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REVIEW

Aromatase inhibitor-induced arthralgia in early breast cancer: what do we know and how can we find out more?

Omar S. Din · David Dodwell · Richard J. Wakefield · Robert E. Coleman

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Abstract Aromatase inhibitors (AIs) are a standard of care for the adjuvant treatment of hormone responsive early carcinoma of the breast as demonstrated in a number of large international phase III randomised trials. Arthralgia was a somewhat unexpected side effect of this class of agents and has proven to be potentially problematic in clinical practice. Although rates of up 35% have been reported in the randomised trials, the figure has been much higher in subsequent case series. There is concern that these symptoms are significant and may affect compliance and thus the overall efficacy of treatment. It is therefore extremely important that we evaluate this syndrome with a view to gaining more information regarding its clinical features and possible aetiological mechanism. The potential aetiological mechanisms and evidence for aromatase inhibitor-induced arthralgia (AIA) are reviewed in this article. Looking forward, it is now important that prospective clinical trials are well designed to evaluate this syndrome and potential therapeutic strategies to circumvent it. Radiological imaging and biochemical analyses may help our understanding of AIA and these are discussed.

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Introduction

The third generation aromatase inhibitors (AIs), anastrozole, letrozole and exemestane, have become the standard of care in the management of both early and advanced hormone-responsive breast cancer in postmenopausal women. For many years, tamoxifen was the cornerstone of endocrine therapy with a substantial body of evidence showing benefits in overall survival [1]. However, more recently, trials of AIs have shown benefits over tamoxifen, in both a metastatic [2–4] and subsequent adjuvant treatment setting [5–11]. The main advantages have been improvements in disease free survival and a more favourable toxicity profile, with lower rates of thromboembolic phenomena and endometrial malignancy. The two main adverse effects of AIs were identified as a reduction in bone mineral density (BMD) and joint symptoms or arthralgia. Much has now been published on the former but the mechanisms behind arthralgia are not clearly understood. It is apparent that arthralgia is a more significant clinical issue than was first envisaged and there is concern that it has been underreported in the clinical trials. There is also increasing awareness that poor compliance due to AI arthralgia may compromise the future effectiveness of therapy.

In this review, the key areas addressed include the frequency and clinical characteristics, possible aetiological mechanisms and methods of assessment and treatment. This review was compiled with the use of PubMed and Medline databases as well as recent abstracts from relevant international meetings. The search terms 'breast cancer,' 'arthralgia' and 'aromatase inhibitors' were used in both databases.

Background

Mechanism of action of aromatase inhibitors

Oestrogen is implicated in the initiation, promotion and progression of breast cancer [12]. Understanding these effects has led to two main therapeutic strategies attempting to interfere with this process. The first, targets the oestrogen receptor (ER) using selective oestrogen receptor modulators (SERMs; e.g. tamoxifen) or pure antioestrogens (e.g. fulvestrant). The second, more recent strategy has been the targeting of oestrogen biosynthesis with the use of AIs. These drugs are licensed for use in the treatment of postmenopausal breast cancer. They selectively inhibit the enzyme aromatase, the last step in oestrogen biosynthesis leading to reduction of oestradiol and oestrone production (Fig. 1). The currently available third generation AIs can be subdivided into the reversible non-steroidal AIs (anastrozole and letrozole) and the irreversible steroidal AIs (exemestane). Non-steroidal imidazole-based AIs reversibly interact with the cytochrome P450 moiety of aromatase and therefore need to be continually present for inhibition [13]. In contrast, exemestane has an androgen structure and competes with the substrate androstenedione. It binds irreversibly with aromatase leading to loss of activity. However, this compound and its metabolite, 17-hydroxyexemestane in particular, have the potential for androgenic effects via their binding to the androgen receptor [14, 15].

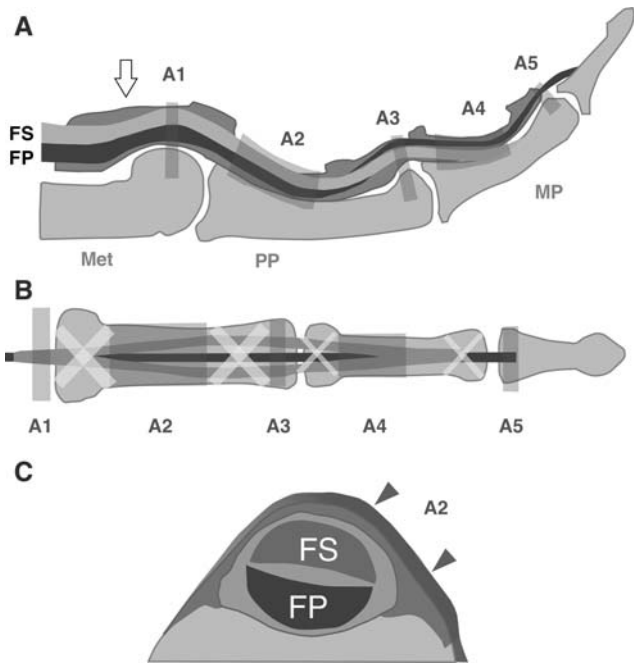

Fig. 1 Schematic of the normal flexor tendon anatomy of the fingers. **a**, **b** Schematic drawing showing the normal anatomy of the flexor tendons of the fingers. *FS* flexor digitorum superficialis tendon, *FP* flexor digitorum profundus tendon. *White arrowhead* synovial sheath, *A1–A5* annular digital pulleys. *Met* metacarpal, *PP* proximal phalanx, *MP* middle phalanx, *DP* distal phalanx. **c** Axial schematic drawing showing the relationship between the A2 pulley and the flexor digitorum superficialis/profundus tendons (FS, FP). Reproduced with permission from Elsevier Masson [96]

Arthralgia in postmenopausal women

Menopause marks the cessation of ovarian function and naturally occurs at an average age of 51 years. It is diagnosed after 12 months of amenorrhoea, but it is preceded by the perimenopause, which precedes the final menses by 2–8 years [16]. Joint symptoms in post menopausal women are well recognised and were described as an entity as early as 1925 [17].

