Investigating the Effects of Aromatase Inhibitors on the Musculoskeletal System

Omar Sadeeq Shujja-Ud-Din

MBChB MRCP MSc FRCR

A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Medicine

MD Thesis

Academic Unit of Clinical Oncology

University of Sheffield

School of Medicine and Biomedical Sciences

Cancer Clinical Trials Centre

Weston Park Hospital

March 2014

The University Of Sheffield.

Table of Contents

List of Figures

List of Tables

1. ACKNOWLEDEMENTS

Firstly I would like to thank my supervisor, Professor Robert Coleman, who is solely responsible for making this research happen. He has also provided invaluable support and guidance through a complicated process of research governance and research trial progress in 2 different cities. I would also like to give thanks Professor David Dodwell as without his support, this project would not have been able to run in Leeds.

I owe a great deal of gratitude to Mike Bradburn and Saleema Rex who spent a significant amount of time helping with analysing the large ARIAD study database.

In Sheffield, I would particularly like to thank Sandra Gutcher, for helping run the study and Carol Crabtree and Janet Horsman for keeping the database updated. Helen Shulver and Brenda Smith were a great asset in keeping track of all the stored study samples. I owe thanks to my collaborators, in Sheffield, Professor Gerry Wilson, Dr Adrian Highland as well as fellow oncologists and breast surgeons.

In Leeds, I would particularly like to thanks both Ruth Thorpe and Sue Hartup, who have both been invaluable in running the ARIAD study. Dr Ai Lyn Tan and Dr Richard Wakefield were instrumental in helping design the rheumatological aspects of the study. I thank Professor Paul Emery who supported the running of this study in his department. I also thank Dr Phil O'Connor for advice and direction with the MRI aspects of the study. Mr Kieran Horgan was superbly supportive in recruiting patients through the Leeds breast unit. Thanks go to the long list of colleagues in breast surgery, oncology and radiology.

It was very kind of Professor Payman Hadji to offer to perform some biochemical investigations. Thanks to his laboratory team for making this process smooth between UK and Germany.

I would like to give thanks to the funders of the ARIAD study. There was a major contribution from the Sanita Merali Research Fund for my clinical fellowship and Astra Zeneca for funding the MRI scans.

Loving thanks go to Alia, Raihaan, Hena and Aadil for their encouragement to complete the thesis. I would never have completed this without their support.

And finally, my wholehearted gratitude goes to the 77 patients that took part in the study, without whom it would never have been such a success.

2. PUBLICATIONS AND PRESENTATIONS

*Din OS, Dodwell D, Wakefield RJ, Coleman RE.
Aromatase inhibitor-induced arthralgia in early breast cancer: what do we know and how can we find out more?
Breast Cancer Res Treat. 2010 Apr;120(3):525-38.

OS Din, D Dodwell, M Bradburn, P Emery, A Highland, K Horgan, P O'Connor, AL Tan,
R Wakefield, AG Wilson, RE Coleman
Investigating early features of Aromatase Inhibitor-Induced Arthralgia (AIA)
San Antonio Breast Cancer Symposium Dec 2010

*Din OS, Dodwell D, Winter M.C, Mori S, Coleman RE
Current Opinion of Aromatase Inhibitor-Induced Arthralgia (AIA) in breast cancer in the United Kingdom
Clin Oncol (R Coll Radiol). 2011 Dec;23(10):674-80.

*Permission has been granted by Elsevier to reproduce these articles in this thesis.

3. LIST OF ABBREVIATIONS

ABCSG	Austrain Breast and Colorectal Cancer Study Group
ASCO	American Society of Clinical Oncology
ADL	Activites of Daily Living
AE	Adverse Event
AI	Aromatase Inhibitor
AIA	Aromatse Inhibitor Arthralgia
AIMSS	Aromatase Inhibitor Associated Musculoskeletal Symptoms
ANA	Antinuclear Antibody
ARIAD	Aromatase Inhibitor Arthralgia in Adjuvant Breast Cancer
ARNO	Arimidex Nolvadex
ATAC	Arimidex, Tamoxifen, Alone or in Combination
ATOLL	Articular Tolerance of Letrozole
AUSCAN	Australian Canadian Hand Osteoarthritis Index
BMI	Body Mass Index
BMD	Bone Mineral Density
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
CCP Ab	Cyclic Citrullinated Peptide Antibody
CI	Confidence Interval
CIRAS	Clinical Immunologic and Radiographic Arthralgia Syndrome
CK	Creatinine Kinase
COMP	Cartilage Oligomeric Matrix Protein
COMPACT	Compliance and Arthralgia in Clinical Therapy
COX-II	Cyclo-Oxygenase II
CRP	C Reactive Protein
CTCAE	Common Terminology Criteria of Adverse Events
CTS	Carpal Tunnel Syndrome
CTX-II	Type II Collagen
DAS	Disease Activity Score
DCIS	Ductal Carcinoma In Situ
dsDNS	Double stranded Deoxyribonucleic Acid
DXA	Dual X-ray Absorptiometry
E2	Oestradiol E2
EBCTCG	Early Breast Cancer Trialists Collaborative Group
ER	Oestrogen Receptor
ESR	Erythrocyte Sedimentation Ratio
FACT-B	Functional Assessment of Caner Therapy-Breast
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
Gd-DTPA	Gadolinium Diethylenetriamine Pentaacetic Acid
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire-Disability Index
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
IES	International Exemestane Study
IGF-1	Insulin-like Growth Factor-1
IL-1	Interleukin-1

IL-6	Interleukin-6
LMP	Last Menstrual Period
IRAS	Integrated Research Application System
ITA	Italian Tamoxifen Anastrozole
MCP	Metacarpophalangeal
MCS	Mental Component Summary
MMP	Matrix Metalloproteinase
MREC	Multi-centre Research Ethics Committee
MRI	Magnetic Resonance Imaging
mRNA	Messenger RNA
NICE	National Institute of Clinical Excellence
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PCS	Physical Component Summary
PIP	Proximal Interphalangeal
PR	Progesterone Receptor
PRO	Patient Reported Outcome
PROMIS	Patient Reorted Outcomes Measurement Information System
QoL	Quality of Life
RAMRIS	Rheumatoid Arthritis MRI Score
REACT	Randomised European Celecoxib Trial
RF	Rheumatoid Factor
ROM	Range Of Movement
SERM	Selective Oestrogen Receptor Modulator
SD	Standard Deviation
SF	Short Form
TEAM	Tamoxifen Exemestane Adjuvant Multinational
TIA	Tamoxifen Induced Arthralgia
TOI	Mean Trial Outcome
TNF	Tumour Necrosis Factor
VAS	Visual Analogue Scale
25OHD	25-Hydroxyvitamin D

4. 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 Arthralgia (AIA) are reviewed in this thesis. 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. This syndrome has been investigated in a prospective controlled study (ARIAD), which forms the main focus of this thesis. In addition, a second study of the attitudes of UK breast clinicians regarding AIA has been completed and is reported here.

5. INTRODUCTION

5.1. BACKGROUND

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 (EBCTCG 2005). However, more recently, trials of AIs have shown benefits over tamoxifen, in both a metastatic (Bonneterre et al. 2000; Nabholtz et al. 2000; Mouridsen et al. 2003) and subsequent adjuvant treatment setting (Goss et al. 2003; Coombes et al. 2004; Howell et al. 2005; Jakesz et al. 2005; Thurlimann et al. 2005; Boccardo et al. 2006; Coombes et al. 2007). 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 introduction, 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.

5.2. MECHANISM OF ACTION OF AROMATASE INHIBITORS

Oestrogen is implicated in the initiation, promotion and progression of breast cancer (Yager et al. 2006). 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 eg. Tamoxifen) or pure antioestrogens (eg. 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 (figure 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) (figure 2). Non-steroidal imidazole-based AIs reversibly interact with the cytochrome P450 moiety of aromatase and therefore need to be continually present for inhibition (Njar et al. 1999). 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 (di Salle et al. 1992; Campos 2004).

Figure 1. Oestrogen biosynthesis pathway

(Adapted from Steroidogenesis http://commons.wikimedia.org/wiki/File:Steroidogenesis.gif)

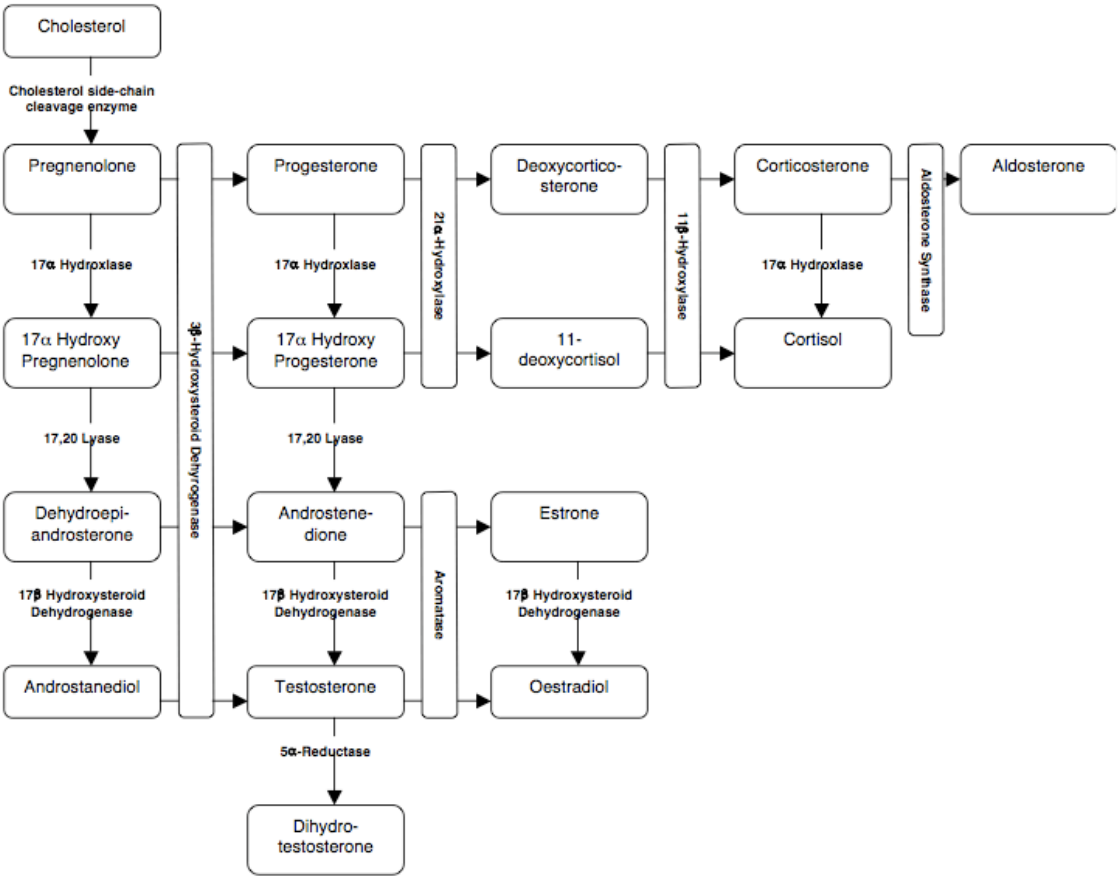
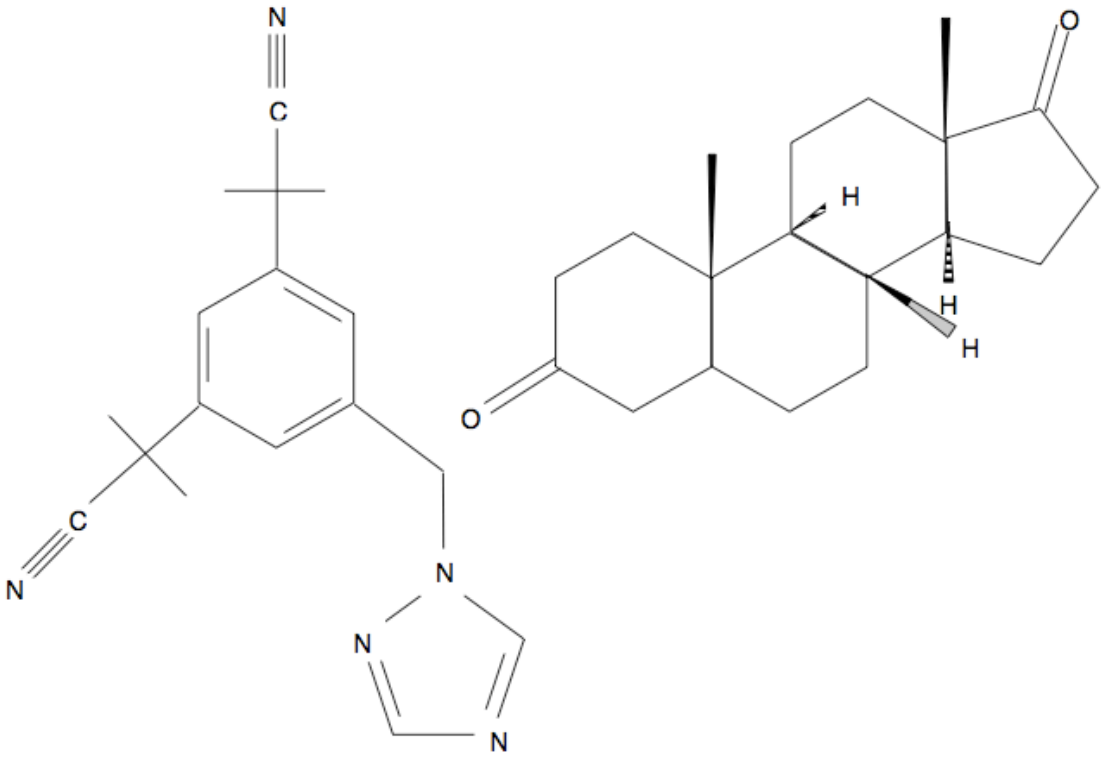


Figure 2. Chemical structure of a non-steroidal (Anastrozole) and steroidal (Exemestane) 3rd generation AI



Anastrozole Exemestane

5.3. 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 (Greendale et al. 1999). Joint symptoms in post menopausal women are well recognised and were described as an entity as early as 1925 (Cecil et al. 1925).

More recently, cross-sectional studies have investigated the presence of musculoskeletal symptoms during the various stages of the menopause. In a telephone survey of 2145 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) (Avis et al. 2004). Dugan et al. reported 1 in 6 women experiencing joint symptoms, again highest in the perimenopausal age range (Dugan et al. 2006). In another cross-sectional study, the rate of joint and muscle pain in post menopausal women was close to 50% (Xu et al. 2005). 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 BMI (Body Mass Index) ($p<0.01$), being unemployed ($p<0.05$) and low mood ($p<0.005$) (Szoeke et al. 2008). 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% (Huang et al. 1997). 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 AIA.

5.4. AETIOLOGY

The mechanism behind AI-induced arthralgia 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 1pmol/l (Dowsett et al. 1997). 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 (Cvoro et al. 2008; Nielsen et al. 2008). Clearly there are several possible causes of arthralgia in a non-breast cancer population, which can make it difficult to elucidate one particular cause.

5.4.1. Role of Oestrogen

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 (Dawson-Basoa et al. 1997). This is particularly evident during pregnancy, when women have elevated thresholds for painful stimuli in the presence of increased levels of oestrogen (Dawson-Basoa et al. 1997). 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 (Riley et al. 1999). 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 (Dietrich et al. 2006). ER-α and β are found in normal cartilage, but are present at increased levels in osteoarthritic joints (Richette et al. 2003; Coleman et al. 2008). Type II collagen, 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 (Oestergaard et al. 2006; Sniekers et al. 2008). However, in humans, hormone replacement therapy is not an adequate treatment of arthralgia in postmenopausal women. (Nevitt et al. 2001).

As discussed in the section of AIA in clinical practice, tenosynovitis has been implicated in the AIA syndrome. The tendon consists primarily of collagen (mostly type I collagen) and elastin embedded in a proteoglycan-water matrix. Other types of collagen (e.g. II, III, V, VI, IX, XI) are also present in much smaller proportions. The tendon sheath has two layers: the synovial sheath and fibrous tendon sheath. The synovium is composed of 2 to 3 layers of specialised cells termed synoviocytes. This provides a frictionless mechanism by which the tendon can slide. The tendon sheath of the fingers is held in place by a series of pulleys to avoid bowstringing (see figure 3).

There is evidence that aromatase may be expressed synovial cells and chrondrocytes of articular cartilage (Sasano et al. 1997; Le Bail et al. 2001). 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 oestrone and oestradiol in synoviocytes by aromatase and this process was positively regulated by glucocorticoids (Le Bail et al. 2001).

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 4 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. (Toesca et al. 2008)

5.4.2. Autoimmume Process

There are reports of autoimmume disease, particularly rheumatoid arthritis and sjogren's syndrome, being associated with aromatase inhibitor therapy (Laroche et al. 2007; Morel et al. 2007). However, studies up to now have not shown increased incidence of autoimmunty or indeed raised systemic inflammatory markers. One prospective study focussing on this aspect only showed minor elevation in a few markers as discussed in the section 'AIA in clinical practice' (Henry et al. 2008). 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 (Le Bail et al. 2001). Therefore, reduction of oestradiol may therefore 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 (Pfeilschifter et al. 2002), 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, which may be linked to cytokine activity (Mao et al. 2009).

5.4.3. Vitamin D

The understanding of the role of vitamin D in general health has increased significantly increased over the last decade. It is well established that it plays an important role in musculoskeletal health. It primarily exists in 2 forms, vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). D3 is predominantly produced in the skin from sunlight exposure, with a small amount coming from foods such as oily fish and egg yolk. D2 comes predominantly from plant sources. (Holick et al 2011)

In the skin, D3 is produced from 7-dehydroxycholesterol following exposure to ultraviolet B radiation. It is then transported to the liver, where metabolism by the cytochrome P450 enzymes to 25-hydroxy vitamin D (25(OH)D). The biologically active form of vitamin D is 1,25-hydroxy vitamin D (1,25 $(OH)_2D$). The enzyme 1α-hydroxylase converts 25(OH)D to the active form in the proximal tubule of the kidney as a part of calcium homeostasis. 25(OH)D is the usual measure of vitamin D status. (Holick et al. 2011; Garg et al. 2012)

Vitamin D increases serum calcium and phosphate and promotes bone mineralisation. The biologically active form is increased in response to stimulus from parathyroid hormone (PTH) and hypophosphataemia. This leads to an increase of bone density via osteoblast secretion of nuclear factor-kB ligand (RANKL). Thus osteoclast activity is increased leading to bone resorption and calcium mobilsation. Deficiency of vitamin D causes osteomalacia in adults and rickets in children as a consequence of the impairment of bone mineralisation. They are associated with bone deformities and pain. Other effects associated with vitamin D deficiency are reduced muscle strength and muscle mass. (Garg et al. 2012) The hypothesis of vitamin D deficiency in association with AIA has rationale and is discussed further in this thesis.

5.5. ARTHRALGIA IN THE PHASE III TRIALS OF ADJUVANT AIS

The indications for use of adjuvant AI therapy can be subdivided into 3 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). Each of these will be discussed below and a summary is shown in table 1.

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

Trial	n	Toxicity	%	%	%	p
			AI	Tam	Placebo	
ATAC (Howell et al. 2005)	9366	Joint Symptoms	35.6	29.4		<0.0001
		Arthralgia	15.1	11.1		
		Carpal tunnel	3	1		<0.0001
BIG 1-98 (Thurlimann et al. 2005)	8028	Arthralgia	20.0	13.5		<0.001
IES (Coombes et al. 2007)	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 (Boccardo et al. 2006)	448	Musculoskeletal/fracture	9.9	6.7		0.2
ABCSG 8/ ARNO 95 (Jakesz et al. 2005)	3224	Bone pain	19	16		0.0546
MA-17 (Goss et al. 2003)	5187	Arthralgia	21.3		16.6	<0.001
		Myalgia	11.8		9.5	0.02
		Arthritis	5.6		3.5	<0.001
ABCSG 6a (Jakesz et al. 2007)	856	Bone pain (inc joint pain)	24.5		18.3	0.009
TEAM (Van de Velde et al. 2011)	9779	Joint disorders	36	31		<0.0001
		Muscle disorders	11	13		0.0014

5.5.1. Upfront Use

Anastrozole has the most data with regard to the incidence of joint symptoms within the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial (Howell et al. 2005). In this study, musculoskeletal symptoms were reported according to 4 terms: arthralgia, arthritis, arthrosis and joint disorder, though in most cases the AEs (adverse events) were just related to pain in the joints. At 68 months of follow up, 1100/3092 (35.6%) of patients receiving anastrozole experienced joint symptoms compared to 911/3094 (29.4%) receiving tamoxifen ($p<0.0001$) (table 1). 46% of these were as part of a pre-existing joint problem. Notably, the rate of carpal tunnel syndrome was significantly increased in patients receiving anastrozole (3% v 1%). Symptoms were usually generalised. Peak occurrence for joint symptoms was 6 months. Rates of serious adverse events were, however, similar in both arms (A 10.6%, T 10.4%). Only a small number of patients withdrew from therapy (A 2.1%, T 0.9%) (Buzdar 2006; Buzdar et al. 2006).

There was a higher rate of arthralgia in anastrozole patients who had received prior chemotherapy (41.3% v 33.9%). The median time to symptoms was also shorter in this group (9.1 months v 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 (Coleman et al. 2008).

Interestingly, when overall quality of life 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 ($p=0.23$) (Fallowfield et al. 2004) and 5 years ($p=0.65$) (Cella et al. 2006). 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 (Khanduri et al. 2007).

Letrozole was studied in the other large upfront adjuvant study (BIG 1-98). In the most recent analysis (51 months median follow up), 489/2448 (20.0%) of patients receiving letrozole and 331/2447 (13.5%) receiving tamoxifen developed arthralgia (table 1) (Coates et al. 2007). There was also a higher proportion in the letrozole treated group experiencing grade 3-4 arthralgia. Again, joint symptoms did not feature specifically as a predetermined adverse event. As of yet, no further information has been published on this specific AE.

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 (Cuzick et al. 2008). 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 (Chlebowski et al. 2006; Fallowfield 2008). There are possible confounding factors in such analyses. It has been suggested that this phenomena may be related to patient self reporting, in that those reporting side effects may be more likely to comply with medication and hence have a reduced risk of cancer recurrence (Pritchard 2008).

5.5.2. Switch Therapy

This protocol, involving changing from tamoxifen to an AI after 2-3 years, has been evaluated in three main randomised phase III trials. The largest of these was the Intergroup Exemestane Study (IES), which used exemestane. On

treatment, the rate of arthralgia on exemestane was significantly higher (432/2320, 18.6%) than tamoxifen (275/2338, 11.8%). These effects emerged during the on-treatment period. 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 aromatase inhibitor. 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 (Coombes et al. 2004; Coombes et al. 2007). Quality of life analysis using the FACT-B TOI, showed no meaningful change between the two study groups (Fallowfield et al. 2006). Again, this instrument did not take into account arthralgia and other joint symptoms.

In the ABSCSG trial 8 and ARNO 95 combined, patients were randomised after completing 2 years of tamoxifen, to either continue or switch to anastrazole for 3 years. Rates of bone pain were reported only in the former study. 117/1117 (16%) reported bone pain in the tamoxifen arm compared with 213/1120 (19%) for those on an AI (p=0.055) (Jakesz et al. 2005). In a similarly designed smaller study (Italian Tamoxifen Anastrozole Trial (ITA)), with a median follow up of 64 months, the incidence of musculoskeletal disorders and fractures was combined, showing a small increase for those taking anastrozole (T 6.7%, A 9.9%) (Boccardo et al. 2006).

One unique study, the TEAM trial (Tamoxifen Exemestane Adjuvant Multinational phase 3 trial), compared upfront AI use with switch AI. Postmenopausal women with hormone-receptor-positive breast cancer were randomised to receive either exemestane or tamoxifen for 5 years. However, after the publication of the IES study, an amendment was approved to switch those patients who had been randomised to tamoxifen, to switch to exemestane after 2 years. Whilst no difference in effectiveness was seen for the two strategies, a unique insight was given into the side effect profiles. Rates of bone disorders were significant for both arms (36% and 31% for upfront and switch arms respectively). Muscle disorders and other musculoskeletal conditions were also reported (11-13% and 13-15% respectively) (van de Velde et al. 2011). In a

retrospective analysis of the German cohort of this study, treatment emergent side effects were evaluated. Patients reporting arthralgia or myalgia or menopausal symptoms seemed to gain benefit in terms of disease free and overall survival. In the first 2 years, arthralgia and myalgia was significantly more common in women receiving an aromtase inhibitor (30.8% versus 15.7%). After the switch from tamoxifen to exemestane, the incidence increased to 29.6%. This indicated the significant contribution of exemestane causing musculoskeletal symptoms over and above tamoxifen (Hadji et al. 2012).

5.5.3. 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). As in most of the other studies, no further information is available regarding the time to onset, duration or resolution of symptoms. However, quality of life was assessed using the SF-36 (Short Form 36) and MENQOL (Menopause Specific Quality of Life) questionnaires. Bodily pain formed a part of the SF-36, but was no different in the two arms. Aching muscles was reported in the MENQOL, showing a higher incidence in the letrozole group (43% v 38%). The authors concluded that there was no detrimental effect on quality of life, but there were small changes attributable to those suffering bodily pain and vasomotor symptoms (Goss et al. 2003; Whelan et al. 2005).

