeopathic treatment combining *Ruta graveolens* 5CH and *Rhus toxicodendron* 9CH. A large, prospective, randomized, double-blind, placebo-controlled trial should be carried out to confirm these results, but this preliminary study could help to establish a protocol of homeopathic care that could improve the quality of life of breast cancer patients and their compliance with AI treatment.

Conflict of interest

All authors declare no conflict of interest.

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