More recently, cross-sectional studies have investigated the presence of musculoskeletal symptoms during the various stages of the menopause. In a telephone survey of 2,145 women aged 44–55 years in Hong Kong, an overall incidence of joint aches and stiffness of 27.2% was reported. Most joint complaints were seen in the perimenopausal women. The prevalence in other countries was variable: 14.5% (Japan), 31.4% (Canada) and 38.6% (USA) [18]. Dugan et al. [19] reported one in six women experiencing joint symptoms, again highest in the perimenopausal age range. In another cross-sectional study, the rate of joint and muscle pain in post menopausal women was close to 50% [20]. In a longitudinal study of 438 Australian women aged 45–55, yearly symptom assessment was undertaken over 8 years to represent the menopausal transition. The most common symptoms were stiff and aching joints, which increased over time. A higher frequency and intensity of symptoms were associated with a higher body mass index (BMI) ($P < 0.01$), being unemployed ($P < 0.05$) and low mood ($P < 0.005$) [21]. Other studies have also shown that BMI is associated with an increasing risk of joint pain. The incidence of pain in at least one joint has been as high as 49% [22]. These data confirm that there is a high background level of joint symptoms in the peri- and postmenopausal female population. It is important to consider this when evaluating the incidence and aetiology of aromatase inhibitor-induced arthralgia (AIA).

Aetiology

Role of oestrogen

The mechanism behind AIA is not clearly understood. Oestrogen deprivation is implicated as per the mechanism of action of AIs. Typical levels of oestradiol in the presence of a potent AI are less than 1 pmol/l [23]. It is known that the

incidence of joint pain peaks at 50–59 years in the general population. Some preclinical studies have shown a protective effect of oestrogen in arthritis and on pro-inflammatory genes [24, 25]. Clearly, there are several possible causes of arthralgia in a non-breast cancer population, which can make it difficult to elucidate one particular cause.

There are a number of ways that oestrogen could be implicated in the pathogenesis of AIA. There is evidence that oestrogen may have an anti-nociceptive and pain modulating effects, for example, through opioid pain fibres in the central nervous system [26]. This is particularly evident during pregnancy, when women have elevated thresholds for painful stimuli in the presence of increased levels of oestrogen [26]. However, others have reported the opposite and one meta-analysis of 16 trials has shown that women tolerated more pain during times of lowest oestradiol and progesterone levels of the menstrual cycle [27]. Methodological differences in the pain literature may explain some of the conflicting results. However, evidence from a meta-analysis is the most robust and therefore throws doubt at the hypothesis of increased pain perception in AIA.

ER-β has been found in normal human synovia and therefore may have a role in the function of the synovial membrane [28]. ER-α and β are found in normal cartilage, but are present at increased levels in osteoarthritic joints [29, 30]. Type II collagen (CTX-II), the main structural protein of articular cartilage, may be influenced by oestrogen. Animal studies have investigated the effect of ovariectomy on cartilage turnover and degradation. Compared with controls, CTX-II correlated strongly with severity of surface cartilage erosion ($r = 0.74$, $P < 0.01$). Thus, oestrogen deficiency is a process that may accelerate cartilage turnover and erosion. In fact, in a review, 11 out of 16 animal studies showed that ovariectomy resulted in cartilage damage. In a further rat study, type II collagen turnover was countered by the use of oestrogen, though other studies have shown variable results for exogenous oestrogen therapy [31, 32]. However, in humans, hormone replacement therapy is not an adequate treatment of arthralgia in postmenopausal women [33].

There is evidence that aromatase may be expressed synovial cells and chrondrocytes of articular cartilage [34, 35]. One study demonstrated synoviocytes from postmenopausal women were able to express aromatase mRNA. In addition, the authors showed that the adrenal androgen, androstenedione, was converted to estrone and estradiol in synoviocytes by aromatase and this process was positively regulated by glucocorticoids [34].

Some of the adjuvant studies of AIs have also shown an increased prevalence of carpal tunnel syndrome. One possible explanation for this could be the presence of fluid around the flexor tendons of the wrist causing compression neuropathy of the median nerve. In a study of 23 women undergoing surgery for carpal tunnel syndrome, tissue from the transverse carpal ligament and synovium was examined and compared with four controls (undergoing hand surgery for trauma with no history of carpal tunnel syndrome). ER and PR were found to be present in these structures and to a higher degree than controls. This implicates these receptors and potentially oestrogen and progesterone in the pathogenesis of carpal tunnel syndrome. Interestingly, the number of ER positive cells in the transverse carpal ligament and synovial tissue increased with age to a peak at 55–70, decreasing thereafter [36].