The ABCSG trial 6a evaluated the use of anastrozole for a further 3 years after 5 years of tamoxifen (with or without the second generation aromatase inhibitor aminoglutethimide for the first 2 years). The rates of bone pain (including joint pain) were reported. 24.5% had this symptom in the anastrozole group compared to 18.3% in the no further treatment arm (HR 1.55 p=0.009). No further details regarding arthralgia were given in this publication (Jakesz et al. 2007).

5.5.4. 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. Firstly, 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 (Felson 2008). 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 (Sestak et al. 2008).

5.6. AIA IN CLINICAL PRACTICE

5.6.1. Case Series

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) (Crew et al. 2007).

Present et al. reviewed 56 consecutive patients receiving third generation AIs in community cancer centres in USA, by interview. 34 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 (Presant et al. 2007). In a retrospective analysis of 600 patients who were receiving or had received adjuvant AI therapy, Dent et al. showed 20% self reporting arthralgia/arthitis. 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%) (Dent et al. 2007).

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%) (Mao et al. 2009).

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 (Renshaw et al. 2007). This strategy was also tested in the ATOLL study which is discussed later (Briot et al. 2010).

Kanetmatsu et al described some of the clinical features of AIA in their prospective database of 328 postmenopausal breast cancer patients receiving adjuvant anastrozole. They reported a 34.8% incidence of AIA, which is comparable to the published literature. Three peaks of AI onset were described with gradually reducing frequency: at 4 months, at 8 months and after 13 months (Kanetmatsu et al).

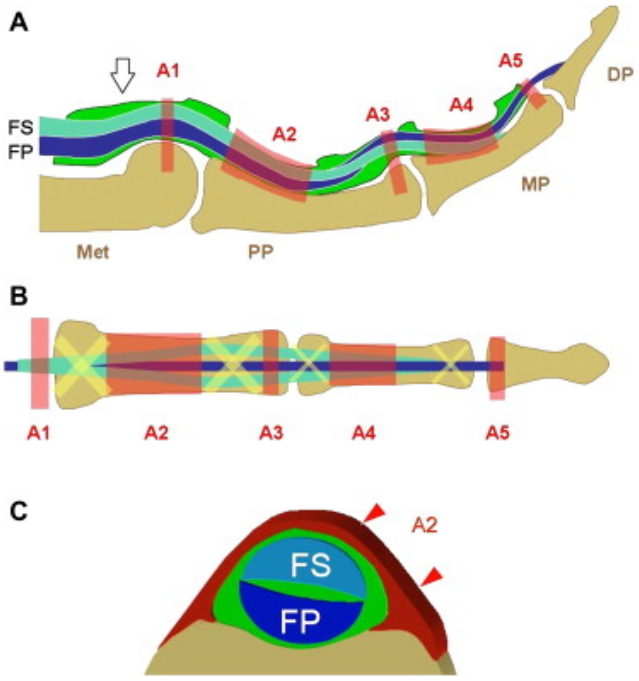
5.6.2. Radiological changes

Some groups have evaluated the radiological aspects of AIA of the hand and wrist. The first important study by Morales and colleagues investigated 12 adjuvant patients with significant joint symptoms due to an AI at a single time point. Eleven were treated with letrozole and 1 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. 6 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 5 patients assessed (see figure 3 for normal anatomy). 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 was 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 (Morales et al. 2007). 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, 3 patients on an AI and 1 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. 2/12 patients discontinued their AI due to severe arthralgia (Morales et al. 2008). 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.

Figure 3 (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 Bianchi et al. Journal of Ultrasound (2007); 10: 85-92. © Elsevier



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 showed that in 7 patients referred to rheumatology for investigation of AIA, all had a clinical diagnosis of bilateral trigger thumb (Alegre-Sancho et al. 2008). 6/7 had carpal tunnel syndrome and 2/7 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 (figure 3)) as the 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 finding differ in that one showed flexor tenosynovitis and the other thickening of the A1 pulley.

5.6.3. Prospective detailed studies

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 CRP (C-reactive protein), 16% had an elevated anti-nuclear factor, 10% had a raised CK (creatinine kinase) and 8% had a raised ESR (erythrocyte sedimentation ratio). The authors concluded that AIA in these patients was a non-inflammatory musculoskeletal syndrome characterised by localised inflammation of the tenosynovial structures.(Henry et al. 2008)

Henry et al. conducted a prospective evaluation of 30 consecutive patients commenced on adjuvant aromatase inhibitor therapy. High resolution wrist ultrasound was performed at both baseline and after 3 months of therapy. They attempted to define the syndrome of AIMSS (Aromatase inhibitor associated musculoskeletal symptoms) as there is currently no universally accepted definition. It was defined as meeting one or more of the following criteria at any point during study:

1) HAQ (Health Assessment Questionnaire) score increased by more than 0.4 over baseline score,

2) Pain VAS (Visual Analogue Scale) value ≥ 5 cm (of a 10 cm VAS) for patients with no pain (VAS = 0) at baseline, and

3) Pain VAS value increased and pain rated much worse or very much worse pain on self-rated clinical global impression scale.

There was a high degree of abnormality seen on baseline imaging. The table below demonstrates this:

Table 2. Baseline ultrasound wrist abnormalities seen in the prospective evaluation by Henry et al. 2010

Site	Total number with abnormalities (%)
Tendon sheath fluid (flexors)	4 (13.8)
Tendon sheath fluid (extensors)	11 (37.9)
Joint recess (volar)	12 (41.4)
Joint recess (dorsal)	24 (82.8)

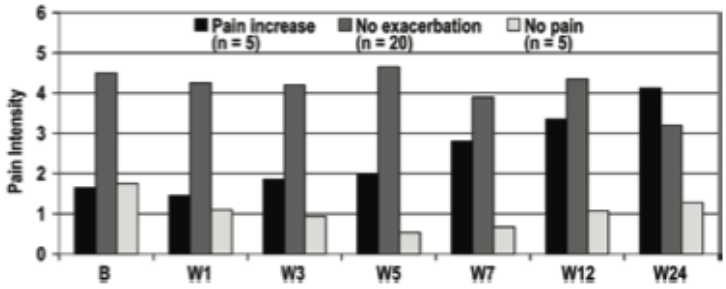
The tendon abnormalities seen, were primarily fluid in the tendon sheaths, with one patient showing evidence of synovitis. The joint abnormalities were a combination of intraarticular fluid and synovitis. Notably 2 patients discontinued AI therapy because of musculoskeletal pain. Almost half of the patients in the study developed new ultrasound findings. These were usually associated with the joint rather than tendon. 12 (48%) had new joint abnormalties, which were primarily fluid and synovitis. 5 (20%) had evidence of new tendon sheath fluid or synovitis. After 3 months of therapy, 72% of patients reported joint pain, 44% moderate to severe. With longer follow up, 15 (52%) fulfilled the above classification at a median of 6.2 months. Treatment was discontinued by 44.8% and a switch to an alternative AI undertaken. Factors associated with early discontinuation were lower body mass index and possibly prior tamoxifen usage. There was a possible association between baseline tendon abnormalities and the development of the AIA syndrome, though small numbers limit definitive conclusions (Henry et al. 2010).

A second prospective study conducted by Robidoux et al, evaluated AIA in 30 patients over a 3 month period. All patents were receiving anastrozole and

calcium/vitamin D supplementation (1000mg calcium and 800IU vitamin D). Assessments were by questionnaire (BPF-SF, HAQ), clinical assessment, oestradiol, vitamin D, urinary N-telopeptide of type I collagen, C-reactive protein, erythrocyte sedimentation rate, bone mineral densitometry, blood samples for gene expression and ultrasound of hand/wrist at baseline and 12 months. Again there was a high degree of baseline joint problems. 63% had evidence of osteoarthritis and rheumatological assessment revealed all patients had musculoskeletal abnormalities.

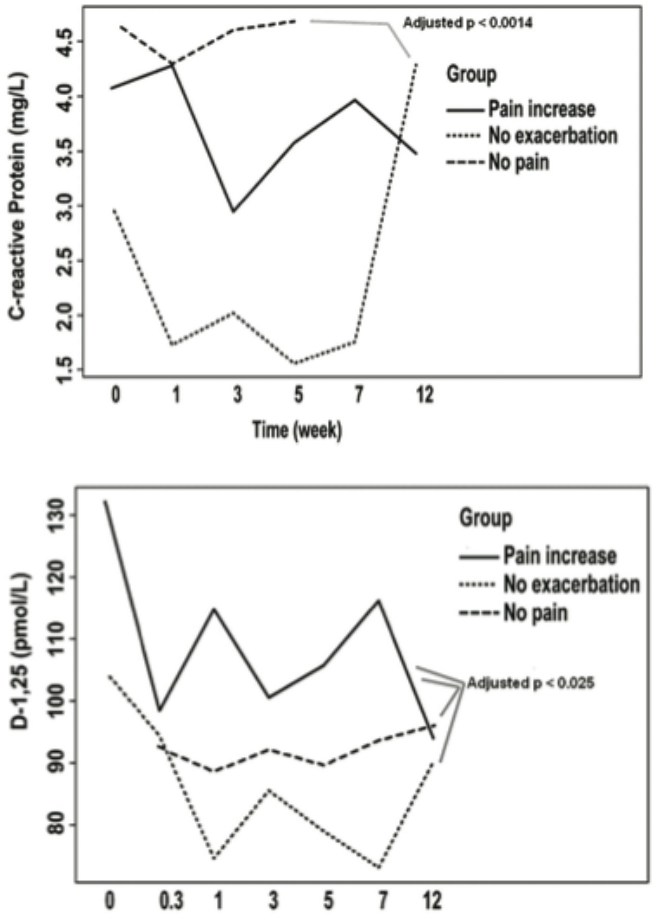
An increase in pain was reported by 5 women (17%), most of which was a worsening of pre-existing arthritis. The change in pain is summarized in figure 4. Pain attributable to a tenosynovial problem was seen in 2 patients. Ultrasound demonstrated increase in median nerve cross-sectional area in 3 patients. Interestingly, only one was due to fluid in the surrounding tendon sheaths. However, neither of these patients developed clinical signs of carpal tunnel syndrome.

Figure 4. Pain profile over 24 weeks. 5 patients experienced an increase in pain with AI treatment. B = baseline; W = week. Reproduced from Robidoux et al (2011)



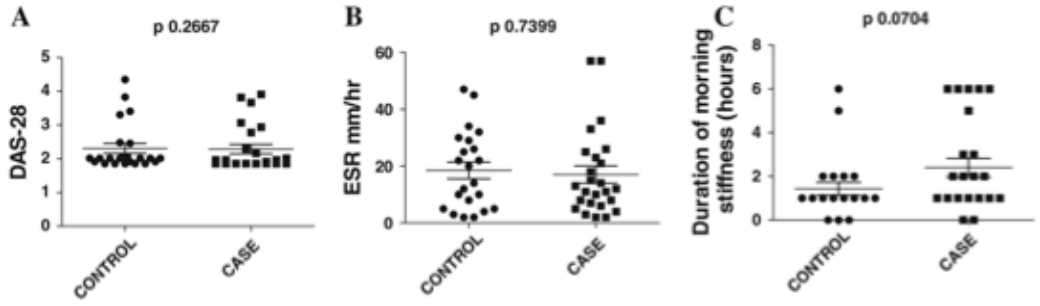
Biological markers were tested to investigate for differences between pain groups. Numbers in each group were too small to draw conclusions. However, those with no pain seemed to have a lower CTX-1. No clear trends were seen for CRP, oestradiol, and Vitamin D. The data is depicted below (Robidoux et al. 2011):

Figure 5. Changes in CRP and vitamin D over time in study by Robidoux et al. 2011



The CIRAS study reported the results of a detailed evaluation in 2012 (Shanmugam et al. 2012). In this trial, only patients with hand pain were included and it involved all assessments being done at one visit. It was powered to look for inflammatory changes according to the DAS-28 score. 48 patients were identified: 25 on AI and 23 controls. The results showed no difference in DAS-28, ESR, duration of morning stiffness or PROMIS-HAQ scores between cases and controls. 6 patients on AIs had a positive ANA titre compared to 4 contols (p=0.39). Mean 25-hydroxyvitamin D levels were similar in cases and controls. The mean duration of AI use before reporting pain was 0.87 years. Doppler ultrasound was also performed and revealed no significant difference between cases and controls in flexor tenosynovitis, soft tissue oedema, or fluid in the metacarpophalangeal joints.

Figure 6. Results of the CIRAS study comparing cases versus controls for A DAS-28, B ESR and C Duration of morning stiffness



A definition of Aromatase Inhibitor Associated Musculoskeletal Symptoms (AIMSS) was devised as listed below. Having 4 or more symptoms out of 5 would classify. Seventeen cases were on AI and 8 were controls (p=0.04). These criteria were thus not very specific for AIA and therefore further refinement is required for future studies. Other weaknesses of this study were the lack of longitudinal follow up, small patient numbers and previous AI exposure in the control group.

AIMSS as defined by Shanmugam et al:
Symmetric joint pain
Symmetric morning stiffness
Sensation of having aged abruptly
Sensation of thickening of the soft tissues
Carpal tunnel syndrome

5.7. 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 (Sestak et al. 2007). Other factors that were not correlated with arthralgia were, alkaline phosphatase and C reactive protein (Azria et al. 2007). Vitamin D was again investigated on the IBIS – II prevention study. Baseline levels were below normal in 85% of subjects, but this did not predict for musculoskeletal problems (Singh et al 2006, Singh et al 2012).

In a large prospective database of 328 patients receiving anastrozole, time from last menstrual period (LMP) was considered. The incidence of AIA was significantly lower when the time since LMP was > 10 years versus < 5-years (odds ratio 0.44, p = 0.002). However, age at menarche showed no association. Symptoms of this syndrome manifested significantly earlier (≤ 6 months) as the time since LMP became shorter (< 5 years) (Kanematsu et al. 2011).

In two follow up publications, the Belgian group (originally Morales et al) interrogated their data in relation to BMI (Lintermans et al. 2011, 2014). By the most recent publication, they had one year follow up data on 188 patients on AI and 104 patients on tamoxifen. The rate of new AI musculoskeletal symptoms (defined as 3 or more of arthralgia, myalgia, joint stiffness, tingling and carpal tunnel syndrome) was reported as 74%. Fifteen percent of AI users discontinued therapy due to joint symptoms. The conclusion was that a there was a quadratic trend of increasing BMI with grip strength reduction (p=0.009) and the probability of AI discontinuation (p=0.042).

5.8. INTERVENTION STUDIES

There have not been any studies investigating the effects of NSAIDs or COX-II inhibitors in this process. Benefits have been anecdotal, but risks need to be weighed up. Certainly COX-II inhibitors appear interesting as they can downregulate aromatase (Bocca et al. 2011). Their effects are currently being studied on breast cancer recurrence and a large international study, the REACT trial has recently completed accrual. It will be interesting to see if the incidence of joint pains in this study is any lower compared to previous data. The role of prednisone 5mg once a day for 1 week has been studied in one small prospective clinical trial of 27 patients with AIA from Japan. Subjective assessments were made with a specific questionnaire. 67% of patients reported improvement of joint symptoms after 1 week, which was down to 43% and 33% after 1 and 2 months. There was no placebo containing arm in this study, so the effect due to the natural improvement in joint symptoms is unknown. This strategy requires further investigation in a randomised fashion (Kubo at al. 2012).

The simplest of interventions is to switch one AI to another. This strategy was investigated formally in the ATOLL study (Briot et al. 2010). This was a prospective non-randomised open label multi-centre trial from centres across France. Patients on anastrozole with musculoskeletal side effects had a 1 month washout and then were converted onto letrozole and observed for 6 months. A variety of assessments were undertaken including morning stiffness, BPI-SF, HAQ, SF-12, ESR, CRP and vitamin D. One hundred and seventy nine patients were recruited. At baseline, 156 patients (87.2%) reported symptoms of arthralgia, 71 (39.7%), myalgia, 49 (27.4%), tendinitis, and 31 (17.3%) arthritis. Knees, hands and spine were the most commonly affected. At the end of the study, 51 (28%) had discontinued treatment due to musculoskeletal symptoms (17 (9.5%) within a month of starting letrozole). At the end of the 6-month treatment with letrozole, 116 (73.9%) patients had arthralgia, 33 (21.0%) myalgia, 25 (15.9%) arthritis and 22 (14.0%) tendinitis (figure 7). Twenty four (15%) did not report any joint pain. Overall quality of life score improved (table

3), but there was no change in biochemical markers. Factors associated with letrozole discontinuation were analysed. The only one that was significant of a higher discontinuation was a shortened duration of anastrozole. This was a unique study demonstrating a simple switch could be effective for some (15%). However, it was limited by the lack of controls and the short follow up period. In addition, although quality of life assessments improved, these were by small amounts and whether clinically relevant remains uncertain for this population.

Figure 7. Changes in musculoskeletal symptoms in the ATOLL study (Briot et al. 2010)

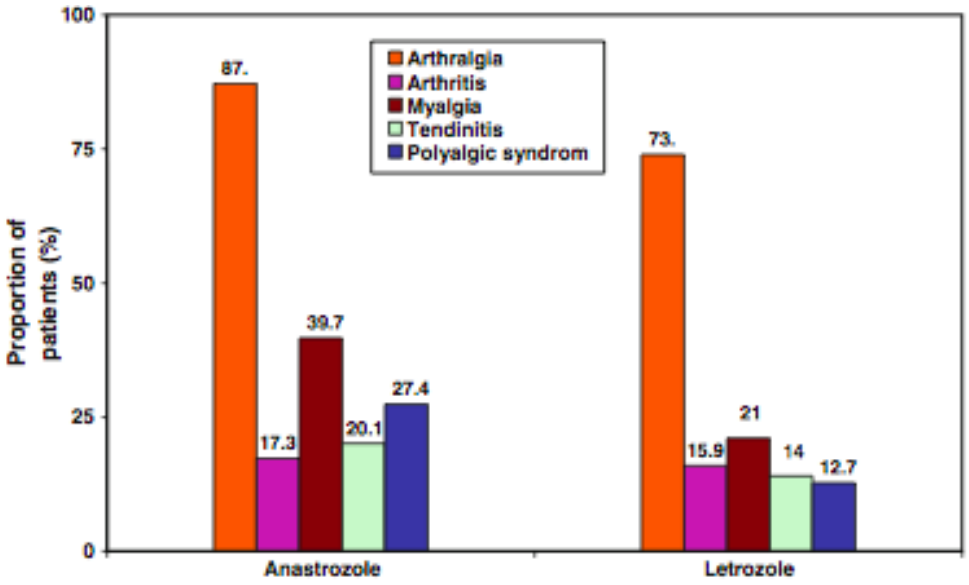


Table 3. Changes in BPI pain severity and HAQ scores from the ATOLL study (Briot et al. 2010)

	N	BPI score (mean ± SD)	Change from baseline (mean ± SD)	*P* value
Visit 1 baseline	176	4.9 ± 1.6		
Visit 2	175	3.7 ± 2.2	−1.1 ± 1.9	<0.001
Visit 3	171	3.5 ± 2.1	−1.4 ± 1.9	<0.001
Visit 5 or premature stop	149	3.8 ± 2.4	−1.2 ± 2.3	<0.001

	N	HAQ score (mean ± SD)	Change from baseline (mean ± SD)	*P* value
Visit 1 baseline	176	2.0 ± 0.5		
Visit 2	176	1.7 ± 0.6	−0.3 ± 0.5	<0.001
Visit 3	175	1.7 ± 0.5	−0.3 ± 0.5	<0.001
Visit 5 or premature stop	150	1.7 ± 0.6	−0.3 ± 0.5	<0.001

Few studies have reported on interventional means of reducing AIA. There has been more interest in the role of using vitamin D as a therapeutic. Vitamin D is linked to oestrogen because oestrogen increases the activity of 1-α hydroxylase, which is an enzyme responsible for conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which is the biologically active form. Oestrogen also increases the activation of the vitamin D receptor. Vitamin D is important for proximal muscle strength and deficiency is associated with non-specific musculoskeletal symptoms. 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 40ng/ml at baseline (ie 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 66ng/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 (Khan et al. 2009). A recent study by Prieto-Alhambra et al. showed that women treated with letrozole, vitamin D and calcium and who achieved 25OHD levels >40 ng/ml experienced less joint pain than women with lower 25OHD levels (Prieto-Alhambra et al 2010).

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 (Mao et al. 2009). 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 BPI-SF (brief pain inventory-short form) (Crew et al. 2009).

In preliminary study, the affect of yoga on AIA was investigated. Patients were given an 8 week course and assessments of function and pain were made before and afterwards. 80% of patients were compliant with this program. There were reductions in functional reach, sit and reach, FACT-B and BPI pain severity scores. These early signs are encouraging, this clearly needs further evaluation in a randomised fashion (Galantino et al. 2012).

There are no universally accepted guidelines for the management of this condition, partly because the underlying mechanism is unclear and partly the questionable benefit of anti-inflammatory medication. Thorne proposed an early algorithm (figure 8) in 2007 (Thorne 2007). An expert panel proposed an alternative algorithm (figure 18) in 2008 (Coleman et at 2008). More recently, Nivarath has produced an updated version (figure 9) encompassing some of the newer data (Nivarath et al. 2013).

Figure 8. Early algorithm for managing aromatase inhibitor musculoskeletal symptoms (Thorne 2007)

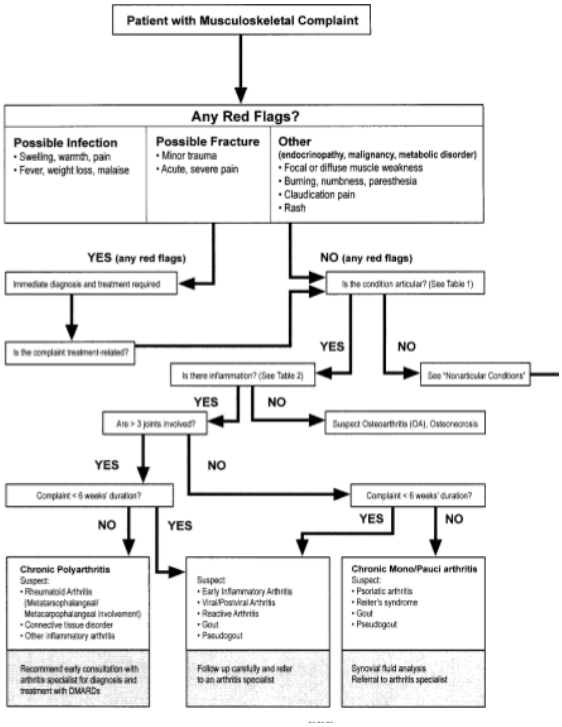
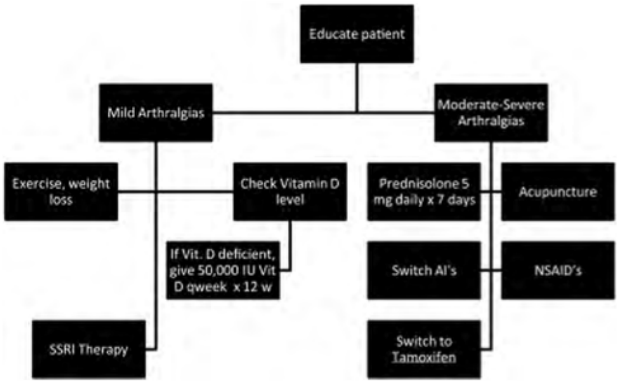


Figure 9. Updated algorithm for the management of AIA (Nivrath et al 2013)



5.9. 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 (Basch et al. 2006). Discussed below are the key areas that need to be considered for evaluating AIA.

5.9.1. Quality of Life (QoL) 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 phenomenen. Subsequently trials are now in progress and will be discussed later, in which more careful attention is being 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 4 shows some arthritis based questionnaires currently in use.

Any future trial of AIA should strongly consider using the Health Assessment Questionnaire-Disability Index (HAQ). 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 its authors consider it as a generic instrument rather than disease specific and hence it would be appropriate to use it to assess AIA (Din et al. 2010). Thus, this is why HAQ was chosen for the ARIAD study.

5.9.2. 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. Location of pain can easily be documented and severity may be evaluated using a visual 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 5), though its usefulness has been questioned in AIA (Hershman 2008). In osteoarthritis, the AUSCAN Index has been validated as a self reported assessment of the hands. It measures hand pain stiffness and function (Allen et al. 2007). In rheumatoid arthritis, disease activity has traditionally been measured by DAS-28 (Disease Activity Score). 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 (Henry et al. 2008).

Grip strength as measured by a modified sphygnomanometer has been shown to deteriorate with AI use as compared to tamoxifen and correlate with semi-quantitative tenosynovial changes on MRI imaging (Morales et al. 2008). However, this form of grip strength measurement has not been validated in clinical studies and actually measures grip pressure. A limitiation 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 (Harkonen et al. 1993), with published normal values across the age ranges (Mathiowetz et al. 1984). Future similar studies

should use this more reliable technique and this is the reason why it was used in the ARIAD study.

5.9.2.1. Clinical Criteria for AIA

Each study that has investigated AIA/AIMSS has used different criteria for its definition. There are a number of clinical features that are clearly associated with AIA. Joint pain, joint stiffness, features of carpal tunnel syndrome, flexor tendon nodules, trigger finger and synovitis encompass most of the reported findings so far (Morales et al. 2007, Morales et al. 2008, Alegre-Sancho et al. 2008, Dizdar et al. 2009, Shanmugam et al. 2012). For clinical study assessing this syndrome, it would be important to include these factors.