Autoimmume process

There are reports of autoimmune disease, particularly rheumatoid arthritis and sjogren's syndrome, being associated with aromatase inhibitor therapy [37, 38]. However, studies up to now have not shown an increased incidence of autoimmunity or indeed raised systemic inflammatory markers. One prospective study focussing on this aspect showed minor elevation in a few markers as discussed in 'AIA in clinical practice' [39]. Pro-inflammatory cytokines may be regulated by oestrogen. In the study on synoviocytes, in which aromatase was shown to convert androstedeione to oestradiol, Il-6 production was reduced [34]. Therefore, reduction of oestradiol may promote local inflammatory changes in the joint by this mechanism. Evidence exists that the pro-inflammatory cytokines, Il-1, Il-6 and TNF-alpha are spontaneously elevated in the first few years after the menopause [40], a time when the natural incidence of joint symptoms is high. Indeed it has been suggested that time since menopause may be an important predictive factor for AIA, and this may be linked to cytokine activity [41].

Other possible aetiologies include direct off target effects of the AI or its metabolites.

Arthralgia in the phase III trials of adjuvant AIS

The indications for use of adjuvant AI therapy can be subdivided into three categories: upfront (anastrozole, letrozole); switch to an AI after 2–3 years of tamoxifen (exemestane, anastrozole, letrozole); and extended adjuvant after 5 years of tamoxifen (letrozole, anastrozole). The incidence of various joint symptoms in the phase III trials is shown in Table 1.

Upfront use

Anastrozole has the most data with regard to the incidence of joint symptoms within the 'arimidex', tamoxifen, alone or in combination (ATAC) trial [5]. In this study, musculoskeletal symptoms were reported according to four terms:

Table 1 Incidence of musculoskeletal symptoms reported in the adjuvant phase III trials

Trial	*n*	Toxicity	AI (%)	Tam (%)	Placebo (%)	*P*
ATAC [5]	9366	Joint symptoms	35.6	29.4		<0.0001
		Arthralgia	15.1	11.1		
		Carpal tunnel	3	1		<0.0001
BIG 1-98 [10]	8028	Arthralgia	20.0	13.5		<0.001
IES [8]	4724	Arthralgia	18.6	11.8		<0.0001
		M/S pain	21.0	16.1		<0.0001
		Carpal tunnel	2.8	0.3		<0.0001
		Joint stiffness	1.9	1.0		0.009
		Arthritis	14.1	12.0		0.03
ITA [11]	448	Musculoskeletal/fracture	9.9	6.7		0.2
ABCSG 8/ ARNO 95 [9]	3224	Bone pain	19	16		0.0546
MA-17 [6]	5187	Arthralgia	21.3		16.6	<0.001
		Myalgia	11.8		9.5	0.02
		Arthritis	5.6		3.5	<0.001
ABCSG 6a [94]	856	Bone pain (inc joint pain)	24.5		18.3	0.009

arthralgia, arthritis, arthrosis and joint disorder, though in most cases the adverse events (AEs) were just related to pain in the joints. The peak occurrence for joint symptoms was 6 months. There was a higher rate of arthralgia in anastrozole patients who had received prior chemotherapy (41.8% vs. 33.6%) [42]. The median time to symptoms was also shorter in this group (9.1 months vs. 15.9 months). These differences were much less significant in the tamoxifen group. Early age was another factor predicting an early onset of joint symptoms (9.8 months in the <60 years subgroup). This may be explained partly by the fact that younger patients are more likely to receive chemotherapy [29, 43]. Only a small number of patients withdrew from therapy (A 2.1%, T 0.9%) [43, 44].

Interestingly, when overall quality of life (QoL) was assessed, in a sub study, using the mean trial outcome (TOI) score of the functional assessment of cancer therapy-breast (FACT-B) questionnaire, there was no difference between the two treatments at 2 ($P = 0.23$) [45] and 5 years ($P = 0.65$) [46]. However, musculoskeletal symptoms did not form a part of this questionnaire. Newer versions of the FACT-B questionnaire do now include more detail on joint symptoms [47].

In a further follow-up investigation from the ATAC trial, symptoms related to endocrine therapy have been correlated with the risk of breast cancer recurrence [48]. Overall, women experiencing joint pains after 3 months of endocrine therapy (anastrozole or tamoxifen) had a significantly reduced risk of developing recurrent disease than those without joint symptoms (HR 0.60 (95%CI 0.5–0.72; $P < 0.0001$). This effect was still present for women receiving anastrozole, if they also had vasomotor symptoms (HR 0.65) or not (HR 0.65). The largest reduction in risk for the anastrozole occurred in those suffering both joint and vasomotor symptoms (HR 0.56). These effects were not present when symptoms at baseline were analysed instead of at 3 months. Both the symptoms were felt to be due to oestrogen deprivation, though the underlying cause for AIA still remains under investigation. This apparent correlation between increased toxicity and greater treatment efficacy may inform any discussion about discontinuing therapy. Several reports have indicated compliance to endocrine therapy still remains an important hurdle to overcome [49, 50].

Switch therapy

As listed in Table 1, other musculoskeletal effects were noted to be more common in those treated with exemestane. In particular, there was a nine fold increase in the rate of carpal tunnel syndrome for those receiving the AI. This study also reported symptoms after treatment cessation and

showed rates of arthralgia of 20.8% and 15.1% for both exemestane and tamoxifen, respectively [7, 8]. QoL analysis using the FACT-B TOI showed no meaningful change between the two study groups [51]. Again, this instrument did not take into account arthralgia and other joint symptoms.

Extended adjuvant

The MA-17 trial investigated the role of using letrozole after 5 years of tamoxifen in a randomised phase III trial comparing outcome with placebo. Although the study was stopped early due to the benefit in preventing disease recurrence seen, increased rates of arthritis, myalgia and arthralgia were observed (Table 1). However, QoL was assessed using the Short Form 36 (SF-36) and Menopause Specific Quality of Life (MENQOL) questionnaires. Bodily pain formed a part of the SF-36, but was no different in the two arms. Aching muscles were reported in the MENQOL, showing a higher incidence in the letrozole group (43% vs. 38%). The authors concluded that there was no detrimental effect on QoL, but there were small changes attributable to those suffering bodily pain and vasomotor symptoms [6, 52].