5.9.2.2. Clinical Assessment of Carpal Tunnel Syndrome

Carpal tunnel syndrome is due to the entrapment of the median nerve at the wrist, as it passes under the transverse carpal ligament. The carpal tunnel has restricted space due to the carpal bones underneath and the other structures that pass through (eight digital flexor tendons, flexor pollicis longus of the thumb, their synovial sheaths and the median nerve) (Katz et al. 2002). It causes pain, numbness and tingling of the fingers, particularly on the lateral side.

The provisional diagnosis is based on clinical features, but ultimately confirmed on electrophysiological testing. Tinel's sign, where the clinician taps along the median nerve at the wrist has a sensitivity of 23-60% and specificity of 64-87%. Another test, Phalen's test, has a sensitivity of 57-91% and a specificity of 33-86%. This involves the patient placing their elbows on a flat surface with the wrists falling into flexion for up to one minute. If paraesthesia develops or increases in the distribution of the median nerve, then the test is deemed to have a positive result. Electrophysiological studies are the gold standard in diagnosing the severity of carpal tunnel syndrome. These tests include nerve conduction studies and electromyography and have a sensitivity of 56-85% and a specificity of at least 94% (Ghasemi-Rad et al. 2014).

High resolution ultrasound has also been investigated in the diagnosis of carpal tunnel syndrome. Both sonography and nerve conduction studies have been compared in a study of 414 symptomatic and 408 control patients (Nakamichi et al 1993). Clear differences were seen between the two groups for median nerve cross-sectional area. Specificity was greater than 95% and sensitivity was 43-57%. Ultrasound currently remains an investigational tool, with the diagnosis still based on electrophysiological studies.

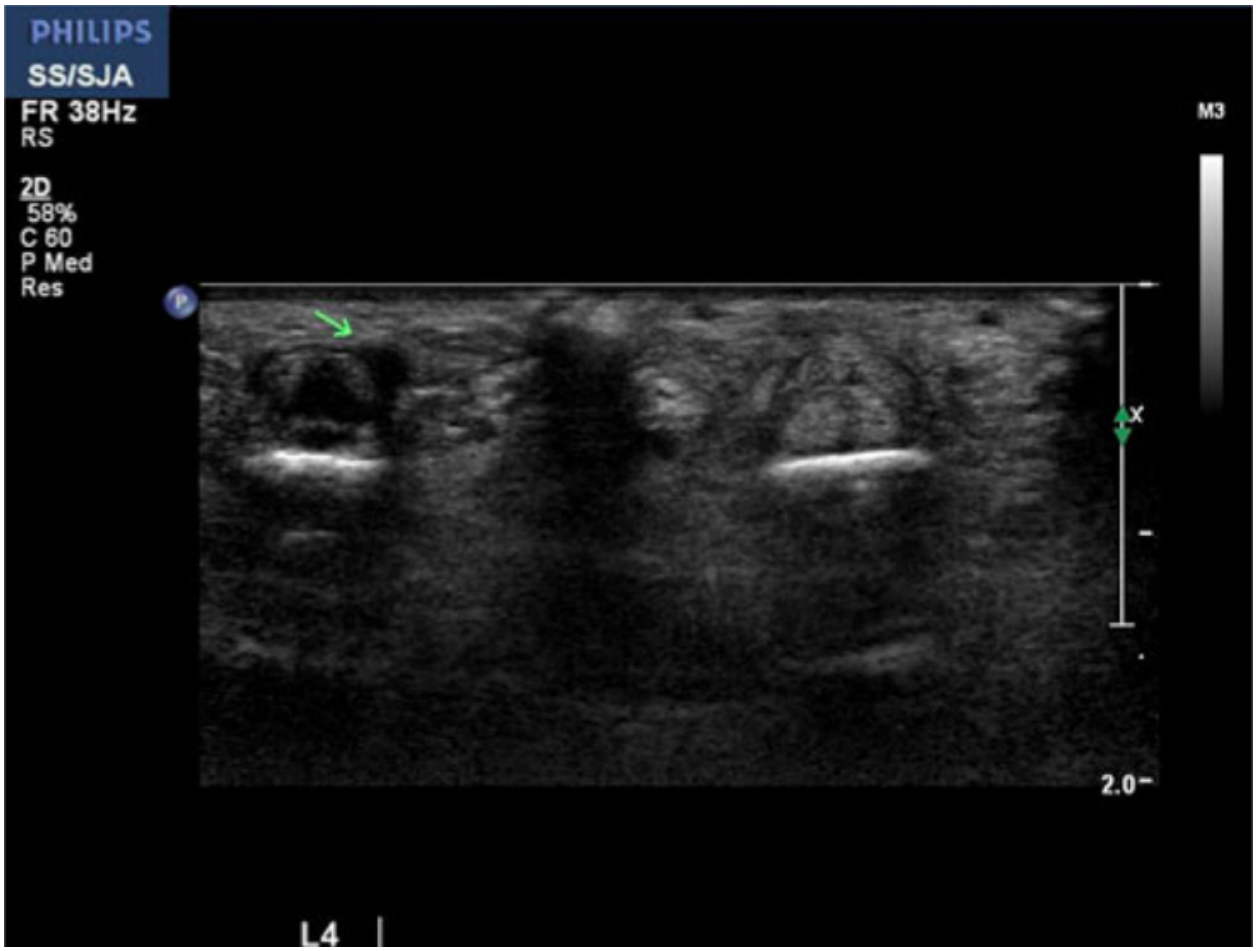
5.9.3. Radiological Assessment

5.9.3.1. Ultrasound

Ultrasound is now a standard investigation performed by rheumatologists for the assessment of musculoskeletal symptoms (Backhaus et al. 2001). 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 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 (Wakefield et al. 2005).

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 (Schmidt 2007). Given there may be some similarities between AIA and early rheumatoid arthritis (Tan et al. 2008), 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 (Morel et al. 2007). Thus it would be logical to use knowledge of this disease process to direct investigation of AIA. For these reasons, ultrasound was chosen for the assessment of synovitis and tenosynovitis in the ARIAD study.

Figure 10. An example of tenosynovitis from the CIRAS study. Cross-sectional ultrasound image of the 4th flexor tendon. Tendon sheath thickening in the left 4th flexor tendon consistent with flexor tenosynovitis (arrow). Adjacent digit has normal tendon sheath for comparison (Shanmugan et al. 2012).

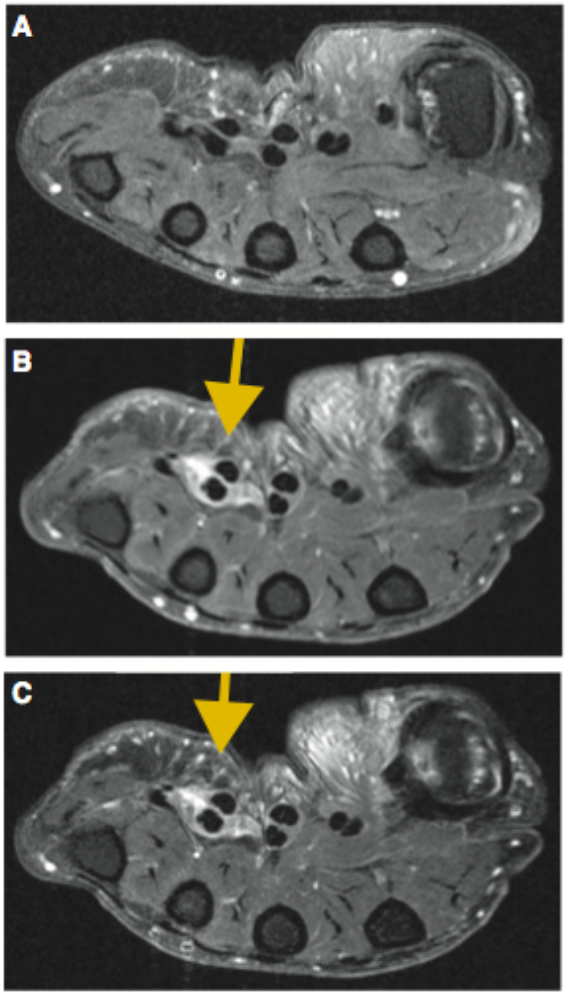


5.9.3.2. Magnetic Resonance Imaging (MRI)

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 among 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 (Tan et al. 2003).

As discussed earlier, only one study has used MRI to investigate AIA. The main abnormalities were seen in the tendon sheaths and soft tissues (Morales et al. 2008). To take this forward, further evaluation of larger cohorts are 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 (Haavardsholm et al. 2007). This effectively grades the degree of synovial proliferation and peritendinous effusion on a scale of 0-3. It stems from the OMERACT (Outcome Measures in Rheumatology Clinical Trials) RAMRIS (Rheumatoid Arthritis MRI Score) score which is a well validated semi-quantitative score of bone erosions, bone oedema and synovitis, used in rheumatoid arthritis trials (Haavardsholm et al. 2005). Thus MRI was chosen as an important assessment of AIA in the ARIAD study.

Figure 11. Axial MRI T2-weighted MRI image of the hand (A, C) T1 weighted post contrast fat suppressed image (B). (A) At baseline. (B, C) After 6 months of AI, (arrow) shows enhancement of the tendon sheath (B) and fluid in tendon sheath (C) Morales et al (2008).



5.9.3.3. Dual Energy X-Ray Absorptiometry (DXA)

The loss of bone density with aromatase inhibitors 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 (Brufsky et al. 2008; Ellis et al. 2008; Lester et al. 2008). 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 (Haugeberg et al. 2006). 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 (Haugeberg et al. 2007). 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 and was therefore used in the ARIAD study.

5.9.4. 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 (Henry et al. 2008).

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 (Hunter et al. 2007; Williams et al. 2008). Other trials have shown urinary CTX-II to be a useful marker of osteoarthritis. In rheumatoid arthritis, anti cyclic 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 (Landewe 2007; Wild et al. 2008). These markers may provide insight into the mechanism behind AI-induced arthralgia.

IGF-1 (Insulin like growth factor 1) and growth hormone axis has been postulated as a cause, but the studies are very preliminary (Lintermans et al 2011).

The measurement of oestradiol E2 levels has shown very low levels of 5.8pg/ml (+/- 4.1) receiving postmenopausal women receiving AI therapy (Santen et al 2007). In most hospital settings, measurements are done by direct immunoassay techniques. Mass spectrometry is the gold standard, but highly specialised and expensive. Jacque et al evaluated 6 commercially available immunoassays. They showed that many of these lacked the sensitivity and accuracy to give reliable results in this group of patients. Some could measure no lower than 20pg/ml and some 5pg/ml. The authors conclude that improved immunoassay E2 techniques are required (Jacque et al 2013).

5.10. CURRENT AND FUTURE PERSPECTIVES

AIA is currently under investigation in a number of clinical trials as shown in table 6 (ClinicalTrials.gov 2009). 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 tumor 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 four cohorts (two on AIs and two controls). In this research, PROs are assessed by the use of 3 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 (Morales et al. 2007, Morales et al. 2008). 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, has also measured ultrasound assessment of tenosynovitis and DAS-28 scores, as described earlier (Shanmugam et al. 2012).

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.

Table 4. Quality of life (QoL) instruments to be considered for future AIA trials

***(adapted from Bernstein (Burstein 2007)*)**

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 5. Common Terminology Criteria for Adverse Events version 3.0 for musculoskeletal symtoms

Musculoskeletal/Soft Tissue					
	Grade				
Adverse Event	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).

Table 6. Current ongoing studies investigating AIA (ClinicalTrials.gov 2009)

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 -	AI	Montreal, Canada	N/K

A Pilot Study			
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).

5.11. 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 prominent and the subject of high quality trials. At present, as discussed in this thesis, 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 200 published cases which have not been sufficiently compared with controls.

Results from further prospective studies, currently ongoing, are required and are investigating 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.

Following review of all the evidence reported in AIA in breast cancer, the ARIAD study was designed. It was clear that more prospective detailed information was needed on AI users and controls, so this formed the basis of the design. As discussed, the HAQ-DI, SF-36 and BPI-SF questionnaires had good supportive evidence and would assess relevant aspects of joint symptoms. Grip strength using the Jamar dynamometer as the gold standard was chosen as an easily reproducible tool. The use of radiological investigations such as ultrasound, MRI and hand DXA would all provide useful insight into the mechanism behind AIA.

6. CURRENT OPINION OF AROMATASE INHIBITOR-INDUCED ARTHRALGIA (AIA) IN BREAST CANCER IN THE UNITED KINGDOM

6.1. INTRODUCTION

Breast cancer is the most common cancer in women with approximately over 10,000 deaths per year in England and Wales. The majority of patients treated for early breast cancer are offered adjuvant treatment and many will be cured from the disease. The number of cancer survivors is increasing, which is due in part to improvements in adjuvant treatment. Thus the longer term effects and compliance to these therapies is becoming increasingly important.

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 (EBCTCG 2005). However, more recently, trials of AIs have shown benefits over tamoxifen, in both a metastatic (Bonneterre et al. 2000; Nabholtz et al. 2000; Mouridsen et al. 2003) and subsequent adjuvant treatment setting (Goss et al. 2003; Coombes et al. 2004; Howell et al. 2005; Jakesz et al. 2005; Thurlimann et al. 2005; Boccardo et al. 2006; Coombes et al. 2007). The main advantages have been improvements in disease free survival and a generally more favourable toxicity profile, with lower rates of thromboembolic phenomena and endometrial malignancy. The two main adverse effects of AIs are (as expected) a reduction in bone mineral density (BMD) and (less anticipated) 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 under-reported in the clinical trials.

Since the large randomised trials, smaller studies have shown AIA in practice is an important clinical problem. In a cross-sectional survey of 200 patients in the United States (US) taking an adjuvant AI, 47% reported joint pain (23.5% new onset) and 44% joint stiffness (26.5% new onset). In 67% and 66% respectively, these patients reported moderate to severe symptoms. Prior taxane based

chemotherapy was associated with a fourfold increase in pain and stiffness (ORs 4.08 and 4.76 respectively) (Crew et al. 2007). Other studies have reported rates between 20 and 61% (Dent et al. 2007; Presant et al. 2007; Henry et al. 2008; Sestak et al. 2008).

There is limited guidance on the management of AIA (Thorne 2007; Coleman et al. 2008). The lack of a clear understanding of the aetiology makes it difficult to recommend a particular strategy. Inflammatory markers do not appear to be elevated (Henry et al. 2008) and the clinical benefit of a NSAID (non-steroidal anti-inflammatory drug) is questionable. Intervention studies investigating this condition have only recently published and suggest there may be a role for acupuncture to relieve symptoms and vitamin D supplementation to reduce the severity and frequency of AIA (Crew et al. 2009; Khan et al. 2009; Mao et al. 2009).

In the United Kingdom (UK), the management of endocrine therapy for early breast cancer rests with either the breast surgeon or oncologist (both medical and clinical) and follow up is often shared. With this in mind, we decided to evaluate the perspective of UK breast specialists on this increasingly important issue.

6.2. AIM

To evaluate current UK opinion on the importance, investigation, management and the need for guidelines for Aromatase Inhibitor-Induced Arthralgia (AIA).

6.3. MATERIALS AND METHODS

An internet-based database was interrogated and list of breast cancer clinicians was downloaded (specialistinfo). This list included breast surgeons, clinical and medical oncologists. A 19 point “tick box” style questionnaire was designed and was sent out to 772 clinicians, along with a covering letter and prepaid return envelope in April 2009. A second round of questionnaires was sent out to non-responders in August 2009. The full questionnaire is shown in the appendix 13.10.

The questionnaire requested background information on the number of postmenopausal women with oestrogen receptor positive (ER+ve) early breast cancer treated by the recipient per year as well as the percentage receiving aromatase inhibitors (AI). Each specialist was asked to gauge the importance of AIA from both a clinical perspective and the likely perceived effect on a patients’ quality of life. The AI (anastrozole, letrozole or exemestane) most frequently associated with arthralgia was determined, with the options of “they are all the same” or “tamoxifen is just as bad” also available. Clinicians were asked what they understood about the aetiology of AIA. The characteristics of this process in terms of joints affected and likely time course were ascertained.

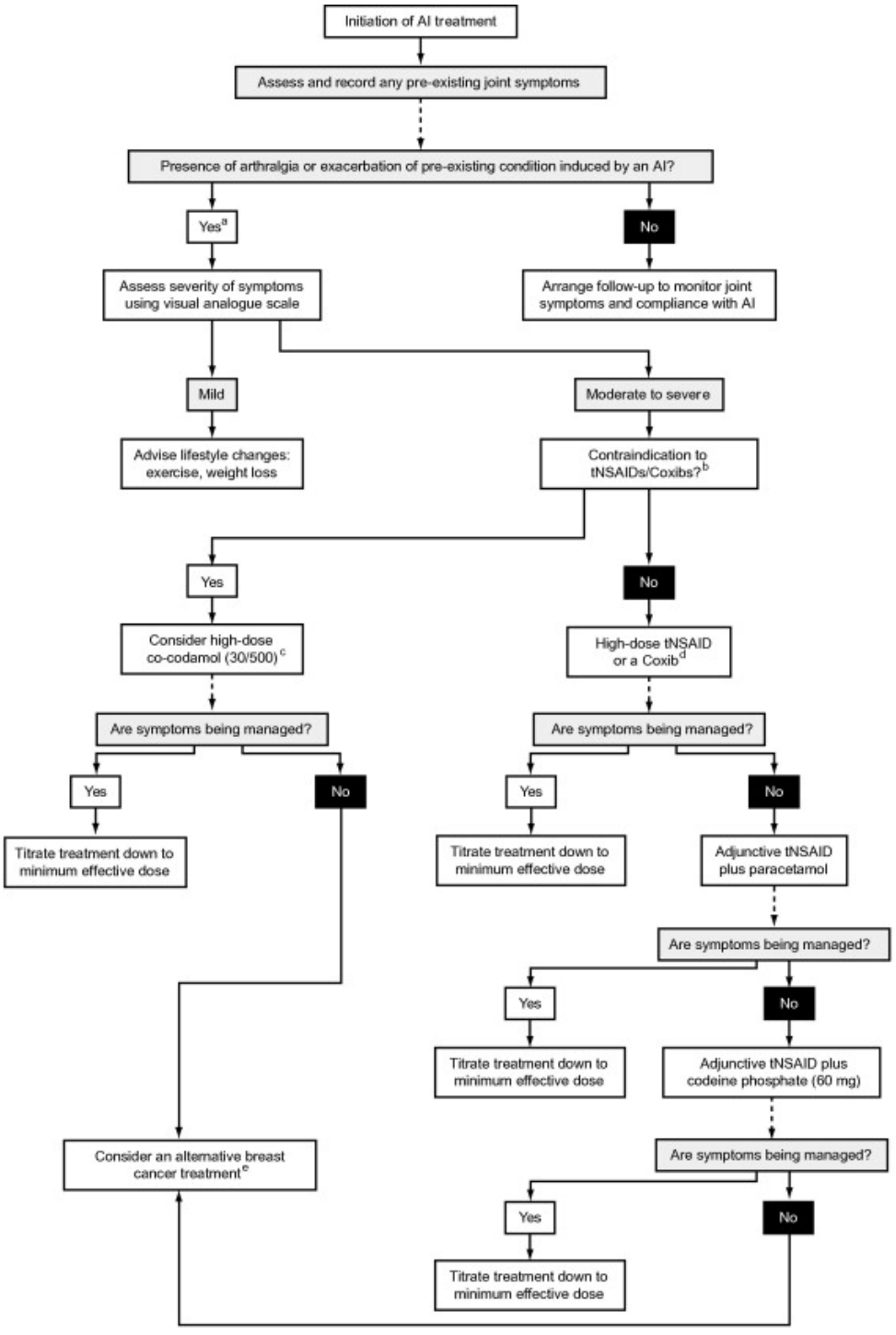
The next section of the questionnaire evaluated current practices in the management of AIA. The frequency of a change of AI due to arthralgia was determined. Clinicians were asked about their first three steps of management, with reference to analgesics, complementary therapy, change in AI and referral to rheumatologist. It was specifically asked if clinicians went on to check blood parameters and/or perform radiological examination(s) of affected joint(s).

Recently, an expert panel designed a treatment algorithm for the management of this condition (Coleman et al. 2008). Specialists were asked if they were aware of any current guidelines and whether they felt their practice would benefit from national guidelines. A 5 point scale was used to grade the confidence of clinicians of managing the arthralgia (from 1=not at all confident

to 5=very confident). Finally, we tried to ascertain opinion on who was the most appropriate person to manage the condition.

The data were collated and are presented in descriptive and graphical form. No statistical testing was considered appropriate.

Figure 12. Algorithm depicting treatment- flow for patients displaying arthralgia symptoms whilst on AI treatment (Coleman et al 2007).



[a]If the arthralgia is an exacerbation of pre-existing symptoms, follow steps according to the medication currently prescribed. [b]See Appendix B for contraindications for tNSAIDs and Coxibs. If patients are currently taking a cardioprotective dose of aspirin (75 mg), then concomitant tNSAIDs or Coxibs may be prescribed. [c]Where available. [d]Recommended start doses include: ibuprofen 1600-2400 mg daily; diclofenac 150 mg daily; naproxen1000 mg daily; celecoxib 400 mg daily; etoricoxib 60 mg daily. [e]If symptoms cannot be adequately managed, switching the patient to tamoxifen may be appropriate. Alternatively a weak opioid may be given alongside the AI in some cases. AI, aromatase inhibitor; Coxibs, cyclooxygenase-2 inhibitors, tNSAID,traditional nonsteroidal anti-inflammatory drugs.

6.4. RESULTS

Out of 772 identified specialists, 445 (58%) returned their questionnaires. Four hundred and sixteen (54%) were suitable for analysis. By specialty, 234 (56%) were completed by breast surgeons, 134 (32%) by clinical oncologists, 45 (11%) by medical oncologists and 1 by a general surgeon. Two responses were unclassified.

6.4.1. Demographics

Most respondents saw between 50 and 100 per year (figure 12). Breast surgeons and clinical oncologists appeared to treat the most patients with a number treating over 150 per year. The majority reported prescribing AIs instead of tamoxifen in over 50% of their patients (figure 13).

Figure 13. How many new (postmenopausal) oestrogen receptor-positive patients do you treat per year?

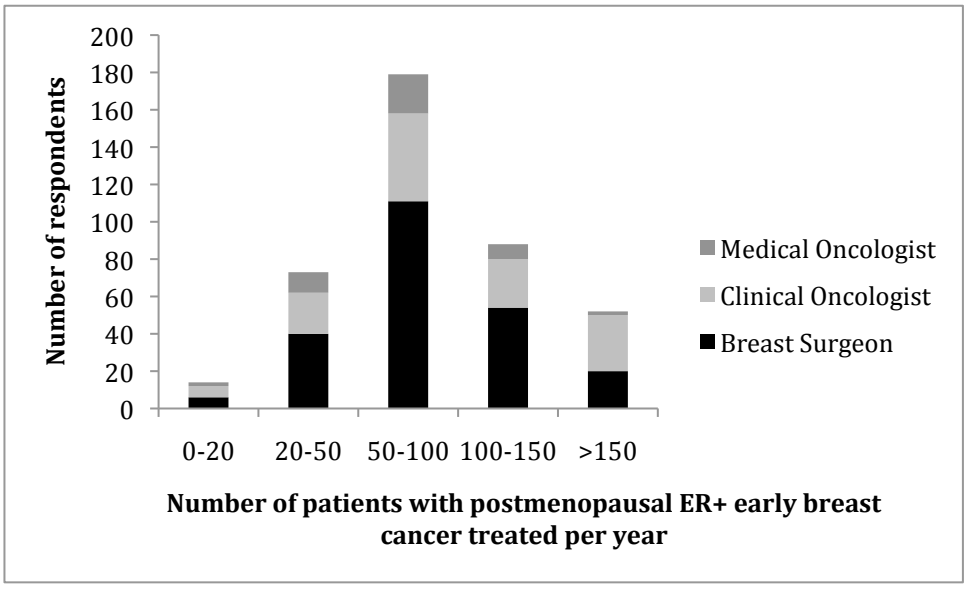
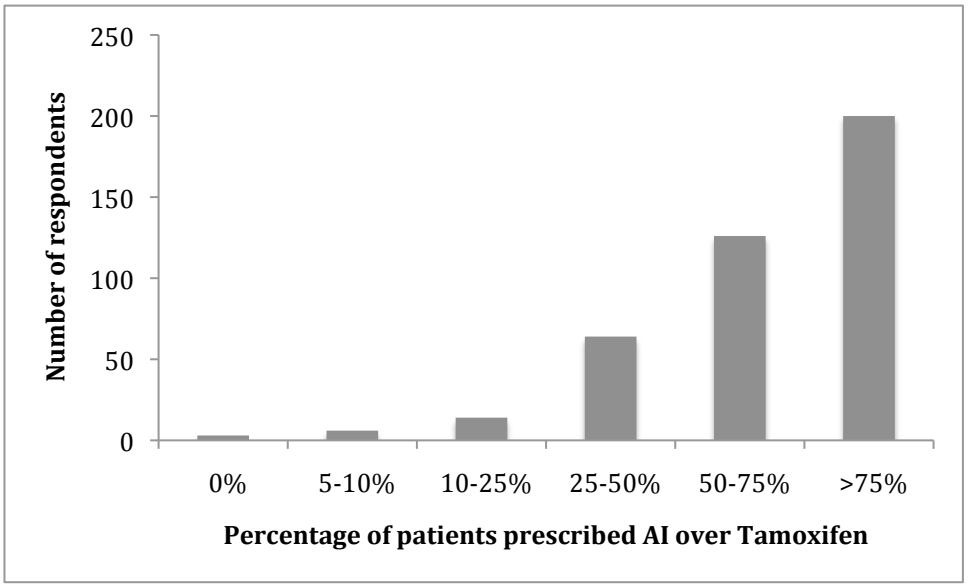


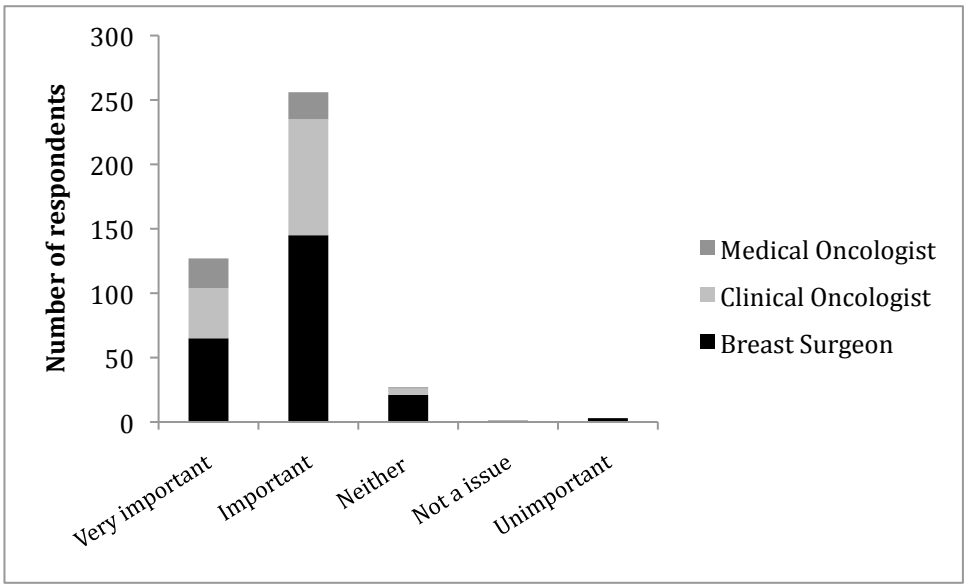
Figure 14. Current use of adjuvant aromatase inhibitors in postmenopausal breast cancer. (To what proportion of your postmenopausal oestrogen receptor-positive early breast cancer patients would you prescribe aromatase inhibitors (upfront or switch) over tamoxifen currently?)



6.4.2. Significance of AIA

As many as 383 (92%) of specialists graded the importance of AIA as either very important (31%) or important (62%) (figure 14). This was reinforced by most clinicians' impression that the effect on a patients' quality of life was very large (23%) or large (60%). Very few felt the impact was small. The general majority viewed the frequency of arthralgia as similar for all the aromatase inhibitors (224 (54%)). However, a number proposed arthralgia was more common with anastrozole (150 (36%)), than letrozole (22 (5%)) or exemestane (6 (1%)).

Figure 15. Importance of AIA. (Do you think arthralgia related to endocrine treatment is an important clinical problem?)



6.4.3. Aetiology

Respondents could tick more than one answer for what they felt was the main cause of arthralgia. One hundred and fifty three (37%) had oestrogen deprivation in their answer. Very few thought a change in pain sensitivity (3 (1%)), exacerbation of prior asymptomatic joint disease (21 (5%)), inflammatory joint condition (24 (6%)) or a periarticular process (34 (8%)) was responsible. However, the most common answer was “don’t know” (211 (51%)). Most of these were breast surgeons (138).

6.4.4. Clinical Features

Many clinicians felt this condition “typically developed within a few weeks of starting an AI” (314 (76%)). Two hundred and fifty eight (62%) indicated symptoms persist until the AI is discontinued. Relatively few suggested it settled spontaneously after a few months (96 (23%)). The minority (48 (12%)) viewed AIA as affecting large joints, whereas 225 (54%) indicated it was more likely to involve small joints such as the hand and wrist. Ninety two (22%) specialists thought it was common for AIA to make all the joints painful.

6.4.5. Investigations

When asked about which blood parameters were usually checked, more than one answer was allowed. Two hundred and eighty (67%) marked that they didn’t check bloods. Eighty one (22%) requested routine blood count, biochemistry and liver function tests. Simple inflammatory markers were checked by 97 (23%). Even fewer (58 (14%)) performed an autoantibody screen.

Specialists were also questioned regarding radiological investigations performed for AIA. Two hundred and fifty four (61%) indicated that they never request such investigations. Very few investigate with ultrasound (2 (0.5%)) or MRI (7 (2%)) of affected joint. It was more common to do an x-ray (99 (24%)). A

common trigger for investigation was if there was concern about metastatic disease of the bone. Radioisotope bone scintigraphy or “investigations to exclude malignancy” were indicated under “other” by 37 respondents (9%).

6.4.6. Management of AIA

The questionnaire attempted to ascertain the first three steps of management of AIA. The most common answers for the first step were: use of an anti-inflammatory (203), non-opioid analagesic (213), change to alternative AI (102), change to tamoxifen (75) and reassurance (60). For those changing to an alternative AI, the most likely choice was exemestane. Eighteen recommended a herbal remedy or supplement (cod liver oils, glucosamine, vitamin E). For the next step in management, the commonest responses were: change to an alternative AI (184), change to tamoxifen (183), use anti-inflammatory (131), reassurance (81), refer to rheumatology (58) For severe persisting arthralgia the respondents recommended: change to tamoxifen (310), refer to rheumatology (158), anti-inflammatory (55), and reassurance (46). At this stage, 17 suggested mild opioid analgesics, 7 would use corticosteroids, 2 strong opioids and 1 vitamin D.

Figure 15 shows the frequency of which AI arthralgia caused the specialists to change endocrine therapy. Most felt a change was required in 5-20% of cases. Of note, 11 respondents reported a change in over 50% of cases. Confidence in the management of AIA was assessed on a scale of 1 (not at all confident) to 5 (very confident) and displayed in figure 16. A score of 3 was the commonest answer to this question (52%).

Figure 16. Change of endocrine therapy due to AIA (How often does AI arthralgia cause you to change endocrine treatment in your patients?).

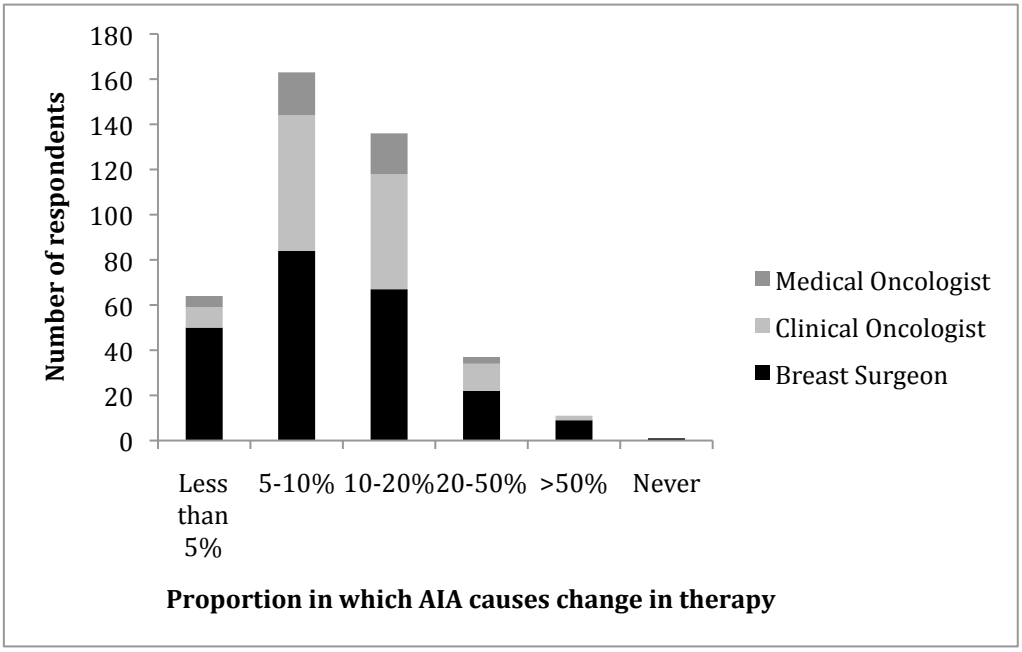
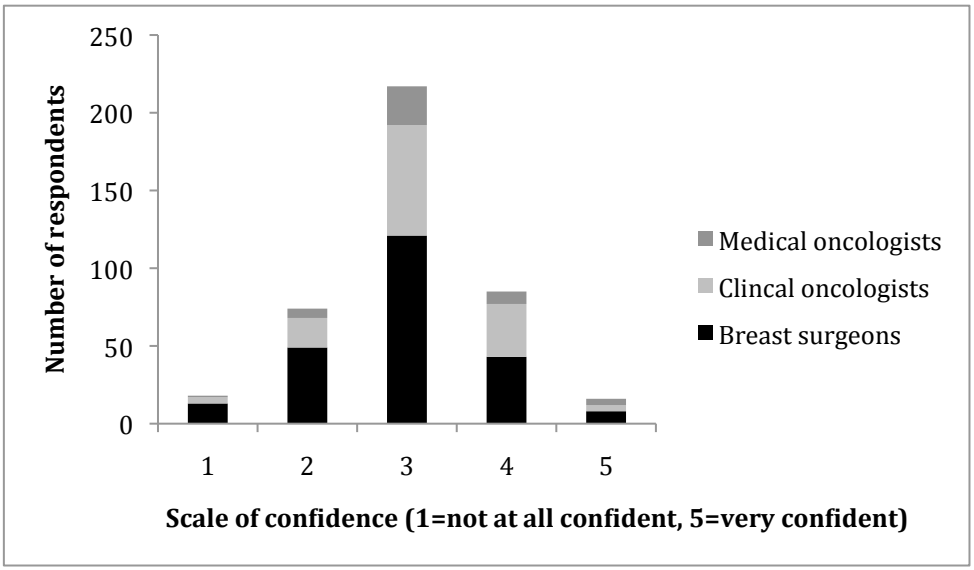


Figure 17. The confidence of breast cancer specialists in the management of aromatase inhibitor-induced arthralgia. [On a scale of 1-5, how confident are you at maganging aromatase inhibitor- induced arthralgia? (1 = not at all confident, 5 = very confident.]



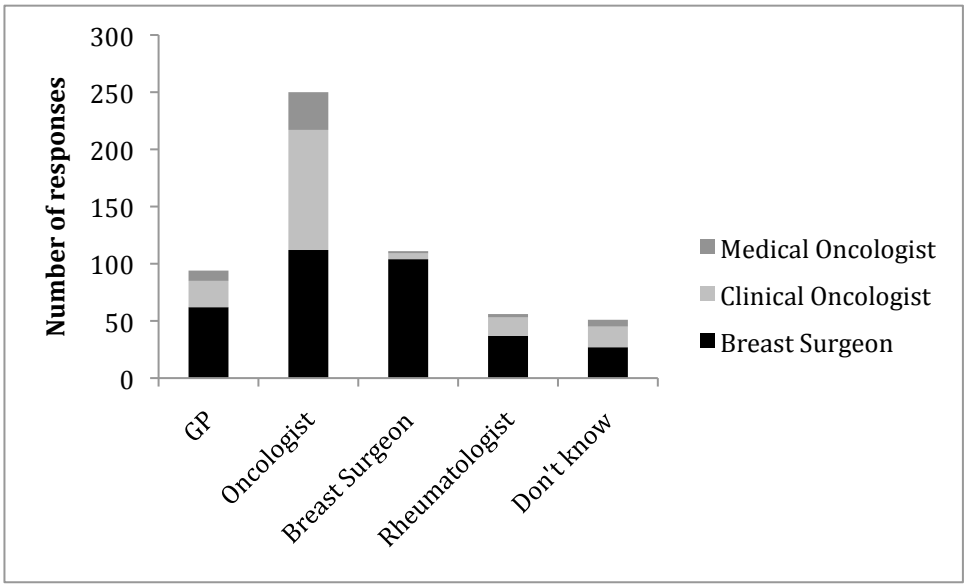
6.4.7. Referral

Most clinicians said that they referred to rheumatology on an occasional basis (302 (73%)). Very few referred routinely and 102 (25%) indicated they do not seek a further opinion.

6.4.8. Responsibility

This question set to determine opinion on who was the most appropriate person or persons to manage AIA. More than one answer was acceptable. Ninety five (23%) respondents felt this should involve the general practitioner (GP). Two hundred and fifty one (60%) indicated oncologists in their answer, whilst 111 (27%) felt the breast surgeon should be involved. Only 58 (14%) proposed it was the responsibility of rheumatology. Few (51 (12%)) didn't know (figure 17).

Figure 18. Responsibilty for management. (Who do you think should be responsible for managing aromatase inhibitor-induced arthralgia?)



6.4.9. Guidelines

Only 32 (8%) respondents were aware of any guidelines for the management of AI arthralgia. Seven specialists quoted guidelines by Coleman et al, 6 were aware of local guidelines, 2 quoted ASCO and 2 quoted NICE guidelines. When asked if their practice would benefit from national guidelines for the management of AIA, 349 (84%) answered “yes”.

6.5. DISCUSSION

This questionnaire has demonstrated the varied practice amongst UK breast clinicians in the understanding and management of AI-induced arthralgia. These data suggest that AIs are the preferred endocrine therapy option over and above tamoxifen, in keeping with recommendations of the National Institute of Clinical Excellence (NICE). We have demonstrated that this phenomenon is viewed as important and may have a significant affect on a patients' quality of life. Although respondents suggested anastrozole as the main offender, it is likely that this represents the most widely used AI.

In keeping with the lack of a clear aetiology, many specialists were unclear about the aetiology of AIA. However, it is largely accepted that oestrogen deprivation is likely to be a cause, though its link with musculoskeletal symptoms in this population has not been fully established. Very few felt it was a periarticular process, although data from the small studies by Morales et al have suggested this may be the case (Morales et al. 2007; Morales et al. 2008). Evidence of a tenosynovitis of the digital flexor tendons was demonstrated in patients on AI compared to tamoxifen. Change in pain sensitivity is linked to oestrogen deprivation (Dawson-Basoa et al. 1997), but few felt it was relevant here. A recent study has shown increased tendon thickness, effusion in hand joints and EMG findings consistent with carpal tunnel syndrome in women receiving AI therapy. In the same study, inflammatory markers such as ESR, CRP, Anti dsDNA, Rh F and anti-CCP Ab were no different between cases and controls (Dizdar et al. 2009). The risk of carpal tunnel syndrome (CTS) in the ATAC trial was increased with prior HRT and chemotherapy. However in most cases it was mild to moderate with only 8/80 cases going on to have surgical decompression (Sestak et al. 2009). The mechanism behind CTS is unclear, but may be related to tenosynovitis causing compression of the median nerve at the wrist or to local inflammation of the transverse carpal ligament, which has been shown to possess oestrogen receptors (Toesca et al. 2008). Interestingly, respondents did not raise CTS as a clinical feature in this questionnaire.

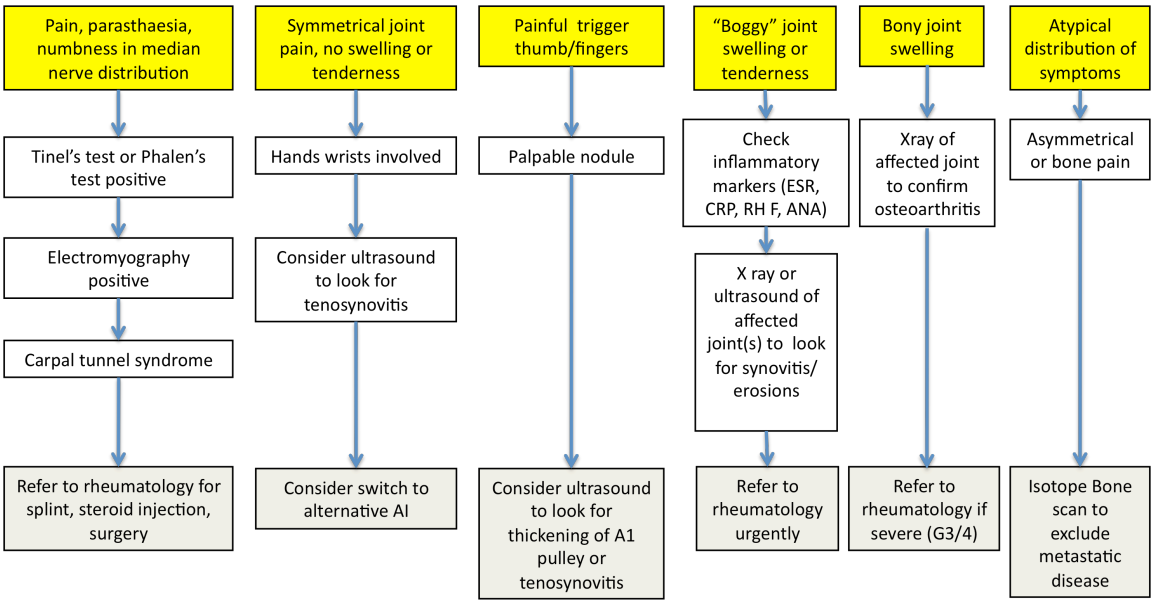
On the whole, UK specialists felt that the clinical features of AIA were of a syndrome that starts after a few weeks, persists until treatment discontinued and mainly affects the small joints such as the hand and wrist. These characteristics are in line with the published case series of AIA in clinical practice (Crew et al. 2007; Presant et al. 2007). The majority did not check blood parameters. To date the current literature has not identified any raised inflammatory markers in this condition, so this approach would not be unreasonable. Most clinicians did not request radiological tests, presumably because the diagnosis is relatively straightforward to make. About one quarter of respondents did request a plain x-ray film of the affected joints. The rationale behind plain film radiography would be to rule out other inflammatory or erosive pathology. However, to date, no diagnostic features of AIA have been reported on plain radiography. In fact the evidence suggests ultrasound and MRI are perhaps more useful in the diagnosis (Morales et al. 2007), although more time consuming and expensive.

The management questions in this study showed that clinicians used non-opioid analgesics and anti-inflammatory agents to manage this condition. This confirms the uncertainty about which agent is best to use and there is limited evidence to support either approach. Early small interventional studies have suggested roles for acupuncture and vitamin D only (Crew et al. 2009; Khan et al. 2009; Mao et al. 2009). A number of clinicians changed to exemestane as a first step, although there are no clear data to support this. However, there is some evidence that joint symptoms are less likely with a switch between anastrozole and letrozole (Renshaw et al. 2007). As expected, the frequency of rheumatology referral increased as the symptoms become more severe.

There were as many who felt confident in managing AIA as not confident and perhaps there is some room for education here. The majority of specialists suggested that the oncologists should be responsible for managing this condition, potentially alongside the GP. AIA is a common side effect and all disciplines will need to be familiar with it’s management, especially as increasing numbers of patients are now being commenced on AIs.

Finally, there was strong support for the use of guidelines for managing AIA. The protocol produced by Coleman et al. perhaps needs emphasising, as few were aware of this. However, as more studies are published on the aetiology and management of AIA, guidelines will require updating. Until now, these guidelines have provided a simplistic guide to the management of pain due to this condition. At present, we would recommend following this guideline in its current form. If a change of medication is necessary, an alternative AI or referral to rheumatology may be considered before switching to tamoxifen. The joint symptoms may be self-limiting, so reassurance and encouragement that the development of arthralgia is associated with a reduced risk of recurrence is also important (Cuzick et al 2008). This strategy is effective for some, but inevitably some patients do not respond and require drug discontinuation. As discussed above, the role of inflammation in this syndrome is still being evaluated. Thus, the effectiveness of anti-inflammatory drugs or other modalities of treatment is still under debate. As there can be a number of potential joint-related symptoms, we have composed an algorithm (Figure 19) to investigate AIA based on current knowledge (Din et al 2010).

Figure 19. Proposed algorithm for investigating aromatase inhibitor-induced arthralgia



6.6. CONCLUSION

This large questionnaire based study has given insight into current practice and understanding of AI arthralgia. There is no doubt that clinicians feel it is an important toxicity, with many uncertainties about its cause and management. Current guidelines for its management do exist, but are not well publicised. However, with several studies due to report over the next few years our understanding of this process will improve and any guidelines will need to be updated over this period.

7. THE ARIAD STUDY - METHODS

An Investigation of ARomatase Inhibitor Induced Arthralgia in the ADjuvant Treatment of Breast Cancer

7.1. INTRODUCTION

Following the publication of the large adjuvant trials of endocrine therapy conducted in women with postmenopausal breast cancer, aromatase inhibitors rapidly became a standard of care. It was not until these drugs were introduced into routine clinical practice that real problems with toxicity were encountered. The lowering of bone mineral density has been well described and was factored into the original trials (Eastell et al 2008). More recent trials have investigated treatment strategies to circumvent bone loss with the use of bisphosphonates (Lester et al 2008, Bundred et al 2008, Greenspan et al 2008). These are now engrained in routine practice and are a success story in managing this long term treatment complication. There are now established algorithms for managing this toxicity (Reid et al 2008).

However the same is not true for other toxicities. It was not until more widespread use of AIs that reports of the more troublesome musculoskeletal effects became apparent (Donnellan et al 2001). There is now growing evidence that AI-induced arthralgia (AIA) or musculoskeletal symptoms are a significant clinical concern. To date there is limited published evidence investigating this issue directly. In particular, there are only a few small prospective studies. As of yet, there is no recommended effective therapy to treat this condition and therefore maintain compliance to endocrine therapy.

The ARIAD study was therefore designed to investigate and provide prospective detailed information with regard to the incidence, clinical parameters, radiological and biochemical changes associated with this arthralgia syndrome. In particular, this study planned to monitor the severity of joint symptoms and related quality of life factors that have been less well described.

7.2. AIMS

The aim of this study was to characterise the frequency and severity of joint symptoms and associated biochemical and radiological changes during aromatase inhibitor adjuvant treatment of early breast cancer.

7.3. STUDY PROPOSAL AND APPROVAL

7.3.1. Protocol Writing

The ARIAD study was initially designed in spring 2008. It was agreed that a prospective detailed evaluation was needed due to the lack of published data at that time. The study involved collaboration between different medical specialities in Sheffield and Leeds. I wrote the entire protocol with advice from collaborators. I co-ordinated several meetings in both cities to fine-tune the study protocol. A list of the clinicians with significant involvement is listed shown below:

Table 7. List of the main collaborators in the ARIAD study

	Sheffield	Leeds
Oncologists	Prof R E Coleman (CI)	Prof D Dodwell (PI)
Statistician	Dr M Bradburn	
Rheumatologists	Prof A G Wilson	Prof P Emery
		Dr A L Tan
		Dr R J Wakefield
Radiologists	Dr A Highland	Dr P O'Connor

7.3.2. Factors important for study design

To conduct a prospective study, we decided that a 12 month follow up period was needed. The published data was variable as to the time of onset of arthralgia. Some reports and clinical experience indicated that most patients would have developed their symptoms within the first 3 months of initiating AI therapy. This was not the case for all and therefore longer follow up was

needed to capture all symptoms. As there was little data indicating the natural history of symptoms, a 12 month period of observation would capture information as to whether musculoskeletal symptoms are self limiting over the timeframe of a few months.

Most studies to date had evaluated patients who had already developed symptoms. We agreed that to gain new information, patients should be evaluated from the commencement of endocrine therapy.

4 groups for evaluation were identified. The most important group of patients to study were those receiving upfront AI therapy following breast surgery. However little was known about the other AI group; those switching to an AI following 2 -3 years of tamoxifen. We felt that these groups should be studied separately, particularly as there is an incidence of joint pain in postmenopausal women receiving tamoxifen. Such a study should have a control. Therefore as separate control groups, those receiving tamoxifen only and no endocrine therapy were also considered important.

7.3.3. Use of grip strength as the primary endpoint

Following review of the published data, it was clear that no consensus had been reached as to how to best evaluate this arthralgia syndrome. The data from Morales et al linking grip strength and MRI derived tenosynovial changes appeared to have the most clinical relevance (Morales et al. 2007, Morales et al. 2008). However this had only been tested in small numbers. In addition, the method of grip strength assessment was with the use of a modified sphygmomanometer. We felt that a more reliable method of grip strength testing was needed. The gold standard method of grip strength assessment in rheumatologial studies in the past had been with a Jamar© Dynamometer. This would give a more reliable objective measure, to assess if patients using AIs had a significant reduction compared to controls.

7.3.4. Rationale for other study assessments

7.3.4.1. Health Assessment Questionnaire – Disability Index (HAQ-DI)

This rheumatological questionnaire has been in use since 1978. There have been many publications on its reliability, validity and use in multiple settings. It has been used in a wide variety of diseases ranging from rheumatoid arthritis to systemic lupus erythmatosis, fibromyalgia as well as normal aging. The disability index is a shortened version with good reliability and validity. It is sensitive to change and therefore a useful tool in longitudinal studies. It consists of twenty questions divided into eight categories. The categories assessed by the disability index are 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reach, 7) grip, and 8) common daily activities. For each of these categories, patients report the amount of difficulty they have in performing two or three specific activities (Fries et al 1980).