Adverse event reporting

It is clear from the data derived from the large international phase III studies that there has been considerable variation in the reporting of AIA. First, arthralgia was only reported as a spontaneous adverse event leading the differences in observed frequencies. Most studies used the Common Terminology Criteria of Adverse Events. The questionnaires used were geared towards assessment of endocrine symptoms and patient reporting of musculoskeletal symptoms was not highlighted in the design. Other factors affecting arthralgia incidence were the different lengths of follow-up and the fact that the patients came from different parts of the world, where the incidence of reported joint symptoms does vary [53]. Thus, there is a need for more detailed prospective evaluations that identify musculoskeletal symptoms from onset of AI. In addition, there are limited data regarding the time course and resolution of symptoms. The ATAC trial did show that the highest incidence of joint symptoms occurred in the first year [42].

AIA in clinical practice

Smaller studies have now started reporting analyses of musculoskeletal pain in postmenopausal women on third generation AIs. In a cross-sectional survey of 200 patients in USA taking an adjuvant AI, 47% reported joint pain (23.5% new onset) and 44% joint stiffness (26.5% new onset). 67% and 66%, respectively, reported moderate to severe symptoms. Interestingly, women who were overweight were less likely to experience joint pain and those who had received prior tamoxifen were less likely to complain of joint stiffness than those who did not. Prior taxane based chemotherapy was associated with a fourfold increase in pain and stiffness (ORs 4.08 and 4.76, respectively) [54].

Presant et al. reviewed 56 consecutive patients receiving third generation AIs in community cancer centres in USA, by interview. Thirty-four patients (61%) reported worsening of arthralgia/bone pain. In 20%, symptoms were severe enough to discontinue the medication after a median of 2 months, significantly higher than was reported in the phase III trials [55]. In a retrospective analysis of 600 patients who were receiving or had received adjuvant AI therapy, Dent et al. [56] showed 20% self reporting arthralgia/arthritis. Notably, 17% of patients discontinued their AI and this was due to a number of reasons including arthralgia (46%), myalgia (18%), hot flushes (16%), fatigue (9%) and headaches (9%).

More recently, a cross-sectional study surveyed breast cancer survivors receiving AI adjuvant therapy. There were 300 respondents and 47% attributed the AI as the cause of their arthralgia. The onset of AIA was most commonly within 3 months. Time since last menstrual period (LMP) was the only significant predictor in multivariate analysis. Women who were within 5 years of their LMP, had a three-fold increase in age adjusted risk compared to women more than 10 years since LMP ($P = 0.02$). Pain was most commonly reported in the hands/wrist (60.4%), knee (59.7%) back (54%), ankle/foot (51.8%) and hip (42.5%) [41].

Henry et al. reported their first 100 patients enrolled into a prospective randomised study comparing the pharmacogenomics of exemestane and letrozole. Referral to a rheumatologist was made if there was evidence of new or worsening pain on a visual analogue scale, health assessment questionnaire or on a self rated clinical global impression scale. The criteria for referral were met in 45.4% of the eligible patients. This study showed an early time to onset of symptoms of 1.6 months (range 0.4–10 months). Thirteen patients discontinued the AI after a median of 6.1 months. The most frequent rheumatological diagnoses were osteoarthritis, tendonitis, carpal tunnel syndrome and bursitis. This study also focussed on biochemical parameters and demonstrated low levels of raised inflammatory markers. Of those referred, 18% had a raised C-reactive protein (CRP), 16% had an elevated anti-nuclear factor, 10% had a raised creatinine kinase (CK) and 8% had a raised erythrocyte sedimentation ratio (ESR). The authors concluded that AIA in these patients was a non-

inflammatory musculoskeletal syndrome characterised by localised inflammation of the tenosynovial structures [39].

One study has compared the risk of joint symptoms with anastrozole and letrozole. They showed no difference in frequency of joint pain between these two, but a higher incidence of joint stiffness with anastrozole (although small numbers). However, over half of patients with joint symptoms on one AI did not have the same problems when switched to an alternative AI. Three quarters of those having joint symptoms due to an AI did not have these symptoms with tamoxifen. The authors conclude that switching from one AI to another may improve joint related symptoms, though there are no data to show that this is not a placebo response [57].