The responses are made on a scale from zero (no disability) to three (complete disability). The scores are added together and divided by the number of categories answered. So the index score ranges between zero and three.

There is no clear understanding as to whether AIA represents an inflammatory condition or not. As the HAQ-DI can be applied across different diseases, we felt it was suited to this study. In addition, it is appended with two visual analogue scales. The first, a pain scale is an important factor when trying to characterise the change in pain over time. The second, more directed towards arthritis sufferers may be less important here (Fries et al. 1980).

Normal scores from the general population that have been reported in a population-based study are 0.49. For patients with rheumatological complaints, mean scores are usually higher. In osteoarthritis and rheumatoid arthritis patients scores are often between 0.8 and 1.2, respectively. In terms of disability, scores of 0 to 1 are generally considered to represent mild to

moderate difficulty. Scores of 1 to 2 represent moderate to severe disability, and 2 to 3 severe to very severe disability.

The HAQ-DI is responsive to change. Previous studies have estimated the minimal clinically important difference as 0.22. Others have suggested change above 0.1 is clinically meaningful (Bruce and Fries 2003).

Since this study was designed, HAQ scores have been reported in a few other studies evaluating AIA. It was chosen for this study as it has been well validated in arthritis sufferers.

7.3.4.2. Medical Outcome Short Form Health Survey (SF-36 version 2)

This questionnaire is a generalised survey of health. It consists of eight scaled scores, which are the weighted sums of the questions in their section. It assesses 8 domains of functioning as listed below:

1) vitality
2) physical functioning
3) bodily pain
4) general health perceptions
5) physical role functioning
6) emotional role functioning
7) social role functioning
8) mental health

The scores are then combined to give a 2 summary statistics: a physical component summary (PCS) and a mental component summary (MCS). The sores are produced using the Quality Metric certified scoring system. The SF-36 is well validated. It's test –retest reliability is between 0.74-0.98. It was chosen for this study as bodily pain is in one of the categories. Arthralgia may therefore produce a change in score and therefore insight into its effects on general

health related quality of life. This questionnaire has been used in both rheumatological and oncological studies.

7.3.4.3. Brief Pain Inventory – Short Form (BPI-SF)

This is a pain assessment tool used in cancer patients used to measure pain intensity and interference in a patient's life. It has been validated in cancer and arthritis (Mendoza et al. 2006). We felt this questionnaire would provide more detailed information about pain status and location.

7.3.4.4. Morning Stiffness

Measured in minutes, stiffness is a key feature of inflammatory arthropathies. Clinical experience has shown that patients receiving aromatase inhibitors suffer with joint stiffness as well as pain. The stiffness is often present in the morning and after periods of rest, but improves with movement. In consultation with rheumatologists, duration of morning stiffness was included as a specific study assessment.

7.3.4.5. Disease Activity Score – 28 CRP (DAS-28)

This is an examination tool for the clinician to assess the activity of the joint disease (van Gestel et al. 1998). This was developed several years ago to monitor disease activity in rheumatoid arthritis. 28 joints are examined for swelling and tenderness, usually by an independent joint counter. In combination with ESR or CRP and a health visual analogue scale, a composite score is calculated. This provides examination-orientated information about the joints, which is important if the process is inflammatory. For the purposes of this study, CRP was chosen, particularly as CRP on it's own is a more useful inflammatory marker which could pick up short-term inflammatory changes. An overall score between 0-10 is calculated and this can be used to monitor changes over time.

7.3.4.6. Biochemical Parameters

CRP was measured to form part of the composite score of DAS-28 CRP. On its own, it is an acute phase protein and can be raised in inflammatory conditions, particularly when synovitis is involved. At the time of study design, there was no clear signal as to whether CRP was an important factor in AIA.

Oestradiol E2 is lowered dramatically with the use of aromatase inhibitors. Oestrogen deprivation is postulated as the reason for joint symptoms, as seen at the menopause. At present, data are lacking linking residual serum oestrogen levels with AIA. To measure the low levels of oestradiol in women on AI therapy requires an ultrasensitive assay that is beyond the resolution of most standard oestradiol assays. However, measuring this accurately may provide a causative link.

Vitamin D has so far not been linked to AIA in the large retrospective analyses from some of the adjuvant trials. Vitamin D deficiency is often associated with musculoskeletal symptoms and thus may be implicated in this process. Details of the assays used are explained later in this chapter.

7.3.4.7. Hand and Wrist Ultrasound

The use of ultrasound in rheumatology has increased over the decades with improved technology. In particular, the development of high frequency transducers has allowed for the evaluation of small joints on the hand and wrist. Since the pathology in AIA may range from synovitis to tensynovitis, it was felt that ultrasound was a key diagnostic tool to evaluate this syndrome. With the use of power Doppler focal inflammation of tendons and joints can be evaluate real-time, a potential advantage over MRI imaging. Given the rare association of AIA with carpal tunnel syndrome, measurement of the median nerve cross-sectional area can easily be achieved with this method.

7.3.4.8. Hand and Wrist Magnetic Resonance Imaging (MRI)

MR imaging has become the gold standard of evaluating joints in rheumatological studies. It also can assess for synovitis and tenosynovitis. Given early studies of AIA were suggesting MR changes, it was important to include this imaging modality in this study.

7.3.4.9. Hand and Wrist Dual X-ray Absorptiometry (DXA)

This has been used in the early assessment of undifferentiated and rheumatoid arthritis before the appearance of plain radiographic bone changes (Haugeberg et al. 2006; Haugeberg et al. 2007). We felt this was a novel assessment which may provide information if hand bone density was at implicated in aromatase inhibitor musculoskeletal symptoms.

7.3.5. Peer Review

The study protocol, once the first draft was completed, was subject to three peer review processes. The first was via the Clinical Trials Executive Committee at the Cancer Clinical Trials Centre (CCTC), Weston Park Hospital on 7th April 2008. Approval was granted to run the study with the support of the CCTC. In addition funding was approved from University of Sheffield Clinical Oncology Research Funds.

The second independent scientific review was external. Dr David Miles, Consultant Medical Oncologist at the Mount Vernon Cancer Centre, Northwood, London, performed this review. Positive feedback was received and the letter is appended (appendix 13.8).

The third review was by the Astra Zeneca team as funding was approved to fund the use of MR imaging.

7.3.6. Ethical Submission

The trial protocol, patient information sheet, GP letter and consent form were all designed by myself. In addition the radiation exposure involved from hand bone densitometry and hand X-ray were reviewed by the Medical Physics Expert. The risk from ionising radiation in this study was classified as negligible.

This was the first study in the department to be submitted to the Ethics Committee via the IRAS (Integrated Research Application System) system. Hence, I was the first to use this system.

The ethics submission was completed and transferred on 24th April 2008.

Given this was a 2 site study, the application was assessed by an external Research Ethics Committee (MREC) to gain approval to conduct the study at both sites. Trent Research Ethics Committee reviewed the study proposal. This involved attending for interview in Derby on 1st May 2008. A favourable opinion was given subject to a few queries. Listed below is a list of some important points raised by the ethics committee:

1) Confirmation that samples could be stored for up to 15 years according to local policy.
2) Clarification that bisphosphonates would be prescribed if clinically indicated.
3) Need to reduce patient identifiers on sample bottles.
4) Confirmation that stored samples were cell free and would be retained for use in future studies.
5) Sample size of 30 per group being able to detect 4.5kg – smaller differences may be missed.
6) Limited power to detect differences in secondary outcomes.
7) Analysis would have more power if baseline grip was used as a covariate, rather than change in grip strength.
8) A repeated measure analysis should be carried out using serial measurements of grip strength.

9) Some changes to Participant Information sheet (title, order of questions, clarity, risks from bloods, MRI, payments)

A reply was submitted on 22nd May 2008. All points were addressed. The statistical queries were answered directly by Mr M Bradburn, study statistician. Details of the reply are shown below.

Risks ethical issues

Participant information sheet (version 1, 27/3/08) and consent form (version 1, 26/2/2008) have been revised to confirm samples would be retained for potential use in future studies.

Confidentiality

Q A43 has been answered on the application form. Data will be retained for 15 years in line with the University of Sheffield Cancer Research Centre Standard Operating Procedures version 2.

Scientific and statistical critique (comments from M Bradburn, study statistician)

1 *With a sample size of 30 per group the researchers would only be able to detect very large differences (around 4.5kg) between groups, and smaller but clinically important differences could be missed.*

See also 2. The study has a 90% power to detect a 4kg reduction and an 80% power to detect 3kg reduction. This calculation allows for a 10% drop out rate. In the only paper to investigate grip strength in this situation (Morales et al), 12 patients had a mean reduction of grip strength of 16%. In their population with a mean age of 68, the normal grip strength should be around 24kg (Mathiowetz et al). Thus a 16% reduction equates to approximately a 4kg reduction. We feel that reductions under 3kg are not clinically significant.

2 *The Trent REC statistician was unable to check the sample size exactly, since the mean values used were not given.*

This detail was omitted in error. As above, previous studies have suggested the typical grip strength in this population to be around 24kg. Therefore a 4kg reduction equates to nearly 20%.

3 *Also there would be very little power to detect differences in any secondary outcomes.*

This is true. The studies that have suggested an association between AI and arthralgia are based on many thousands of patients - which we are unable to achieve. What this study does is to demonstrate the extent to which severity of arthralgia (as measured by grip strength) is associated with AI, and provide an indication as to how quality of life may be affected by this. As some of the secondary outcomes are exploring some of the mechanistic aspects behind this effect, they are hypothesis generating rather than being the subject of rigorous statistical testing.

4 *The analysis would have more power if baseline grip was included as a covariate rather than using change in grip strength.*

Agreed, this will be added to the statistics plan.

5 *A repeated measures analysis should also be carried out using the serial measurements of grip strength, so all of these measurements contribute to the analysis.*

I suggest the primary analysis should concentrate on the difference at pre-planed times for two reasons:

* We envisage the onset of deterioration in grip strength to be accelerated in the AI arms and gradual (if at all) in other arms. In other words, we envisage the difference to be maximised soon after commencing treatment and gradually

reduced over time thereafter. We would not want these early differences to be masked by analyses that give greatest weight to later time points.
* Because this is easier to interpret and describe.
Nonetheless, we can add this as a secondary analysis.

Participant Information Sheet

All changes have been made in line with the recommendations apart from item 5 'What will happen to me'.

This has been adjusted to make it clearer. The table of appointments and tests has been brought forward so patients can see straight away that there are 6 appointments. Headings have also been added to the investigations to make it clear what each investigation involves. Making a list visit by visit would make a lot of repetition and the section longer, if all the details of the tests are to be included.

Confirmation of ethical opinion was given on 11th June 2008.

7.3.7. Research and Development Submission

Research and development submissions were made to both Leeds and Sheffield Teaching Hospitals NHS Trusts. Approval was granted on 11th July and 24th July 2008 respectively.

7.3.8. Protocol Amendments

Two protocol amendments were made during the course of the study, one minor and one substantial amendment. All are listed below with the reasons behind them.

The first was a minor amendment and was approved on 12th September 2008, notifying the ethics committee that the layout of the SF-36 was being altered to that of the SF-36 version 2. This was approved to be used immediately and therefore was able to be implemented prior to the start of the study. NHS Research and Development approval was also obtained.

The second amendment was a substantial amendment and was approved on 12th February 2009 and given NHS research and development approval on 2nd March 2009.

The amendment was to adjust the inclusion criteria for the study. Confirmation of postmenopausal status has been adjusted for those under the age of 55 years. Instead of giving specific values for FSH and oestradiol, this has been replaced by "**and serum FSH (follicle stimulating hormone) and oestradiol levels consistent with local laboratory values for post menopausal status"**.

This change has been made because we felt the criteria for post menopausal status under the age of 55 years were too stringent and in fact it is uncommon for patients, even those under 60 years, to have an oestradiol under 30pmol/l. In fact other trials investigating aromatase inhibitors (eg IBIS-II), use criteria such as FSH greater than 30IU/l only in women without a uterus; they don't measure biochemical levels of oestradiol due to difficulty with accurate measurement at these low levels with routine assays. In those with a uterus amenorrhoea for more than 12 months is sufficient to establish postmenopausal status.

7.4. STUDY OBJECTIVES

7.4.1. Primary Objective

- To investigate for an increase in the degree of arthralgia as measured by reduction in grip strength in the AI population compared to the control groups receiving tamoxifen or no endocrine treatment.

7.4.2. Secondary Objectives

- To use HAQ-DI (Health Assessment Questionnaire-Disability Index), SF-36 (Short Form 36) and BPI-SF (Brief Pain Inventory-Short Form) questionnaires, duration of morning stiffness and DAS-28 (Disease Activity Score-28) examination scores to explore for differences in the frequency and severity of joint symptoms due to AI therapy.
- To assess for changes in serial measurements of surrogate markers of joint disease, including inflammatory, immunological and biochemical markers (particularly novel markers of cartilage metabolism).
- To investigate for radiological changes in the joints of the hand using plain film radiography, ultrasound and hand DXA (Dual Energy X-ray Absorptiometry). In a subset of 40 patients (AI and controls), MRI of the hand was performed.

7.5. PLAN OF INVESTIGATION

7.5.1. Cohorts under investigation

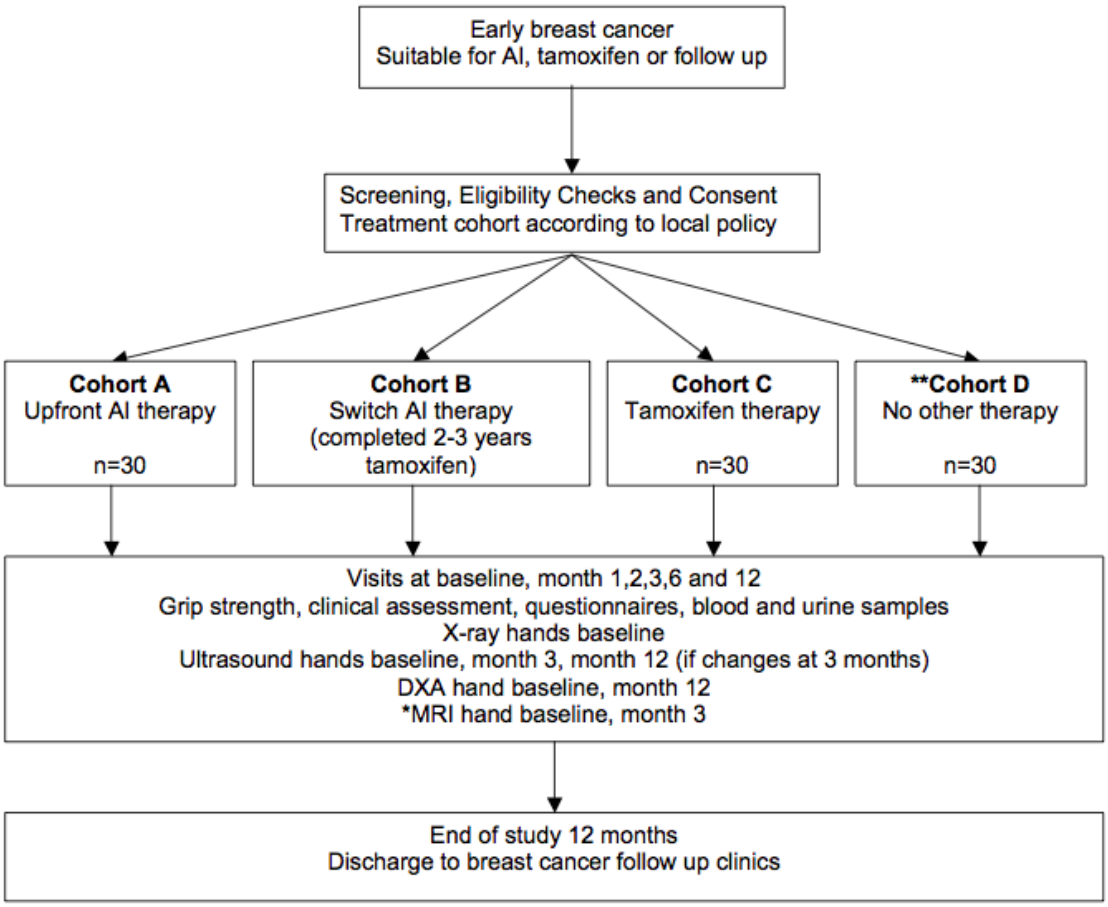
This was an observational 2 centre study (Sheffield and Leeds) designed to evaluate the severity and aetiology of AI-induced arthralgia in postmenopausal women with hormone receptor positive resected breast cancer, who were eligible for treatment with an AI according to local guidelines. Comparison was to be made with controls receiving tamoxifen and controls having no endocrine treatment (eg. oestrogen receptor negative or ductal carcinoma in situ). This study provided mainly descriptive information about the cohorts investigated and did not influence any of the treatment given.

The following 4 groups of patients were investigated:

A) Patients due to start AI as upfront endocrine therapy for 5 years.
B) Patients due to start AI as switch endocrine therapy after 2-3 years of prior tamoxifen treatment.
C) Control group due to start tamoxifen for 5 years.
D) Control group not receiving any endocrine therapy or chemotherapy (including patients with Carcinoma In Situ or benign breast disease).

The study outline is shown in figure 20.

Figure 20. ARIAD Trial Schema



*30 patients in cohorts A and 10 patients in D. Repeated at 3 months (or earlier if grade 3-4 symptoms)

**includes resected carcinoma in situ not receiving endocrine therapy and benign breast disease

In cohorts A, C and D, there was a minimum of 2 weeks between definitive surgery and baseline measurements. In cohort B, patients were enrolled at the point of switching from tamoxifen to AI.

After providing consent, all patients were screened for eligibility. Patients were treated with aromatase inhibitor therapy or tamoxifen as per local policy. Follow up was standardised across all four groups. Cohort D controls were included as there is an increased incidence of musculoskeletal symptoms in the postmenopausal population, so comparison with controls is important. It was presumed that there was no difference between the different types of AI, so choice was governed by local policy.

Treatment commenced within 8 weeks of final definitive surgery or within 6 weeks of completing adjuvant chemotherapy or radiation therapy. For the switch patients, AI therapy commenced within 6 weeks of discontinuing tamoxifen. All the cohorts were evaluated in exactly the same manner. At baseline, symptom questionnaires, rheumatological assessment, blood, urine, plain film hand radiography, ultrasound of the hands and hand DXA was performed. Further assessments took place at 1, 2, 3, 6 and 12 months as per the assessment schedule (table 5). Notably, ultrasound was repeated at 3 months (and 12 months if any changes at 3 months) and DXA was repeated at 12 months for all patients. 12 months of follow up marked the end of the study period. At this time, the patient was referred back to the appropriate physician for continued long term follow up as per local guidelines. In those reporting significant joint symptoms (grade 3-4 (CTC v3.0)), the ultrasound was repeated earlier than the 3 month assessment.

A subsets of 40 patients (30 in upfront AI group, 10 in no treatment group) were selected for MRI of the hand at baseline and at 3 months. In those reporting significant arthralgia earlier than 3 months, imaging was arranged before this timepoint, as per the ultrasound scan.

7.5.2. Patient Population

The aim was that 120 patients from Sheffield and Leeds would be enrolled into this study. There would be 30 patients in each of the 4 groups shown above. The patient population included postmenopausal women with resected stage I, II or III, ER+ and or PgR+ breast cancer, with no clinical or radiological evidence of recurrent or metastatic disease before baseline assessment. Patients must have had a complete tumour resection and margins of the resected specimen should have been microscopically free of disease. Pre-menopausal women who developed amenorrhoea as a result of chemotherapy within the past 2 years, were not eligible for this study.

7.5.3. Project Setting

This project was conducted at Weston Park Hospital Cancer Research Centre, Sheffield and Chapel Allerton Hospital, Leeds. Patients were identified through the relevant Multi Disciplinary Team Meetings and follow up clinics, by the principal investigator. They were subsequently screened and enrolled via a research clinic at each of the 2 centres. They were followed up as part of this study for 12 months, following which, they were discharged back to the appropriate follow up clinic.

7.6. INCLUSION CRITERIA AND EXCLUSION CRITERIA

7.6.1. Inclusion Criteria

The study inclusion criteria are listed below:

Signed written informed consent
WHO performance status 0,1,2
Post-menopausal status as defined by one of the following:

- Age >55 and more than 12 months since cessation of menses
- Age ≤55 with cessation of menses for more than 12 months and
  - serum FSH (follicle stimulating hormone) and oestradiol levels consistent with local laboratory values for post menopausal status
- Bilateral oophorectomy

Oestrogen receptor positive (except for COHORT D who were ER negative). This was defined as a Quick score greater than or equal to 3.
Any HER 2 status
May have completed adjuvant chemotherapy (NOT COHORT D) or radiotherapy

7.6.2. Exclusion criteria

The study exclusion criteria are listed below:

Pre menopausal
Menopausal as a result of cytotoxic chemotherapy or LHRH analogue within 2 years.
History of metabolic bone disease (Paget's disease, hyperparathyroidism)
Daily use of NSAIDs or corticosteroids. For NSAIDs, a 2 week washout was satisfactory for inclusion.
Evidence of recurrent or metastatic breast cancer or active other malignancy
Medical, social or psychiatric condition making participation undesirable

The presence of joint symptoms at baseline was not an exclusion criterion.

7.7. INVESTIGATIONS

7.7.1. Assessment of Grip Strength

All women who consented to the study had their grip strength determined at each of the specified visits. The Jamar® Hand Dynamometer was used by a single clinician. Each grip strength test consisted of 3 maximal repeated contractions lasting 3 seconds on the second handle position of the dynamometer. Three repetitions were performed using the right hand first, then the left. A 30 second rest period was allowed between each contraction. All patients performed the test in the seated position as recommended by the American Society of Hand Therapists (ASHT): “the patient will be seated comfortably in a chair without arm rests, with feet fully resting on the floor. Hips and knees will be placed at approximately 90 degrees. The ipsilateral shoulder will be adducted and in the neutral position. The elbow will be flexed at 90 degrees, with the forearm in neutral position. The wrist needs to be in 0-30 degrees of dorsiflexion and 0-15 degrees of ulnar deviation. Standard commands were used for testing.”

Grip strength was performed at baseline, month 1, 2, 3, 6 and 12.

7.7.2. Musculoskeletal/Health Assessments

The following 3 questionnaires were given to the patients by the research nurse at each study visit.

1) Health Assessment Questionnaire – Disability Index (HAQ-DI)

2) SF-36 (Short Form 36)

3) Brief Pain Inventory (Short Form)

The time required to complete these 3 questionnaires was approximately 20 minutes. They were completed at baseline, month 1,2,3,6 and 12.

4) Morning Stiffness

This was recorded as the total time a patient has stiffness for in the morning. Its severity was recorded in minutes. The same standard question was asked on each occasion: “how long does it take you to get going in the morning?” This was recorded at baseline, month 1,2,3,6 and 12.

5) Disease Activity Score-28 (DAS-28)

This was recorded at baseline, month 1,2,3,6 and 12. The 28 joint count was performed by at independent joint assessor. In Sheffield, this was Sister Sandra Gutcher, who was trained by myself to perform this assessment. In Leeds, Sisters Ruth Thorpe and Sue Hartup performed this role. They also had study specific training by me, though Ruth Thorpe had previous experience in performing this role in rheumatological studies. Where possible, the same independent joint assessor was used for each patient throughout the duration of the study. 28 joints are examined for swelling and tenderness. A general health visual analogue scale was also completed. In combination with CRP, a composite score calculated.

7.7.3. Biochemical, inflammatory and immunological markers

7.7.3.1. Sample Processing

Samples were be taken at baseline, 1, 2, 3, 6 and 12 months and stored. The original intent of the study was to measure markers of cartilage synthesis (PIINP (N terminal propeptide of type II collagen)) and degradation (CTX-II (C terminal telopeptide of type II collagen)) as well as and serum oestradiol and potentially other biochemical and inflammatory/immunological factors. Due to a diurnal variation of serum and urine biomarkers, samples were taken at the same time ideally 8-10 am and fasted, with the time recorded (Kong et al. 2006). For urine, the second voided sample was taken. Patients who were unable to attend morning clinics were still included and did not need to fast until their clinic visit. However, these patients were assessed at a constant time of day.

Serum samples were prepared by mixing blood in the tubes and allowing them to stand for 30 minutes, followed by centrifugation at 2000g for 10 minutes. Plasma samples were collected in an EDTA tube and gently inverted to prevent clotting. The tube was then centrifuged for 10 minutes at 2000g, within 30 minutes, with time recorded. Four aliquots of 0.5ml of the serum and 2 aliquots of plasma were labelled with a unique identifier ie trial number, date of birth and visit date. Samples were stored at -80^{o}C. Urine samples were stored in 2 aliquots under the same conditions as the serum and plasma samples. These samples were analysed as a batch at the end of the study.

In Sheffield, the samples were processed by the research laboratory team at Weston Park Hospital Cancer Research Centre. In Leeds, the research laboratory team in the academic department of rheumatology at Chapel Allerton Hospital processed, labelled and stored samples, before transferring them all to Sheffield at the end of the study.

7.7.3.2. Oestradiol and Vitamin D

Frozen serum samples were sent in dry ice Marburg, Germany for analysis. This was performed in the laboratory of Prof. Dr. P. Hadji, University hospital of Giessen and Marburg.

Oestradiol E2 was measured using the Cobas® Elecsys Oestradiol II assay. This assay employs a competitive test principle using a polyclonal antibody specifically directed against 17β-oestradiol. Endogenous oestradiol released from the sample by mesterolone competes with the added estradiol derivative labeled with a ruthenium complex for the binding sites on the biotinylated antibody. This could measure levels of oestradiol as low as 5pg/ml. The intra-assay precision was 1.4-3.3%. The inter-assay precision was 2.2-4.9%.

Total 25-hydroxyvitamin D was measured using the Cobas® Elecsys Vitamin D assay. The measuring range of the test is 3.0-70.0ng/ml. The intra-assay precision was 2.2-6.8%. The inter-assay precision was 3.4-13.1%.

7.7.4. Hand X-rays

Plain radiographs of the hands were performed at the start of the study. These were done to assess for any significant joint pathology at baseline. A single DP (dorsum plantar) study was done of both hands. This was repeated only if clinically indicated. This was reported as per standard practice.

7.7.5. Hand Ultrasound

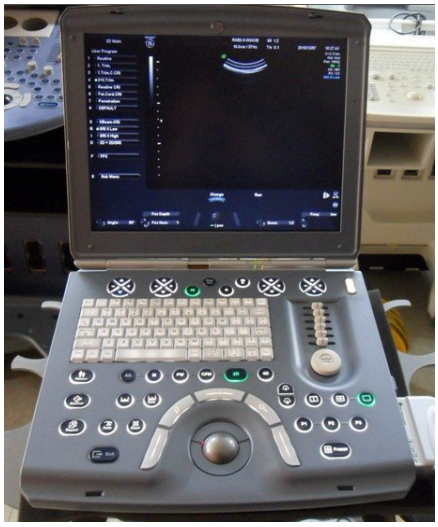
7.7.5.1. Ultrasound Training

I performed all the study ultrasound scans. To gain competence in this ultrasound technique, I spent April – September 2008 in training. I underwent formal training at the Bournemouth University musculoskeletal diagnostic ultrasound course on 14-15th June 2008. In addition, I attended the British Society of Rheumatology ultrasound course in Leeds, in September 2008. I received informal training in Leeds with Dr Richard Wakefield, performing scans on patients on a weekly basis. I was also able to scan patients in rheumatology clinics in Sheffield.

7.7.5.2. Ultrasound Scoring

All ultrasound scans were conducted by me. Ultrasound of both hands was performed in all patients at Leeds and Sheffield at baseline and repeated after 3 months. If there were any changes at 3 months, the scan could be repeated at 12 months. If severe symptoms developed before 3 months, then the scan was performed earlier ie if grade 3-4 joint symptoms developed. The same make of portable laptop scanner was used throughout the study (GE voluson i). Ultrasound is a very good tool for assessing the tendons, tendon sheaths, ligaments and cartilage, which may be implicated in this process.

Figure 21. GE Healthcare Voluson i portable ultrasound scanner



A standardised form was created in collaboration with Dr Richard Wakefield, Senior Lecturer in rheumatology, and is appended. The same areas were scanned for each of the baseline and 3 month ultrasound. At the wrist, 3 joint areas were imaged, the radio-carpal, ulna-carpal and inter-carpal joints. Each was scored for the presence or absence of osteophytes or erosions on a binary scale. To assess for synovitis, both a grey scale and a colour doppler image were taken. These were both graded on a scale of 0-3. The presence of intra-articular fluid and synovial thickening were assessed on grey scale and active synovitis by Doppler investigating for increased blood flow around the joint. This process was repeated for the metacarpophalangeal (MCP) joints 1-5 and the proximal interphalangeal (PIP) joints 1-5.

The flexor tendons were also evaluated for evidence of tenosynovitis. Tendons 1-5 imaged from their entire length from distal phalanx to wrist. These were assessed in grey scale as well as power Doppler. The presence of thickening or fluid was graded 0-3 according to the following scale adapted from MRI scoring of tenosynovitis (Havaardsholm et al 2007).

Grade 0 (normal): no peritendinous effusion or synovial proliferation with enhancement

Grade 1: <2mm peritendinous fluid and/or synovial proliferation with enhancement

Grade 2: ≥2 and <5mm peritendinous fluid and/or synovial proliferation with enhancement

Grade 3: ≥5mm peritendinous fluid and/or synovial proliferation with enhancement

The median nerve was also identified at the wrist. The cross-sectional area of each nerve was measured in cm^2. In carpal tunnel syndrome, the median nerve cross-sectional area increases (Hammer et al 2007).

7.7.6. DXA scans

This examination was performed in all patients at baseline and repeated at 12 months. Left and right hands were scanned separately. The patients were asked to remove any heavy attenuating materials such as rings or watches. The height and weight of each patient was measured and recorded. The scans were performed to allow good coverage around the hand and wrist. Using the regions of interest facility on the computer, the radius and ulna were excluded from the bone mineral density (BMD) calculation.

The scans were acquired by one of two operators using a dedicated GE Healthcare Lunar Prodigy machine. Procedure was followed in line with the operator's manual and in accordance with the Ionising Radiation (Medical Exposure) Regulations 2000 (IR(ME)R 2000).

Patients' were required to sit alongside the machine resting their hand palm down on the tabletop without leaving spaces between each finger and the thumb. The typical irradiation time was 67 seconds with an estimated skin

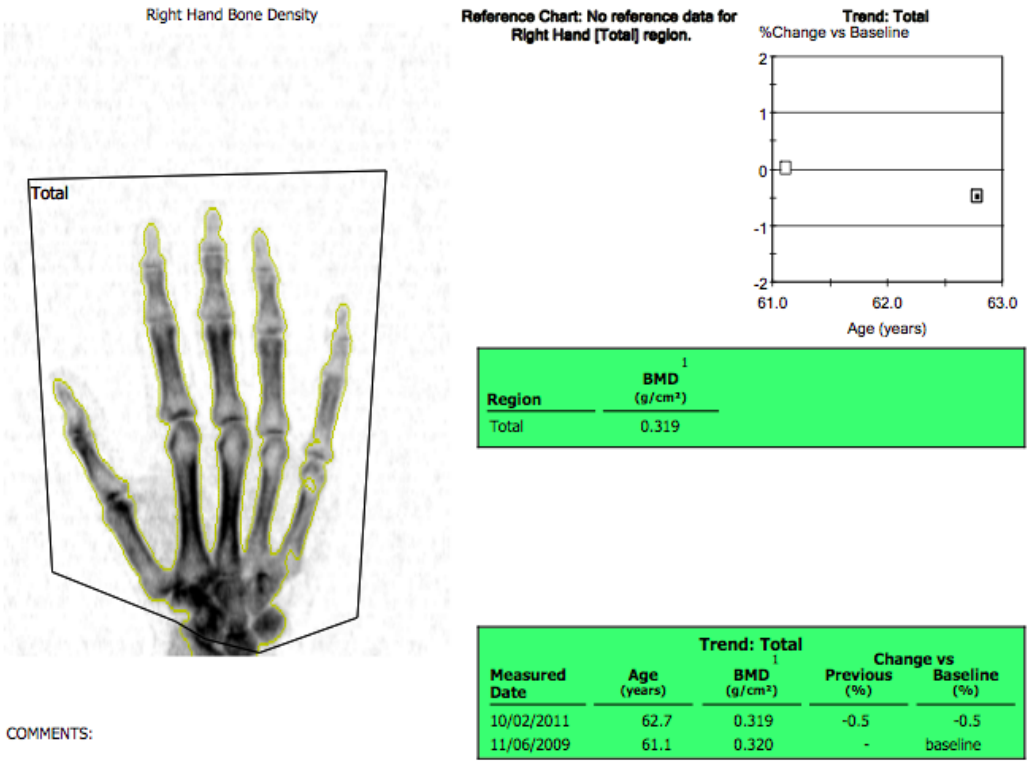
exposure dose of 2 micro Gray. Each hand was scanned from the fingertips to the ulna styloid process.

A quality assurance test to calibrate and examine the functionality of the machine was performed each morning prior to any scans being acquired or/and at least three times a week. This also served to monitor the precision and accuracy of the machine over time.

The same process was repeated at 12 months and a percentage change from baseline was noted.

The equipment used was the same for the whole study. Both Sheffield and Leeds used GE Lunar Prodigy scanners.

Figure 22. Example of a 12 month hand DXA scan showing the change in BMD over time.



7.7.7. Hand MRI

Forty patients were planned to have MRI imaging of the hand/wrist, 30 from cohort A and 10 from cohort D. This number was increased from 20 patients following a successful grant application to Astra Zeneca (£30,000). Scans were performed at baseline and repeated at 3 months (or earlier if grade 3-4 joint symptoms develop). Patients not completing their second scan were replaced. Centres tried to perform the MRI at the same visit as the ultrasound, though this was not always possible. The MRIs were done at Leeds and Sheffield using their Siemens Avanto 1.5T (tesla) MRI scanners. Every effort was made to ensure that the same equipment was used for the duration of the study in each centre. Scans were performed of the hand/wrist contralateral to the breast/axillary surgery, as the arm was required to be abducted above the head. The following sequences were performed: 3D T1W VIBE pre and post contrast, T2W TSE coronal, 3D T2W DESS and pre and post contrast UTE.

Two consultant radiologists scored the MRI scans, Dr Phil O'Connor in Leeds and Dr Adrian Highland in Sheffield. They agreed to use the same the scoring system: OMERACT RAMRIS MRI hand and wrist score (Ostergaard et al 2005). Joints were scored for the presence of synovitis (0-3). Bones were scored for the presence of erosions or oedema (0-3). Total scores for synovitis, erosions and oedema were added and an average taken for the two radiologists scores.

However this scoring system, primarily used in inflammatory arthropathies, did not include any assessment of the tendon. Therefore in a modification, the tendon compartments were scored as per the Haavardsholm et al MRI grading system (as used in the ultrasound).

7.8. PHARMACY

All aromatase inhibitors were supplied from standard pharmacies. Anastrozole 1mg, Letrozole 2.5mg and Exemestane 25mg were all available for use. This study did not influence the prescribing of AIs which was determined by local policy.

7.9. RECRUITMENT

The first patient was recruited in September 2008 and recruitment continued until October 2009. The last patient completed their 12 month follow up in September 2010.

7.10. STUDY DISCONTINUATION

The study planned for a number of reasons for discontinuation as listed below:
After completion of 12 months of follow up
Patient wishes
Recurrence of breast cancer
Death

Table 8. ARIAD Study Flow chart

Study Period	Screening Days -28 to Day 1	1m	2m	3m	6m	12m
Informed consent	X					
Medical History (to include menopausal status, HRT)	X					
Concomitant Drugs	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X					
Prior anticancer therapy	X					
WHO performance status	X	X	X	X	X	X
BMI	X	X	X	X	X	X
Morning stiffness	X	X	X	X	X	X
SF-36	X	X	X	X	X	X
HAQ-DI	X	X	X	X	X	X
Brief Pain Inventory	X	X	X	X	X	X
Physical examination Inc Rheumatological	X	X	X	X	X	X
DAS-28	X	X	X	X	X	X
Grip strength	X	X	X	X	X	X
CRP	X	X	X	X	X	X
Baseline blood tests	X					X
Serum/plasma and urine for storage	X	X	X	X	X	X
X-ray[#]	X					
Ultrasound*^	X			X		X
DXA	X					X
MRI*	X			X		
End of study						X

[#]Repeated only if clinically indicated

*Earlier if joint symptoms grade 3 or 4

^Repeated at 12 months if any changes on 3 month scan

7.11. DATA MANAGEMENT

7.11.1. Measurement and Quality Assurance

The same Jamar dynamometer was used to measure grip strength in all patients by the same clinician as above. The dynamometer was calibrated by the manufacturer and checked by local technicians for accuracy before the start of the study. Maximal grip strength for each hand was measured in kilograms and recorded at each visit. An average of 3 readings was taken for each hand. Percentage change from baseline was calculated. Similarly, centres used the same ultrasound, DXA and MRI equipment throughout the duration of the study.

7.11.2. Data Collection

All data were collected by the study clinician and inputted “real-time” on a hard copy case report form (appendix 13.9). A database was then created by the data management team at the Cancer Research Centre in Sheffield. All data queries were investigated by myself and returned to the data mangers to update the database.

All data were recorded in the case report from. Some examples of other data collected are listed below:

Patient and tumour characteristics, menopausal status, prior use of hormone replacement therapy (HRT) and past medical history.
Prior anti-cancer therapy, particularly type of chemotherapy.
Concomitant medications (prescribed and non-prescribed).
Other activity (eg physiotherapy).
WHO Performance Status
Body Mass Index (BMI)

7.12. STATISTICAL CONSIDERATIONS

7.12.1. Primary Endpoint

The primary endpoint was the percentage change in grip strength at 3 months. For each patient, the grip strength was evaluated by taking the average of three successive readings in each hand separately. The patient's overall grip strength was defined as the average of the grip strengths in the left and right hands.

7.12.2. Secondary Endpoints

- Changes in the mean maximal grip strength over time.
- Changes in HAQ-DI, SF-36, BPI(SF), morning stiffness and DAS-28 scores over time.
- Changes in biochemical and inflammatory/immunological markers over time.
- Changes in ultrasound (and MRI in selected patients) appearances over time.
- Changes in bone mineral density of the hands over time

7.12.3. Statistical Analysis (by Michael Bradburn – study statistician)

All analyses will be performed by intention-to-treat. Grip strength values were analysed using analysis of covariance with the covariates being baseline grip strength, treatment cohort, age at baseline and prior chemotherapy. Pair wise comparisons were carried out using contrasts between the cohorts. A repeated measures analysis was done using serial measures of grip strength. Questionnaire scores were analysed using the Kruskal-Wallis test.

The primary focuses of the study were, in order, the following comparisons:

1: Upfront AI (A) v No treatment (D)
2: Switch AI (B) v No treatment (D)
3: Upfront AI (A) v Tamoxifen (C)
4: Switch AI (B) v Tamoxifen (C)
5: Upfront AI (A) v Switch AI (B)

After further discussions within the trial team, a further comparative analysis was undertaken.
6: A and B combined v C and D combined

All p-values and confidence intervals were two-sided. All hypotheses were tested at the 5% level of significance. We used a closed-test procedure control the false positive rate of 5% focusing our comparisons on the 3 month time point and the hierarchy of comparisons as above. We chose the 3 month time point as the primary comparison since onset of symptoms were expected to follow soon after initiation of treatment and this analysis would best assess the changes in grip strength following initiation of treatment. The 6 and 12 month comparisons were to help establish whether any change in grip strength had been maintained.

All analyses were undertaken using the SAS statistical software, version 9.3 (SAS® 9.3:.Cary, NC: SAS Institute Inc.) or Stata version 12.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.)

7.12.4. Study numbers/statistical power

For the five comparisons listed above, 27 patients will were required in each arm for a 90% power to detect a 20% drop in grip strength and with significance at the $p<0.05$ level. Assuming a 10% dropout rate, there would need to be 120 patients enrolled (30 in each group). These calculations were performed by a assuming a standard deviation of 5kg and using normal values for grip strength according to Mathiowetz et al (Mathiowetz et al. 1984; Machin et al. 1997).

A recalculation occurred when it became clear that 120 patients would not be recruited in the study time period and allow for thesis completion. The power was dropped to 80% allowing for a reduced sample size of 88 (22 per group).

7.13. STUDY PROGRESS

After approval by the ethics committees and research and development committees, I arranged and chaired trial start up meetings in Leeds and Sheffield in September 2008. The first patient was recruited at the end of September 2008.

Recruitment progressed well with an average of 6-7 patients recruited per month. In just over one year, the total number reached 77 (Leeds 34, Sheffield 43) (figure 22). More than 30 were recruited to cohort A, as the participants who did not complete their 2 MRI scans were replaced. The overall recruitment per centre and by cohort is shown in figure 23.

The study closed to recruitment due to time constraints at the end of October 2009. However all patients already recruited still continued follow up and all completed the study by November 2010.

Figure 23. ARIAD recruitment from August 2008 to October 2009

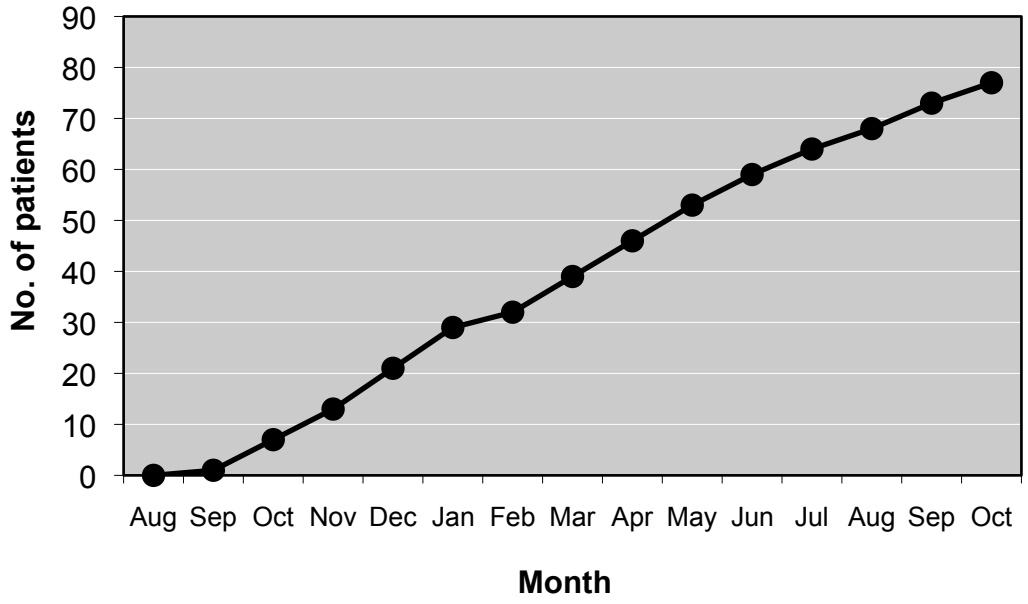
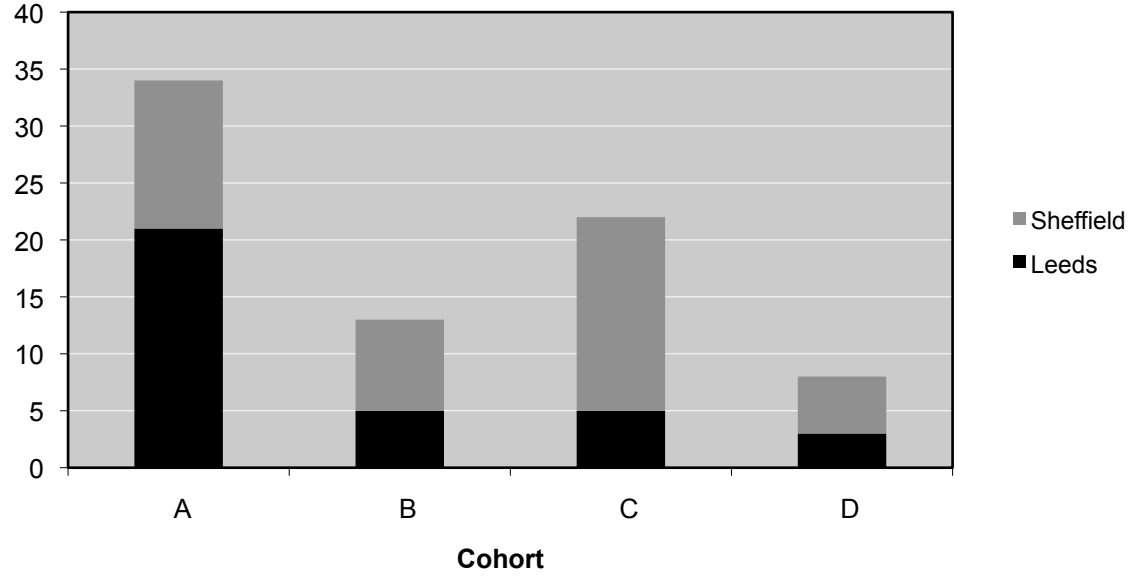


Figure 24. ARIAD recruitment by cohort and centre



8. THE ARIAD STUDY – RESULTS OF CLINICAL INVESTIGATIONS

8.1. INTRODUCTION

Between September 2008 and October 2009, 77 patients were recruited to the ARIAD study. All had been treated for early breast cancer or ductal carcinoma-in-situ (controls). All were recruited via breast cancer multi-disciplinary team meetings, oncological and surgical clinics. All had received the participant information sheet prior to entering the study. The inclusion criteria were satisfied in all cases. It was not possible to recruit to the full target, given the time constraints of the study research time and follow up. Therefore a recalculation of the statistical power was performed. To allow an 80% power rather than 90% for the same primary endpoint of grip strength, 88 patients were required; 22 in each group.

8.2. BASELINE CHARACTERISTICS

8.2.1. Patient and tumour characteristics

Of the total recruited, 43 (56%) patients were recruited from Sheffield and 34 were recruited from Leeds (44%). For the purposes of data analysis, the cohorts will be coded as follows:

Cohort A	Upfront AI	n=34
Cohort B	Switch AI	n=13
Cohort C	Tamoxifen control	n=22
Cohort D	No treatment control	n=8

73 of the 77 (95%) were followed up for the study duration.

Unfortunately it was not possible to recruit to target for cohorts B and D. It was difficult to identify patients suitable for switch as these patients weren't

discussed via multi-disciplinary team meetings and were seen in a variety of follow up clinics. For the control group D, the numbers of patients with ER negative breast not receiving chemotherapy were few. Those who had DCIS or benign breast disease were not keen on coming back for multiple appointments. These factors are very important when it comes to the design of future studies.

The median age for the whole study population was 61 years (range 46-79). The age across groups was balanced, except in cohort B (switch AI) where the median age was significantly lower at 51 years. Patients in this cohort were on average 9 years younger than cohorts A and C (global test $F(3,73)=6.90$, $p=0.0004$). Most had typical histology in form of ductal or lobular carcinoma. The majority had low or intermediate grade disease and this was reflected in the number receiving adjuvant chemotherapy. In total, 13 (17%) received adjuvant chemotherapy. These patients were in the AI groups: 6 in group A, 7 in group B. This perhaps also partly explains the lower age in cohort B, in view of a higher number with a chemotherapy induced early menopause. Previously, taxane based chemotherapy had been implicated in AIA. In this study, only 4 patients had received docetaxel chemotherapy, representing 5% of the study population. About half of the patients had had mastectomy and half wide local excision. The summary of baseline features is shown in table 9.

Joint pain at baseline was common. Overall nearly half the study population reported some degree of pain (37/77 (48%)). This was similarly reported between the groups, but a little lower in those in cohort B (23%). Whether or not this is related to the fact that these patients were more than two years from their original treatment is unclear. In addition, 30% gave a history of osteoarthritis. These patients were mainly in cohort A and C, with notably none from cohort B. Mean baseline grip strength was similar between the groups and consistent with values expected for this population. Morning stiffness was similar for all the groups except D, in which it was higher (23 minutes compared to the group mean of 7 minutes). However, one patient reporting 120 minutes of stiffness in this small group of 8 skewed this. A summary of the baseline joint related features is tabulated below (table 10).