Two groups have evaluated the radiological aspects of AIA of the hand and wrist. The first important study by Morales et al. investigated 12 adjuvant patients with significant joint symptoms due to an AI at a single timepoint. Eleven were treated with letrozole and one with exemestane. All were assessed with examination, ultrasound and magnetic resonance imaging (MRI) of the hand/wrist. The median age was 57 years (49–70), an average of 8 years after the menopause. Six patients had received prior chemotherapy. Most patients had vague joint pains prior to starting AI therapy, one with a previous diagnosis of rheumatoid arthritis. The median duration to onset of joint symptoms was 8 weeks (6 weeks–9 months). Morning stiffness and hand/wrist pain were the most common symptoms. In particular, limited flexion and extension of the fingers, trigger finger and carpal tunnel syndrome were the most frequently reported clinical signs. Ultrasound showed fluid in the tendon sheath in all five patients assessed. More significantly, MRI showed fluid in the tendon sheaths of the digital flexor tendons ($n = 11$), fluid surrounding extensor tendons ($n = 4$), intra-articular fluid in the metacarpal joints ($n = 2$) and synovitis of the radiocarpal joint ($n = 1$). Enhancement and thickening of the tendon sheath were seen in all 12 patients, 10/12 having inflammatory oedema in the soft tissues. Half of the patients obtained relief from their symptoms only after discontinuing the AI [58]. In a further study by the same group, 17 patients (12 AI, 4 tamoxifen) were prospectively investigated from baseline. They were evaluated with MRI of both hands and wrists at baseline and 6 months as well as rheumatologic assessment including grip strength with a modified sphygmomanometer. Notably, three patients on an AI and one on tamoxifen had baseline abnormalities (fluid in the joints and tenosynovial changes). At follow-up, 11 AI patients had had evidence of new or worsening changes compared to 2/4 tamoxifen patients (less pronounced). Grip strength was more likely to reduce on an AI compared to tamoxifen (median decrease AI −16%, Tam +0.16%, $P = 0.0049$). There was a three-fold increase of significant tenosynovial changes for AI compared to tamoxifen users. These changes were also correlated with a higher decrease in grip strength ($r = -0.64$, $P = 0.074$). There was no association of intra-articular fluid and grip strength. Two out of 12 patients discontinued their AI due to severe arthralgia [59]. These are the first studies to provide insight into the mechanism of AI-induced arthralgia, and to show a correlation of MRI changes with grip strength for tenosynovial changes.

The second radiological study has given insight into the pathological mechanism behind AIA, although it has been presented in abstract only. Alegre-Sancho et al. [60] showed that in seven patients referred to rheumatology for investigation of AIA, all had a clinical diagnosis of bilateral trigger thumb. Six out of seven patients had carpal tunnel syndrome and two had de Quervain's tenosynovitis. There was no evidence of flexor tendon sheath tenosynovitis in contrast to the study by Morales et al. Ultrasound examination, however, confirmed thickening of the A1 pulley (which secures the position of the tendon sheath close to the phalanx to stop bowstringing) as a cause for the trigger thumb. Again this study's findings are limited by its size and the lack of a control group. Also baseline imaging was not done. The findings are nevertheless interesting and throw doubt as to the pathological mechanism behind AIA. Although it seems that the peritendinous structures may well be involved, these two studies' findings differ in that one showed flexor tenosynovitis and the other thickening of the A1 pulley (Fig. 1).

Carpal tunnel syndrome has recently been investigated in two trials. In a prospective study, patients receiving AI and controls were assessed by ultrasound and electromyography (EMG). There was a higher rate of joint and tendon effusions as well as EMG findings consistent with carpal tunnel syndrome in those reporting AIA [61]. In a subset analysis of the ATAC study, although the incidence of carpal tunnel syndrome was higher in those receiving AI therapy, it seemed to be of mild to moderate intensity. Receiving prior hormone replacement therapy, chemotherapy and age under 60 years were identified as risk factors [62].

Risk factors for AIA

As part of the ATAC trial, further investigation has been carried out looking for risk factors associated with arthralgia in 1,921 patients. Those with baseline symptoms were excluded. Prior use of HRT, hormone receptor positivity, obesity, prior chemotherapy and treatment with anastrozole were all associated with a higher risk of joint symptoms [63]. Other factors that were found not to be correlated with arthralgia were 25(OH) vitamin D, alkaline phosphatase and CRP [64, 65].

Intervention studies

Few studies have reported on interventional means of reducing AIA. Khan et al. evaluated the role of vitamin D on joint pain and fatigue in 60 women starting adjuvant letrozole therapy. All initially received standard calcium and vitamin D, but after 4 weeks, only those with vitamin D levels below 40 ng/ml at baseline (i.e having insufficiency or deficiency), $n = 42$, received additional vitamin D3 supplementation (50,000 IU per week) for 12 weeks. After 16 weeks of letrozole, the absence of joint disability was reported in more women with 25-OHD levels above rather than below 66 ng/ml (52 vs. 19%, $P = 0.026$). This suggests that there may be a role of vitamin D, although a limitation of this study was that it was not randomised and there was no placebo control [66].

Two studies have reported the use of acupuncture in AIA. The first was a single arm feasibility trial of electroacupuncture, which involves electrical stimulation of needles around painful joints. Although small ($n = 12$), reductions in pain severity, stiffness and joint symptom interference with physical function were all statistically significant [67]. Crew et al. have conducted a randomised, single blinded placebo controlled acupuncture trial that has been reported in abstract form. Thirty-eight patients were evaluable. The treatment consisted of full body/auricular acupuncture with a joint prescription; the sham procedure involved superficial needle insertion at nonacupoint locations. The treatment resulted in a 50% decrease in pain scores as per the brief pain inventory-short form (BPI-SF) [68].

Methods of assessment

Any future study investigating AIA would need to carefully consider which tools to use. Increasing importance is being given to the use of patient reported outcomes (PRO) over observer graded events as per the Common Terminology Criteria of Adverse Events. Studies have shown that there is a poor correlation between the two [69]. Discussed below are the key areas that need to be considered for evaluating AIA.

Quality of life instruments

In the large scale randomised controlled trials investigating the efficacy and safety of the third generation AIs, no questionnaires included the prospective reporting of joint symptoms, as this was an unexpected phenomenon. Subsequently, trials are now in progress and will be discussed later, in which more careful attention will be paid to the patient reported musculoskeletal symptoms. There are a number of rheumatological questionnaires in use that are validated in arthritis and particularly used in the longitudinal assessment of rheumatoid arthritis. Although the pathological processes are likely to be different, such questionnaires may be useful in the evaluation of AIA. Table 2 shows some arthritis based questionnaires currently in use.