Table 9. Summary of baseline general characteristics

Characteristics		Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
Centre	Leeds	21 (62%)	5 (38%)	5 (23%)	3 (38%)	34 (44%)
	Sheffield	13 (38%)	8 (62%)	17 (77%)	5 (63%)	43 (56%)
Age (years)	Median (IQR)	62 (59 to 69)	51 (47 to 61)	64.5 (60 to 69)	61 (52.5 to 64)	61 (58 to 68)
Performance status	0	26 (76%)	13 (100%)	13 (59%)	5 (63%)	57 (74%)
	1	7 (21%)	0 (0%)	9 (41%)	3 (38%)	19 (25%)
	2	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Dominant hand	Left	2 (6%)	0 (0%)	3 (14%)	0 (0%)	5 (6%)
	Right	32 (94%)	13 (100%)	19 (86%)	8 (100%)	72 (94%)
Histology	Ductal/NST	25 (74%)	10 (77%)	12 (55%)	1 (13%)	48 (62%)
	Lobular	4 (12%)	2 (15%)	4 (18%)	0 (0%)	10 (13%)
	Other	5 (15%)	1 (8%)	6 (27%)	7 (88%)	19 (25%)
Grade	1	10 (29%)	2 (15%)	5 (23%)	0 (0%)	17 (22%)
	2	17 (50%)	7 (54%)	17 (77%)	1 (13%)	42 (55%)
	3	6 (18%)	3 (23%)	0 (0%)	0 (0%)	9 (12%)
	Unclassified	1 (3%)	1 (8%)	0 (0%)	7 (88%)	9 (12%)
ER status	Negative	0 (0%)	0 (0%)	0 (0%)	2 (25%)	2 (3%)
	Positive	34 (100%)	13 (100%)	22 (100%)	0 (0%)	69 (90%)
	Unknown	0 (0%)	0 (0%)	0 (0%)	6 (75%)	6 (8%)
HER 2 Status	Negative	31 (91%)	8 (62%)	22 (100%)	4 (50%)	65 (84%)
	Positive	3 (9%)	4 (31%)	0 (0%)	0 (0%)	7 (9%)
	Unclassified	0 (0%)	1 (8%)	0 (0%)	4 (50%)	5 (6%)
Side of Surgery	Left	14 (41%)	7 (54%)	11 (50%)	3 (38%)	35 (45%)
	Right	20 (59%)	6 (46%)	11 (50%)	3 (38%)	40 (52%)
	Missing	0 (0%)	0 (0%)	0 (0%)	2 (25%)	2 (3%)
Type of Breast Surgery	Mastectomy	8 (24%)	7 (54%)	3 (14%)	3 (38%)	21 (27%)
	WLE	26 (76%)	6 (46%)	19 (86%)	3 (38%)	54 (70%)
Type of Axillary Surgery	Sample	10 (29%)	4 (31%)	14 (64%)	3 (38%)	31 (40%)
	Sentinel node biopsy	23 (68%)	4 (31%)	10 (45%)	0 (0%)	37 (48%)
	Clearance	5 (15%)	7 (54%)	0 (0%)	0 (0%)	12 (16%)

Characteristics		Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
Prior Chemotherapy	Yes	6 (18%)	7 (54%)	0 (0%)	0 (0%)	13 (17%)
	No	28 (82%)	6 (46%)	22 (100%)	8 (100%)	64 (83%)
Prior Taxanes	Yes	2 (6%)	2 (15%)	0 (0%)	0 (0%)	4 (5%)
	No	32 (94%)	11 (85%)	22 (100%)	8 (100%)	73 (95%)
Prior Radiotherapy	Yes	27 (79%)	9 (69%)	16 (73%)	1 (13%)	53 (69%)
	No	7 (21%)	4 (31%)	6 (27%)	7 (88%)	24 (31%)
Prior Trastuzumab	Yes	0 (0%)	2 (15%)	0 (0%)	0 (0%)	2 (3%)
	No	34 (100%)	11 (85%)	22 (100%)	8 (100%)	75 (97%)

Table 10. Summary of baseline joint related characteristics

Joint Characteristics		Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
Joint Pain	Yes	20 (59%)	3 (23%)	11 (50%)	3 (38%)	37 (48%)
	No	14 (41%)	10 (77%)	11 (50%)	5 (63%)	40 (52%)
History of Osteoarthritis	Yes	13 (38%)	0 (0%)	9 (41%)	1 (13%)	23 (30%)
	No	21 (62%)	13 (100%)	13 (59%)	7 (88%)	54 (70%)
Overall average grip strength (kg)	Mean (SD)	22.6 (6)	23.1 (4.8)	20.3 (4.8)	22.8 (4.7)	22.1 (5.4)
	Median (IQR)	23.1 (19.2-25.6)	23.2 (18.9-26.6)	20.9 (16.6-23.4)	21.8 (19-26.6)	22.2 (18.1-25.2)
Duration Morning Stiffness (minutes)	Mean (SD)	6.2 (16.4)	1.1 (1.9)	5.2 (11.3)	23.1 (44.3)	6.8 (19.2)

8.3. GRIP STRENGTH

8.3.1. Baseline Grip Strength

Baseline grip strength was calculated by taking an average of the 3 readings for the dominant and non-dominant hand. Mean baseline (with standard deviation) values for cohorts A-D were 23(6)kg, 23(5)kg, 20(5)kg and 23(5)kg respectively. The overall study population mean was 23kg. Figure 25 shows the spread of baseline values across groups. Although, cohort C had slightly lower baseline values, the spread of values shows that this was unlikely to be significant (global test F93,73)=1.13, p=0.342).

For the dominant hand and non-dominant hand, baseline values are shown in tables 11 and 12 respectively. A similar pattern was seen in both of these as compared to the overall figures. As expected, baseline values were slightly lower in the non-dominant hand.

Figure 25. Baseline grip strength (kg) according to cohorts.

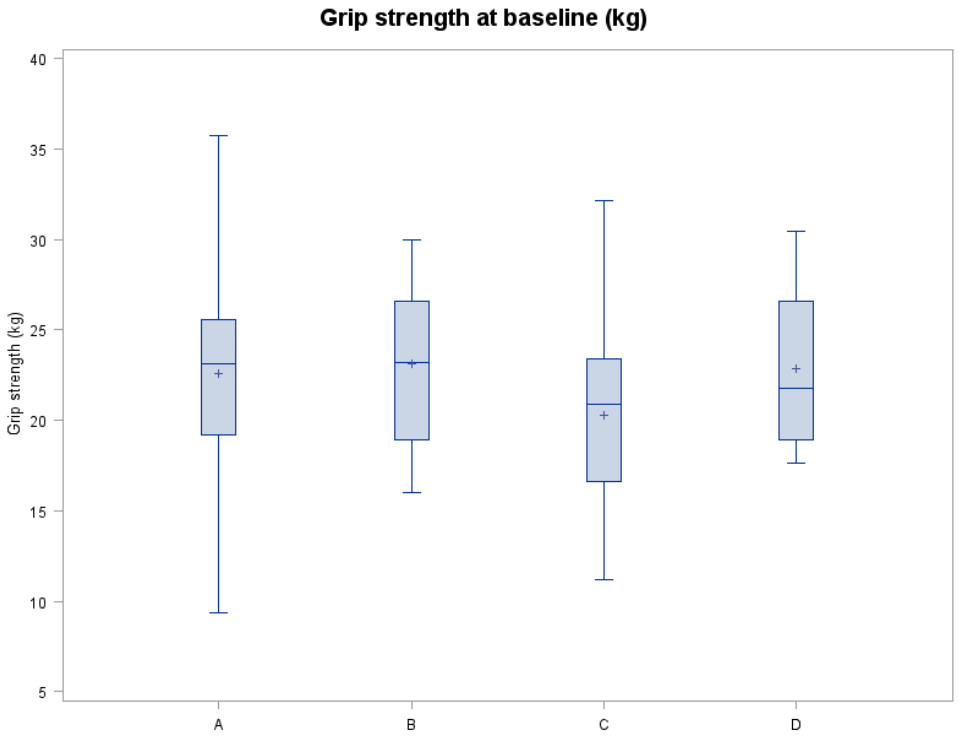


Table 11. Baseline grip strength values for dominant hand

	Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
Mean (SD)	23 (6.1)	23.7 (5.5)	21 (4.6)	23.9 (5.2)	22.6 (5.5)
Median (IQR)	23.3 (19.3-27)	24.3 (19.5-27.5)	21.7 (17.7-23.7)	22.8 (19.5-28)	22.3 (19-26)
Min to Max	10.8 to 34.2	15.3 to 32.2	12.3 to 31.7	18.3 to 32.3	10.8 to 34.2

Table 12. Baseline grip strength values for non-dominant hand

	Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
Mean (SD)	22.2 (6.4)	22.6 (4.2)	19.6 (5.6)	21.8 (4.7)	21.5 (5.7)
Median (IQR)	21.9 (19-25.5)	22.7 (18.3-25.7)	20.1 (15.5-23.3)	22.6 (17.4-25.2)	21.5 (18.2-24.7)
Min to Max	5.7 to 37.5	16.7 to 28.7	10 to 32.7	15.3 to 28.5	5.7 to 37.5

8.3.2. Change in grip strength over time

The data was analysed on an intention to treat basis. The primary endpoint of the ARIAD study was change of grip strength at 3 months, as this was felt to be the key time point for the onset of arthralgia symptoms. Data for the 12 month time point and averaged over the 12 month period are presented below. The data were analysed using the analysis of covariance for percentage change in average grip strength, adjusted for age at baseline, baseline grip strength (kg) and prior chemotherapy.

At 3 months, the adjusted mean percentage change in grip strength from baseline was +0.6% (upfront AI), +3.7% (switch AI), +1.7% (tamoxifen) and +4.2% (no treatment controls). There were no statistical associations.

At 12 months, the adjusted mean percentage change in grip strength from baseline was -0.3% (upfront AI), +1.3% (switch AI), +2.4% (tamoxifen) and +9.2% (no treatment controls). None of these were statistically significant.

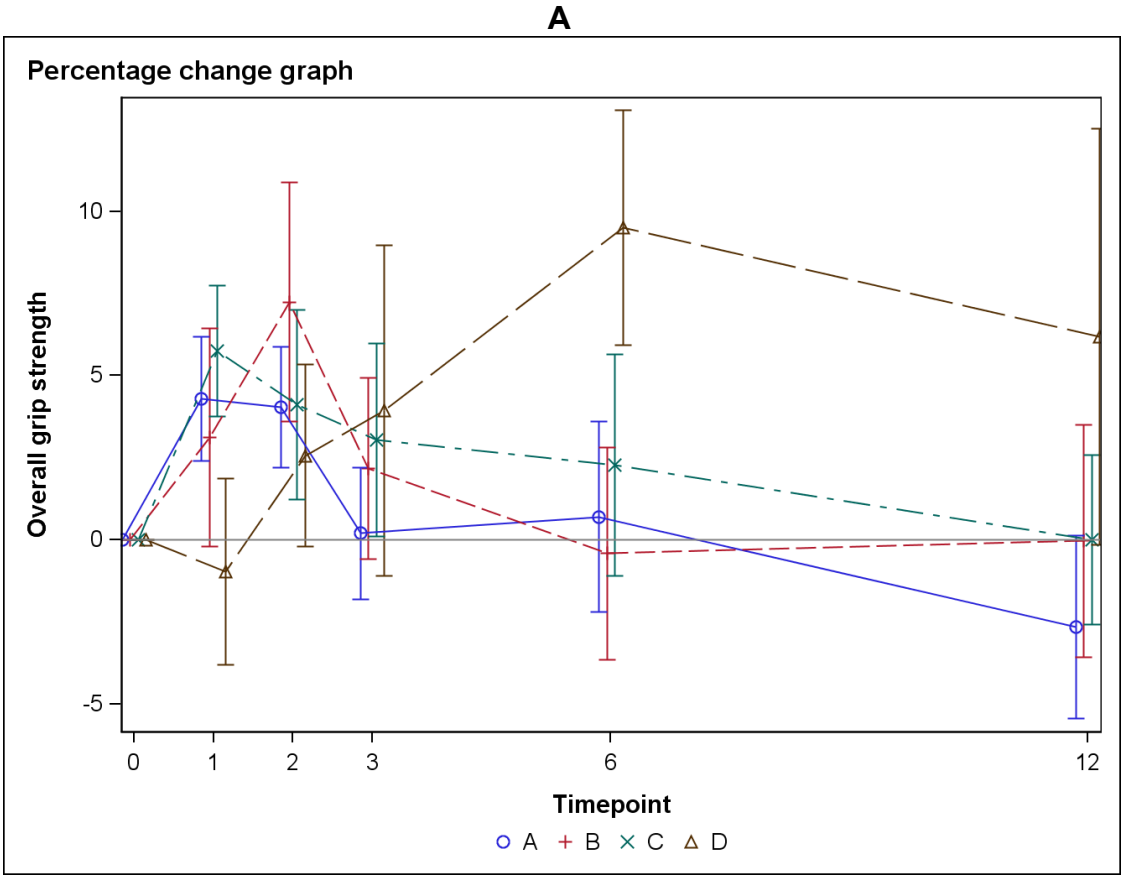
When averaged over the 12 months, the adjusted mean percentage change in grip strength from baseline was +2.9% (upfront AI), +3.3% (switch AI), +5.3% (tamoxifen) and +4.2% (no treatment controls). Again none, of these were statistically significant.

Thus given this study was looking at a clinically significant reduction of approximately 20%, there appears to be no meaningful difference in grip strength between patients taking AIs, tamoxifen or nil. These findings are summarised in table 13. The change of grip strength at each of the study time points is displayed in figure 26 with error bars. These are also shown for the dominant and non dominant hands.

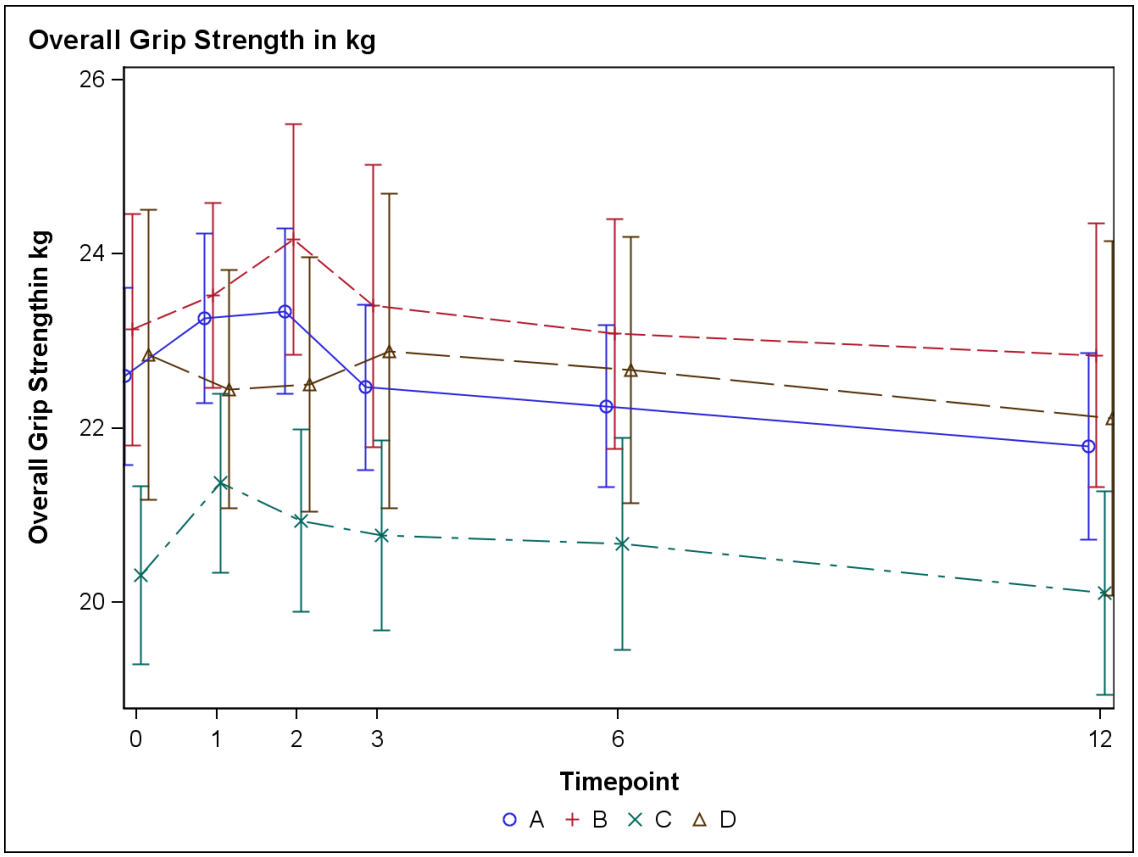
Table 13. Adjusted mean %change in grip strength (standard error) from baseline

Adjusted mean % change from baseline	Month 3	Month 12	Overall /averaged
A	0.6% (2.4%)	-0.3% (2.9%)	2.9% (1.5%)
B	3.7% (3.5%)	1.3% (4.3%)	3.7% (2.1%)
C	1.7% (3.1%)	2.4% (3.9%)	3.3% (2.5%)
D	4.2% (4.7%)	9.2% (6.1%)	5.3% (3.5%)

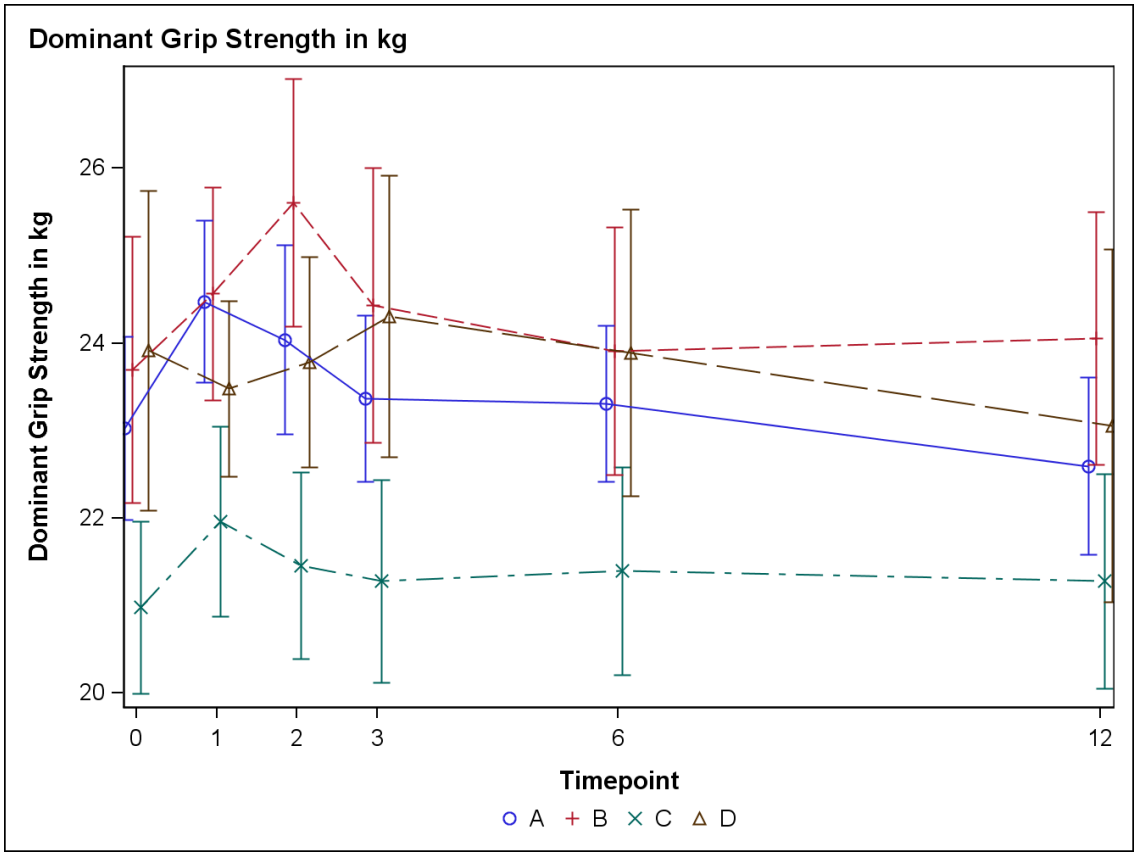
Figure 26. Change in grip strength over the study period with error bars. (A) percentage change with both hands averaged, (B) both hands averaged (kg), (C) dominant hand (kg), (D) non-dominant hand (kg)



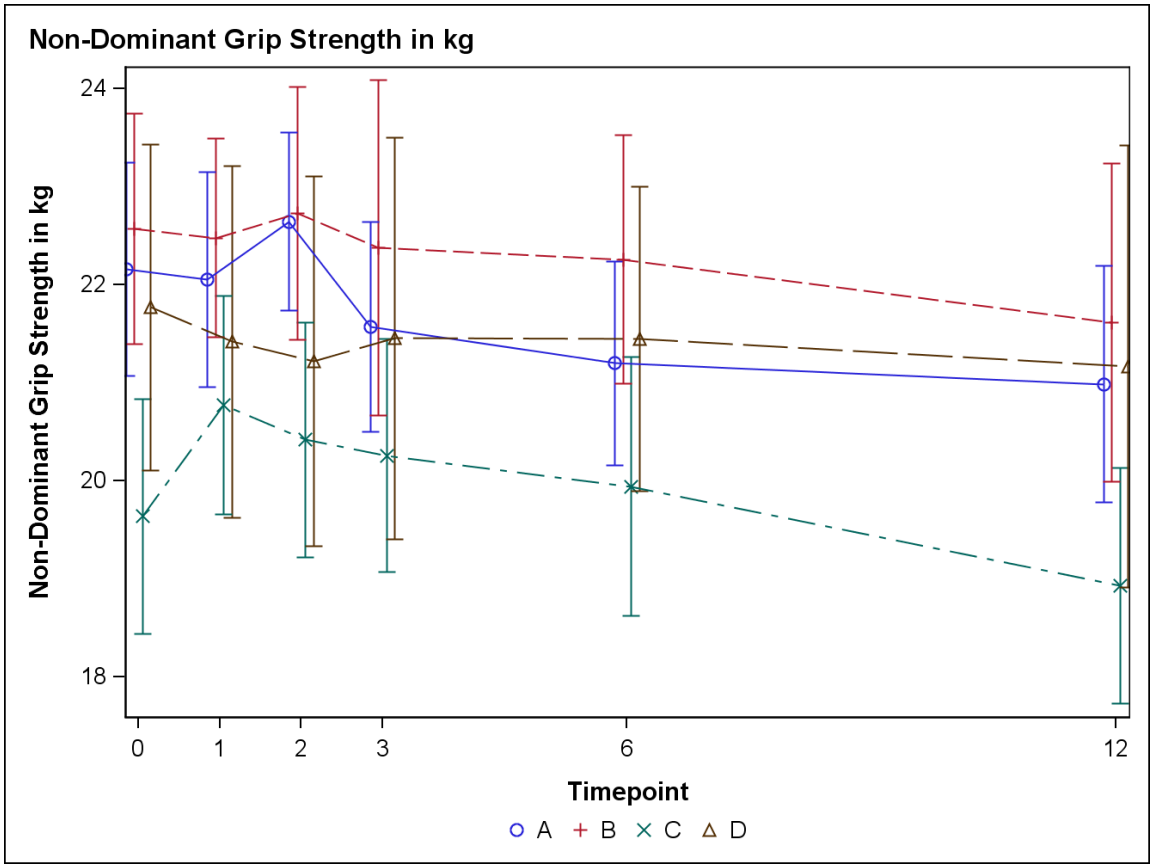
B


Overall Grip Strength in kg
Overall Grip Strengthin kg
26
24
22
20
0
1
2
3
6
12
Timepoint
A B C D

C


Dominant Grip Strength in kg
Dominant Grip Strength in kg
26
24
22
20
0
1
2
3
6
12
Timepoint
A B C D

D


Non-Dominant Grip Strength in kg
Non-Dominant Grip Strength in kg
24
22
20
18
0
1
2
3
6
12
Timepoint
A
B
C
D

8.3.3. Pairwise Comparisons

Form the study outset, a key list of 5 pairs comparisons was produced in order of priority for the statistical analysis. Due to the small numbers of patients in group D, a sixth comparison was added. The order is shown below:

1: Upfront AI (A) v No treatment (D)
2: Switch AI (B) v No treatment (D)
3: Upfront AI (A) v Tamoxifen (C)
4: Switch AI (B) v Tamoxifen (C)
5: Upfront AI (A) v Switch AI (B)
6: A and B combined v C and D combined

The summary of statistical testing for these comparisons is shown in table 14. None of the comparisons were statistically significant. The largest numerical differences were seen in the comparison of upfront AI versus control at 12 months where the mean difference was -9.5% (95% CI -21.6 - +2.7). A smaller difference was seen at 3 months, but neither met conventional significance. It is noted that at 12 months, all comparisons showed a larger negative value, but unfortunately due to small patient numbers, none were significant.

Table 14. Pairwise comparisons showing mean percentage differences over time

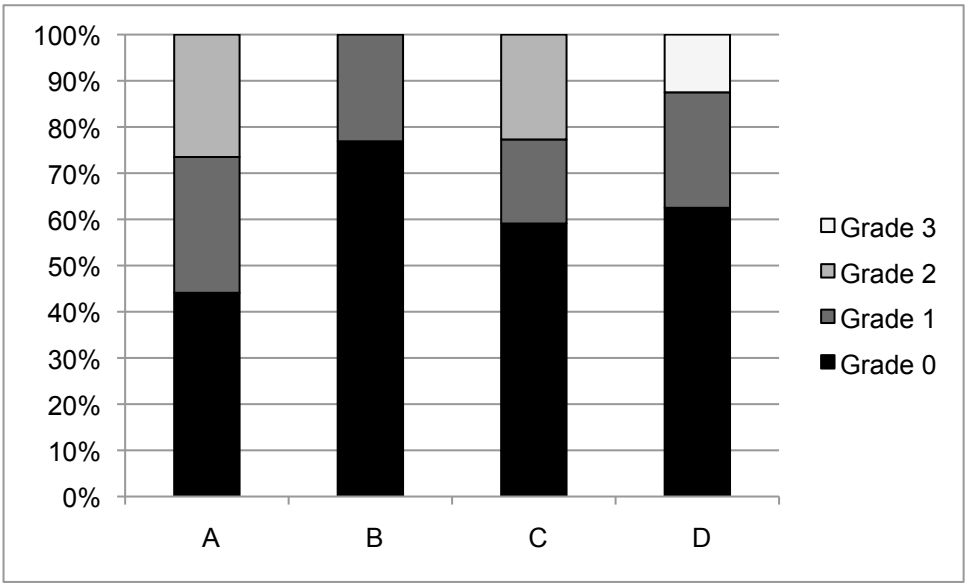
Comparison	Month 3		Month 12		Overall /averaged	
	Mean difference (95% CI)	P	Mean difference (95% CI)	P	Mean difference (95% CI)	P
1. Upfront AI (A) v No treatment (D)	-3.6 (-12.8, 5.7)	0.452	-9.5 (-21.6, 2.7)	0.126	-3.6 (-12.8, 5.7)	0.526
2. Switch AI (B) v No treatment (D)	-0.5 (-11.8, 10.9)	0.936	-7.9 (-22.4, 6.6)	0.285	-0.5 (-11.8, 10.9)	0.680
3. Upfront AI (A) v Tamoxifen (C)	-1.1 (-7.4, 5.2)	0.733	-2.7 (-10.4, 5.1)	0.498	-1.1 (-7.4, 5.2)	0.878
4. Switch AI (B) v Tamoxifen (C)	2.0 (-7.3, 11.3)	0.674	-1.1 (-12.7, 10.4)	0.848	2.0 (-7.3, 11.3)	0.911
5. Upfront AI (A) v Switch AI (B)	-3.1 (-11.5, 5.3)	0.468	-1.6 (-11.8, 8.7)	0.766	-3.1 (-11.5, 5.3)	0.741

8.4. JOINT PAIN

8.4.1. Baseline CTC joint pain

Joint pain was assessed in a number of different ways in this study. CTC grading was performed by the investigator at each time point. Questionnaire assessments are reported later. At baseline, it was clear that a significant number of patients reported grade 1 or more pain. This varied from 56% in group A to 22% in group B. Grade 3 joint pain was only documented in group D (13%). These baseline findings are shown below in figure 27.