Any future trial of AIA should strongly consider using the Health Assessment Questionnaire-Disability Index (HAQ), as used in the study by Henry et al. [39]. The HAQ was originally developed in 1978 at Stanford University and is now the cornerstone for assessment of rheumatoid arthritis in clinical trials. It can be used in a variety of rheumatic diseases, including rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis, lupus, scleroderma, ankylosing spondylitis, fibromyalgia and psoriatic arthritis. However, authors considered it as a generic instrument rather than disease specific and hence it would be appropriate to use it to assess AIA. Location of pain can easily be documented and severity may be evaluated using a visual

Table 2 QoL instruments to be considered for future AIA trials (adapted from Bernstein [95])

QoL instrument	Purpose
Short Form 36-Item Health Survey (SF-36)	General health related QoL
Menopause-specific Quality of Life Questionnaire (MENQOL)	QoL for menopausal women
Functional Assessment of Cancer Therapy-Breast + Endocrine Subscale (FACT-B + ES)	Focuses on endocrine symptoms with the recent addition of joint pain
FACT-B TOI (Trial Outcome Index)	Assessment of well being of cancer patients
NSABP–BCPT Symptom Checklist-musculoskeletal pain subscale	Assessment of musculoskeletal symptoms
Ritchie Articular Index (RAI)	Assessment of arthritis
Health Assessment Questionnaire-Disability Index (HAQ-DI)	Assessment of arthritis
Beck Depression Inventory (BDI)	For the measurement of depression
EORTC QLQ-C30	QoL for a cancer population

Abbreviations: NSABP National Surgical Adjuvant Breast and Bowel Project, *BCPT* Breast Cancer Prevention Trial, *EORTC* European Organisation for Research and Treatment of Cancer

Table 3 Common terminology criteria for adverse events version 3.0 for musculoskeletal symptoms

Adverse event	Musculoskeleltal/soft tissue				
	Grade				
	1	2	3	4	5
Arthritis (non-septic)	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
Joint function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25–50% decrease in ROM	Stiffness interfering with ADL; >50–75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	
Joint pain	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	

Abbreviations: *ADL* Activities of daily living, *ROM* range of movement

analogue scale (VAS). Alternatively, the Brief Pain Inventory-Short Form (BPI-SF) is a questionnaire for the assessment of pain related to any disease site. The Common Terminology Criteria for Adverse Events has a section on musculoskeletal pain and stiffness (grade 0–5) and is a simple assessment (Table 3), though its usefulness has been questioned in AIA [70]. In osteoarthritis, the Australian/Canadian osteoarthritis hand index (AUSCAN Index) has been validated as a self reported assessment of the hands. It measures hand pain, stiffness and function [71]. The Modified Score for the Assessment and quantification of Rheumatoid Affections of the Hands (M-SACRAH), a shortened version of the SACRAH, is another self administered questionnaire assessing functional status, stiffness and pain in patients suffering with both hand osteoarthritis and rheumatoid arthritis [72]. It has been compared to the AUSCAN and demonstrated good correlation ($r = 0.73, 0.75, 0.76$ for pain, stiffness and function, $P < 0.001$) [73]. The Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC) is a well validated PRO assessment used to evaluate hip and knee osteoarthritis using 24 parameters. It evaluates pain, stiffness and physical function and is being tested in AIA in at least one study (Table 4).

Clinical assessment

In the clinical assessment of AIA, other causes of joint symptoms need to be excluded. There are a large number of both inflammatory and non-inflammatory diseases that form the differential diagnosis. Pain and stiffness have been the two main reported symptoms of AIA. Morning stiffness should be assessed and the duration recorded. In rheumatoid arthritis, disease activity has traditionally been measured by Disease Activity Score (DAS-28). This is an assessment of 28 joints for synovitis and combines scores for a general health VAS and ESR or CRP to give an overall score. This score is used longitudinally to gauge response to treatment. However, the limitation of this score is that current evidence suggests inflammatory markers may not be raised in AIA [39].

Grip strength as measured by a modified sphygmomanometer has been shown to deteriorate with AI use as compared to tamoxifen and correlate with semi-quantitative tenosynovial changes on MRI imaging [59]. However, this form of grip strength measurement has not been validated in clinical studies and actually measures grip pressure. A limitation with this technique is that results vary with different hand surface areas. Although grip strength is now much less used in rheumatological studies, it does have evidence behind its use. The gold standard measuring instrument for which most data exists is the Jamar dynamometer, which has been shown to be the most accurate and reproducible [74], with published normal values across the age ranges [75]. Future similar studies should use this more reliable technique.

Radiological assessment

Ultrasound

Ultrasound is now a standard investigation performed by rheumatologists for the assessment of musculoskeletal symptoms [76]. Its use has recently been directed towards the assessment of patients with inflammatory arthritis. This includes the detection of bone erosions, synovitis, tendon disease and enthesopathy. Ultrasound has a number of advantages over magnetic resonance imaging (MRI). In particular, the operator can scan multiple joints in a brief period of time. Patient tolerability is excellent and the

Table 4 Current ongoing studies investigating AIA [93]

Name of study	AI	Location	Assessment
Longitudinal assessment of arthralgia and related symptoms in breast cancer	Anastrozole	Texas, USA	Questionnaire and telephone symptom log
Rheumatological evaluation of anastrozole and letrozole as adjuvant treatment in post-menopausal women with breast cancer (REAL)	Letrozole, intolerant to Anastrozole	Arkansas, USA	N/K
Vitamin D deficiency and muscle pain and/or joint pain in postmenopausal women receiving letrozole for Stage I, Stage II, or Stage III breast cancer	Letrozole	Seattle, USA	Vitamin D levels
Vitamin D3 for aromatase inhibitor induced arthralgias (VITAL)	Letrozole	Kansas, USA	HAQ, BPI, BFI, VAS, MENQOL, serum 25OHD, letrozole, SNPs of vitamin D receptor genes
Androgen therapy for breast cancer patients with aromatase inhibitor induced side-effects	Anastrozole	Adelaide, Australia	Testosterone VAS
Breast cancer tumor care observational programme	Anastrozole	Graz, Austria	Questionnaires
Trial of blue citrus compared to placebo in patients receiving aromatase inhibitor therapy for estrogen receptor positive post-menopausal breast cancer	AI	Oregon, USA	Blue Citrus VAS SF-12
Arthralgia during anastrozole therapy for breast cancer	Anastrozole	France	VAS Cochin Index
Changes in knee articular cartilage volume in women on aromatase inhibitors	Anastrozole, Letrozole	Melbourne, Australia	Knee MRI MENQOL
Musculoskeletal pain in postmenopausal, early breast cancer patients receiving aromatase inhibitor therapy—a pilot study	AI	Montreal, Canada	N/K
Glucosamine and chondroitin for aromatase inhibitor induced joint symptoms in women with breast cancer	AI	New York, USA	OMERACT-OARSI
An investigation of aromatase inhibitor-induced arthralgia in the adjuvant treatment of breast cancer (ARIAD)	AI	Sheffield, UK	BPI-SF HAQ-DI SF-36, DAS-28 Hand U/S, DXA, MRI
A case control study to define clinical, immunologic and radiographic features of the aromatase inhibitor arthralgia syndrome (CIRAS)	AI	Washington DC, USA	DAS-28, ESR, TNF-α, IL-6, ultrasound
Randomized trial of acupuncture for aromatase inhibitor induced joint pain	AI	New York, USA	BPI-SF WOMAC index FACT-B Il, TNF
Acupuncture or medication in reducing pain in postmenopausal women with breast cancer and joint pain	Anastrozole	Arizona, USA	WOMAC index, biomarkers
Arimidex: compliance and arthralgias in clinical therapy (COMPACT)	Anastrozole	Germany	Descriptive

Abbreviations: *N/K* not known, *HAQ* health assessment questionnaire, *BPI-SF* brief pain inventory short form, *BFI* brief fatigue inventory, *VAS* visual analogue scale, *MENQOL* menopause-specific quality of life questionnaire, *25OHD* 25-hydroxyvitamin D, *SNP* single nucleotide polymorphisms, *SF-12 & 36* short form 12 & 36, *MRI* magnetic resonance imaging, *OMERACT-OARSI* outcome measures in rheumatology clinical trials – osteoarthritis research society international, *HAQ-DI* heath assessment questionnaire disability index, *U/S* ultrasound, *DAS-28* disease activity score 28, *ESR* erythrocyte sedimentation ratio, *TNF* tumour necrosis factor, *Il* Interleukin, *WOMAC* Western Ontario and McMaster Universities, *FACT-B* functional assessment of cancer therapy-breast

rheumatologist with clinical understanding of the patient's complaints, can image the problem at initial consultation. This allows for rapid interpretation of the images and immediate decision-making, for the benefit of the patient. There are, however, some disadvantages to joint ultrasound. It is often perceived as an imperfect and operator-dependent tool. In comparison with MRI, there are limited data regarding its validity, reproducibility and responsiveness to change. Thus, interpretation and comparison of different studies can be difficult. In particular, there are limited data describing standardised scanning methodology and standardised definitions of ultrasound detected pathologies [77].

In addition to grey scale images, the use of colour and power Doppler is now standard. Grading levels of inflammation, assessing response to anti-inflammatory agents such as systemic corticosteroids and aiding in the differentiation between degenerative, inflammatory and normal tissue are the key uses of this technology [78]. Given there may be some similarities between AIA and early rheumatoid arthritis [79], this modality may provide insight into the mechanism of AIA. There is also a question as to whether AIs can worsen pre-existing rheumatoid disease [37]. Thus, it would be logical to use knowledge of this disease process to direct investigation of AIA. However, the apparent lack of inflammatory synovitis and systemic elevation in inflammatory markers, may point towards a process similar to osteoarthritis.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) has multiplanar capabilities that can be used to assess joint and peri-articular disease. Tendons, tendon sheaths, ligaments, synovial membrane, cartilage and bone are amongst the structures that are delineated well by this modality. T1 sequences give good anatomical appearances of the musculoskeletal system, whilst T2 sequences pick up high water content such as that seen in inflammatory processes. The use of contrast [usually gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA)] is used to delineate areas of inflammation as increased vascular permeability allows accumulation at sites of synovitis and osteitis [80].

As discussed earlier, only one study has used MRI to investigate AIA. The main abnormalities were seen in the tendon sheaths and soft tissues [59]. To take this forward, further evaluation of larger cohorts is required with comparison with control groups as some of these findings can also be seen in the background population. It would also be important to be able to grade the degree of abnormality, particularly in the tendons. Extrapolating from rheumatoid arthritis, a novel scoring system for tenosynovitis has shown a high degree of multireader reliability [81]. This effectively grades the degree of synovial proliferation and peritendinous effusion on a scale of 0–3. It stems from the Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis MRI Score (RAMRIS) score which is a well validated semi-quantitative score of bone erosions, bone oedema and synovitis, used in rheumatoid arthritis trials [82].

Dual energy X-ray absorptiometry (DXA)

The loss of bone density with AIs was well characterised by the large phase III adjuvant trials of AIs. In addition, there is now evidence that this can be circumvented with therapeutics such as the bisphosphonates (zoledronic acid and ibandronic acid) and more recently monoclonal antibodies targeting bone resorption [83–85]. Bone density of the hand has been investigated in early undifferentiated arthritis. In a study of 74 patients, the greatest loss of bone density (−4.3% at 12 months) occurred in those subsequently developing rheumatoid arthritis [86]. A follow-up study looked at 79 patients who had been diagnosed with rheumatoid arthritis for less than 12 months. Hand bone densitometry was shown to be more sensitive than scoring plain radiographic changes for the assessment of disease related joint damage [87]. The mechanism for bone loss in this disease has been shown to be due to overall loss of bone density and periarticular osteoporosis. Whether or not similar processes are associated with AIA remains unknown. If there are similarities between AIA and rheumatoid arthritis then clearly this modality requires further investigation.

Biochemical assessment

Biochemical markers have had limited investigation in this context. So far there has been no evidence of a rise in the commonly tested inflammatory markers (CRP and ESR). However, one recent study has suggested lower baseline concentrations of a number of interleukins (1b, 2, 10, 15, 17, 1Ra, 2R, 7 and 12 p40) and colony stimulating factors (GM-CSF, G-CSF) in cases as compared to controls, suggesting an anergic cytokine phenotype in those developing AIA [88].

There is evidence for various markers in rheumatological diseases such as osteoarthritis and rheumatoid arthritis. Potentially useful markers of cartilage metabolism are cartilage oligomeric matrix protein (COMP), c-telopeptide of type II collagen (CTX-II), aggrecan 846 epitope, c-propeptide, C1,2C and C2C. The Boston Osteoarthritis Knee Study evaluated levels of cartilage degradation and synthesis products and showed only COMP was a significant predictor of cartilage loss as assessed by MRI imaging [89, 90]. Other trials have shown urinary CTX-II to be a useful marker of osteoarthritis. In rheumatoid arthritis, anticyclic

citrullinated peptide antibody (second generation assay) has similar sensitivity to rheumatoid factor, but a greater specificity for the diagnosis. Urinary glucosyl-galactosyl-pyridinoline (Glc-Gal-PYD) is a marker of destruction of the synovium and serum matrix metalloproteinase 3 (MMP-3) is a proteinase expressed by synovial tissue and chondrocytes [91, 92]. These markers may provide insight into the mechanism behind AI-induced arthralgia.

Current and future perspectives

Aromatase inhibitor-induced arthralgia (AIA) is currently under investigation in a number of clinical trials as shown in Table 4 [93]. These include descriptive studies to imaging and intervention studies. A study from the MD Anderson Cancer Center is currently recruiting to a longitudinal evaluation of joint symptoms. It is focussing primarily on questionnaire and telephone assessment. The breast cancer tumour care observational programme based in Austria is another ongoing descriptive study. The COMPACT trial is a large observational study with a recruitment target of 3212 patients. Compliance to therapy and scores of arthralgia are the main end points, though it commences after 3–6 months of anastrozole therapy, not from baseline. The AIMS study will provide prospective observational data on cases of AIA.

There are four clinical studies, which are investigating the radiological basis for AIA. A French single arm open label trial is using ultrasound as well as collecting data on PROs. Bone and cartilage biomarkers are also being measured. The second Australian study is focussing on changes in knee articular cartilage volume using MR imaging. The third study being conducted by the authors is the ARIAD study (An Investigation of Aromatase Inhibitor-Induced Arthralgia in the Adjuvant treatment of Breast Cancer). This is an observational phase IV study examining the incidence and aetiology by investigating the joint symptoms of the four cohorts. In this research, PROs are assessed by the use of three questionnaires (SF-36, HAQ-DI and BPI-SF) and clinical evaluation is recorded by grip strength and DAS-28 scoring. Imaging of the hands is being performed to corroborate the findings of Morales et al. Patients will undergo plain X-ray, ultrasound, DXA and MRI of the hand(s). Blood and urine samples will be examined for biochemical, inflammatory and immunological markers of joint disease. Another study, the CIRAS study, is also measuring ultrasound assessment of tenosynovitis and DAS-28 scores.

There are now a number of interventional studies underway investigating the treatment of AIA. The REAL Study is evaluating patients who are intolerant to anastrozole to gauge if joint symptoms are better with letrozole. Other trials are investigating the use of acupuncture, vitamin D supplementation in deficient patients, testosterone, blue citrus, glucosamine and chondroitin. The results of these studies may provide alternative treatment strategies to opioid and anti-inflammatory analgesics.

Conclusion

It is clear that AIA remains an important clinical issue requiring further investigation. From a patient perspective, the joint pain and stiffness can have a significant impact on function potentially leading to non-compliance or to treatment discontinuation. As survival from breast cancer has improved, the issues behind survivorship have become more important and the subject of high quality trials. At present, as discussed in this document, there are relatively few data on the aetiology of AIA and in particular, prospective studies are lacking.

So far, the assumption is that oestrogen deprivation is the underlying pathological process, though the mechanism remains unclear. Certainly the presence of tenosynovitis of the digital flexor tendons and trigger thumb imply an association with the periarticular tendon sheath, though this evidence is limited to less than 30 published cases which have not been sufficiently compared with controls.

Further prospective studies are required and underway to investigate the symptomatic, rheumatological, radiological and biochemical changes in AIA. With this knowledge, future research can be directed at what may be the best intervention to maintain patients on their AI despite joint symptoms.

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