Figure 27. Joint pain at baseline for each group according to CTC grade



8.4.2. Change of joint pain over time

Figure 28 demonstrates the change of CTC joint pain over the twelve month study period. For women taking aromatase inhibitors, there was an increase in the percentage experiencing CTC grade 2 or more joint pain over time. For those on an upfront AI, the increase was 27% at baseline to 53% by 12 months. For those switching to an AI, it was 0 at baseline to 23% by 12 months. For the two control groups, there was less of a change; a slight increase was seen in the tamoxifen group from 23% to 32%.

Figure 28. Percentage with ≥ CTC grade 2 joint pain over the 12 month study period

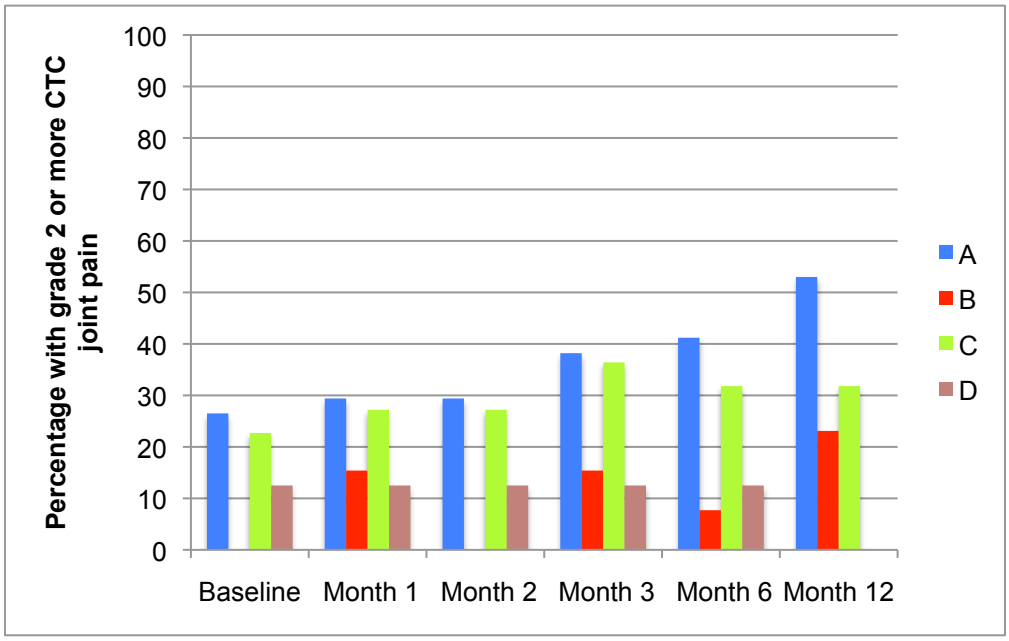


Figure 29 gives insight into how many women had any deterioration in their joint pain compared to baseline. Whilst there was a worsening in both AI cohorts, this was matched by the tamoxifen controls. Group D controls didn't have any worsening of joint pain. Deterioration of joint pain at 12 months was statistically significant for both AI groups compared to no treatment controls. However, this was not the case when comparisons were made between AI groups and tamoxifen. These findings are summarised in table 15.

Figure 29. Percentage with worsening CTC joint pain compared to baseline

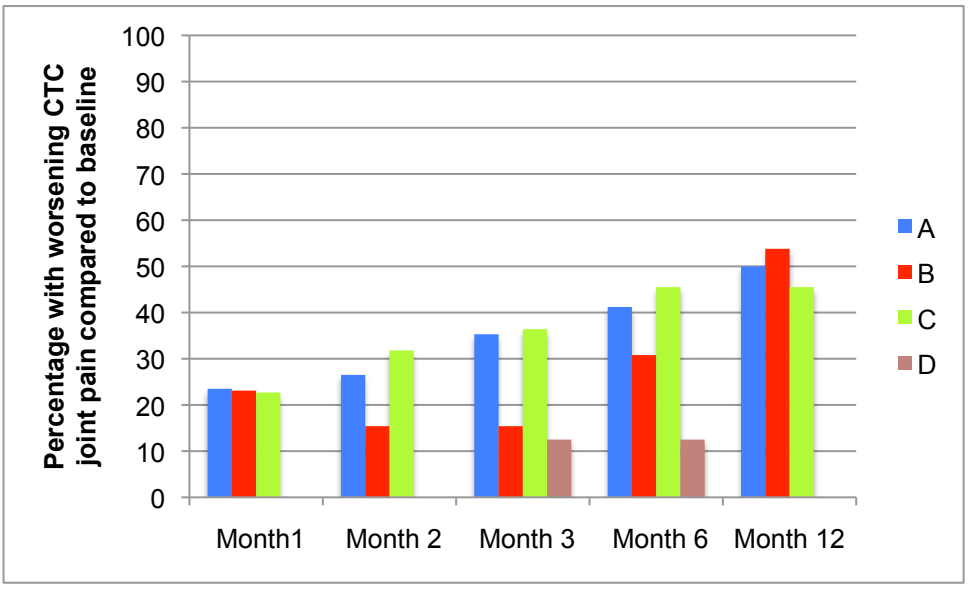


Table 15. Statistical comparisons for worsening of joint pain at 12 months compared to baseline

Comparison of deterioration rates at 12 months	p value (Fisher's exact test)
1. Upfront AI (A) v No treatment (D)	0.030
2. Switch AI (B) v No treatment (D)	0.038
3. Upfront AI (A) v Tamoxifen (C)	1.000
4. Switch AI (B) v Tamoxifen (C)	0.721
5. Upfront AI (A) v Switch AI (B)	0.742
6. AI (A/B) v Tam/no treatment (C/D)	0.234

8.5. MUSCULOSKELETAL SYMPTOMS RELATED TO AI THERAPY

8.5.1. Definition

There is currently no clear definition of what constitutes AIA or what others have termed AIMSS (AI associated musculoskeletal symptoms). By considering the published data and clinical experience from this trial, the following clinical (not radiological) criteria were devised.

1) Worsening joint pain
2) Worsening joint stiffness
3) Developed flexor tendon nodules/triggering
4) Developed clinical features of carpal tunnel syndrome (a positive Tinel's or Phalen's test)
5) Developed clinical features of synovitis

In this study, patients in A and B who developed musculoskeletal symptoms (AIA) over the 12 month period needed to satisfy defined 2 or more of the above criteria. The numbers of patients satisfying these criteria are shown in table 16 below:

Table 16. The incidence of AIA in cohorts A and B over the whole study period

Variable	Scoring	Cohort A (N=34)	Cohort B (N=13)
Developed AIA	Yes	23 (68%)	9 (69%)
	No	11 (32%)	4 (31%)

The same scoring system was applied to the cohort of patients receiving tamoxifen. As shown in the table below, a significant number of these patients satisfied the arthralgia criteria (TIA), mainly because of pain and stiffness. However the proportion was lower than for the AI groups.

Table 17. The incidence of Tamoxifen Induced Arthralgia (TIA)

Variable	Scoring	Cohort C (N=22)
Developed TIA	Yes	7 (32%)
	No	15 (68%)

8.5.2. Grip strength according to Aromatase Inhibitor Arthralgia

Figures 30 and 31 show the changes in grip strength for those taking AIs only (cohorts A and B combined). The comparison is made here as to whether grip strength changes varied according to AIA or not. With both actual grip strength values and percentage change, the lines and error bars overlap indicating no differences. There was an improvement in mean grip strength over the first 3 months, followed by a decline, particularly for the AIA group, but in percentage terms, these changes were generally less then 5% from baseline.

Figure 30. Change in mean grip strength (kg) for AIA v No AIA in A and B

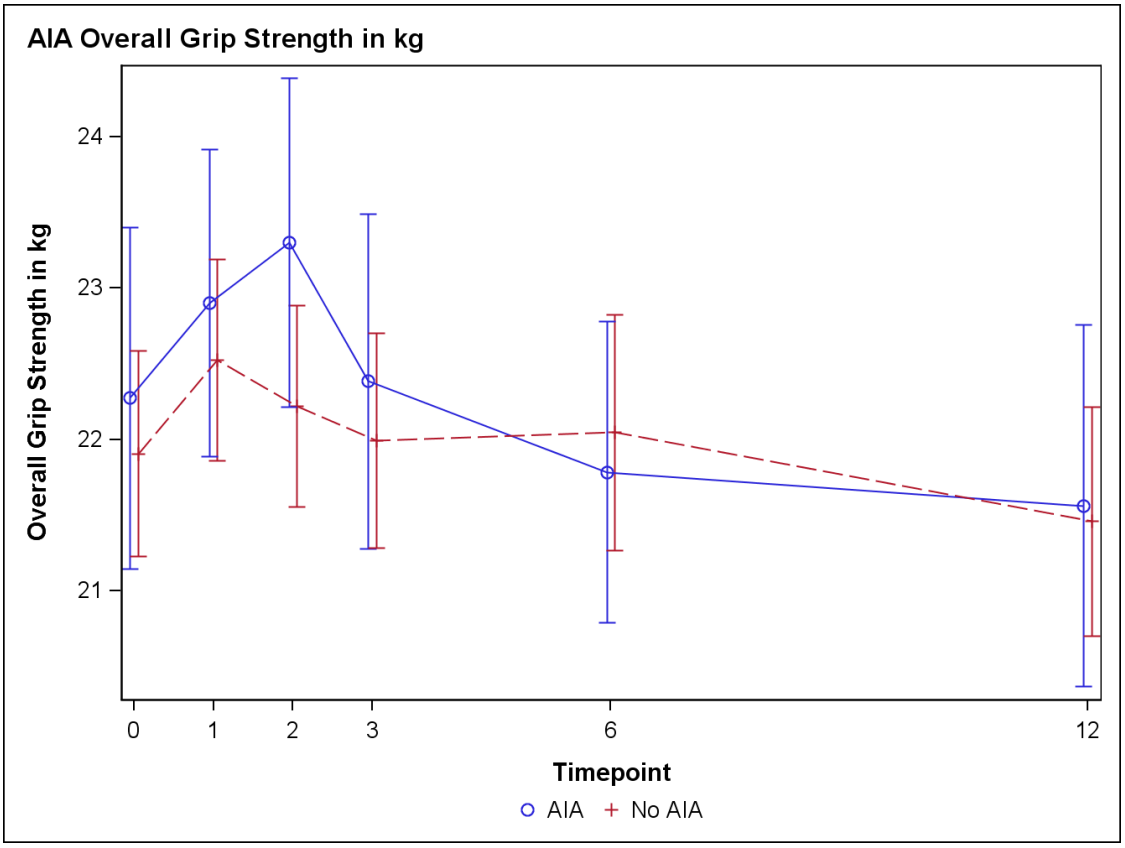
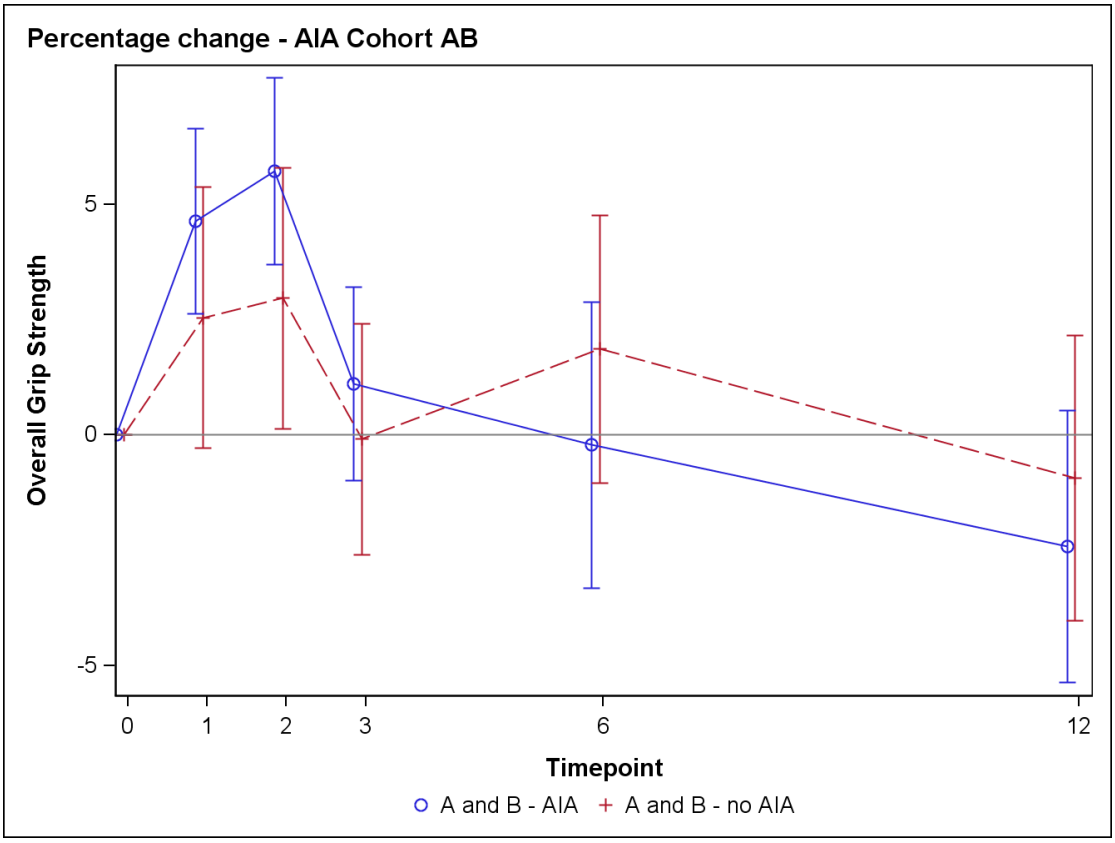


Figure 31. Percentage change in mean grip strength over time for AIA v No AIA in A and B combined.



8.5.3. Morning Stiffness according to Aromatase Inhibitor Arthralgia

Morning stiffness, measured in minutes, was skewed as over half of the responses were zero. The distribution of the individual patient data for cohorts A and B is shown in figure 32. Given the data were discrete, the values were categorised for analysis. The analyses were made using the non-parametric Mann-Whitney U-test. The difference in stiffness was minor, although at the final time point morning stiffness was more prevalent in the AIA group with nearly 1 in 4 experiencing stiffness lasting more than 15 minutes compared to 1 in 14 for the non-AIA group.

Figure 32. Individual patient data for morning stiffness for cohorts A and B combined

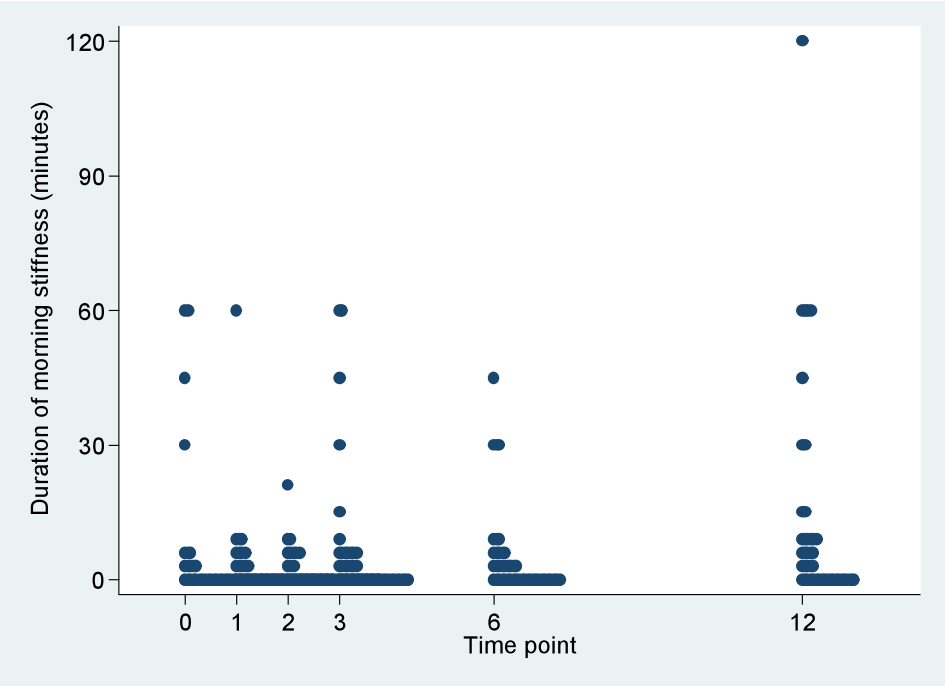


Table 18. Duration of morning stiffness (minutes) categorised for AIA and non-AIA. P values derived from Mann-Whitney U test

	AIA						Non-AIA						
	Duration (mins)						Duration (mins)						
		0	1-2	3-7	8-15	>15		0	1-2	3-7	8-15	>15	p-value*
Month	n						n						
0	32	22 (69%)	5 (16%)	2 (6%)	0 0	3 (9%)	15	10 (67%)	1 (7%)	3 (20%)	0 0	1 (7%)	0.856
1	32	20 (63%)	3 (9%)	6 (19%)	2 (6%)	1 (3%)	15	11 (73%)	1 (7%)	2 (13%)	1 (7%)	0 0	0.525
2	30	18 (60%)	7 (23%)	3 (10%)	1 (3%)	1 (3%)	14	10 (71%)	0 0	3 (21%)	0 0	0 0	0.692
3	31	13 (42%)	5 (16%)	7 (23%)	2 (6%)	4 (13%)	14	9 (64%)	2 (14%)	3 (21%)	0 0	0 0	0.123
6	30	11 (37%)	9 (30%)	6 (20%)	0 0	4 (13%)	14	10 (71%)	1 (7%)	3 (21%)	3 (21%)	0 0	0.143
12	31	8 (26%)	3 (10%)	7 (23%)	6 (19%)	7 (23%)	14	9 (64%)	1 (7%)	1 (7%)	2 (14%)	1 (7%)	0.026

*Mann-Whitney U test (based on actual values

8.6. QUESTIONNAIRES

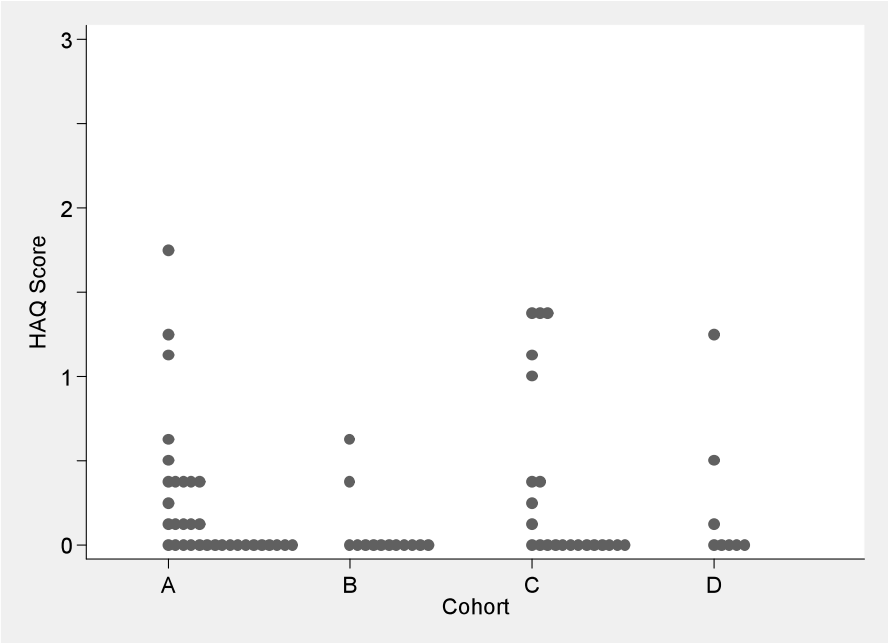
8.6.1. Health Assessment Questionnaire Disability Index (HAQ-DI)

8.6.1.1. HAQ-DI scores

There was overall good compliance with 72 (94%) of questionnaires completed at 12 months.

Baseline HAQ-DI scores are depicted on figure 33. As expected, many have a score of zero leading to a skewed distribution. Therefore data was analysed using the non-parametric Kruskal-Wallis test. Nevertheless, mean baseline scores for the four groups (with standard deviation) were as follows: A 0.2 (0.4), B 0.1 (0.2), C 0.3 (0.5), D 0.2 (0.4), overall 0.2 (0.4). These are low scores that one would expect in the general population and signify either no or mild disability (Bruce and Fries 2003). Few had scores over 1, which indicates they may have been having moderate to severe difficulty. This may have been joint related or due to effects of previous breast cancer treatment.

Figure 33. Individual spread of baseline HAQ-DI scores



Over the 12 month study period, mean HAQ-DI scores changed relatively little and no statistically significant changes were seen (figure 34 and table 19). The mean changes in all groups except D were less than the 0.22 clinically meaningful difference. Due to the small patient numbers in group D, the error bars are wide, indicating the fluctuation of values is unlikely to be significant. Notably for the women receiving AI therapy in cohorts A and B, HAQ-DI did not deteriorate over time. This suggests AI use did not imapct on functional ability, in this study.

Figure 34. Change in HAQ-DI scores over time with error bars

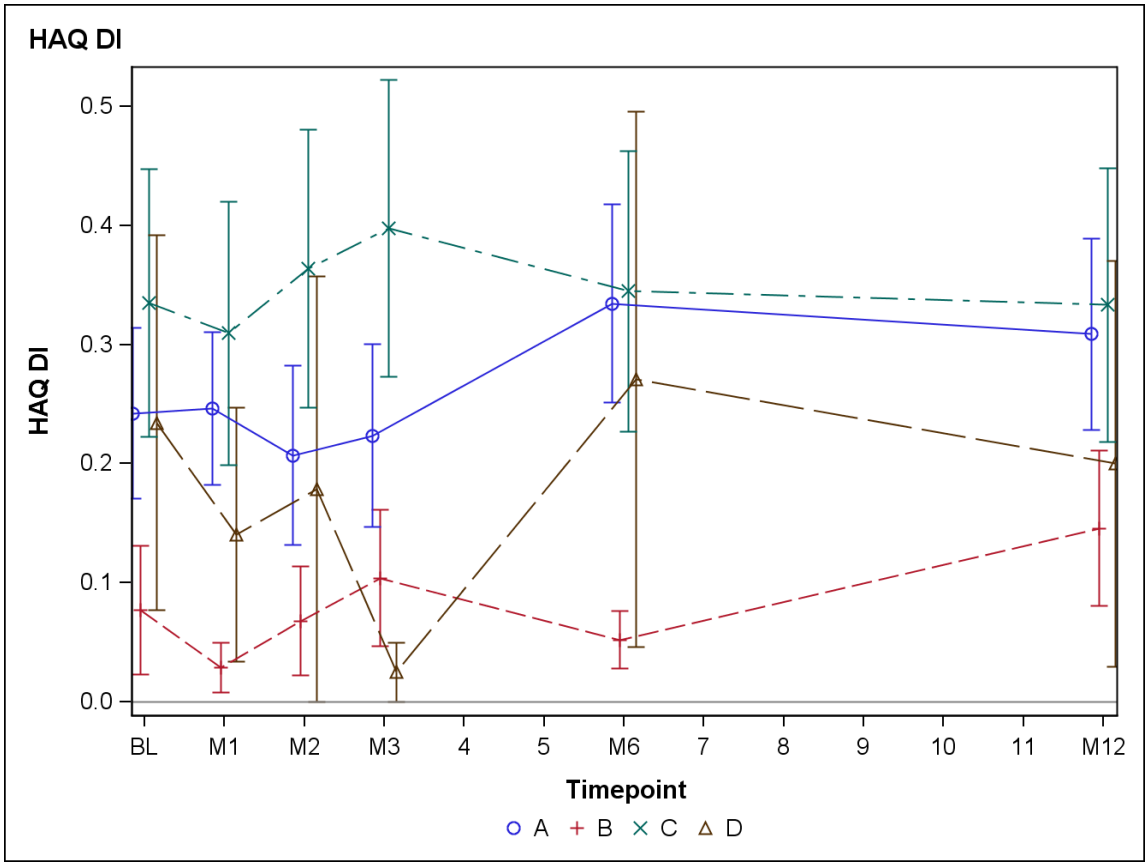


Table 19. Pairwise comparisons showing mean differences of HAQ-DI scores

	Month 3		Month 12		Overall	
	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
1. Upfront AI (A) v No treatment (D)	0.0 (-0.2, 0.2)	0.969	0.1 (-0.1, 0.4)	0.349	0.0 (-0.2, 0.2)	0.269
2. Switch AI (B) v No treatment (D)	-0.0 (-0.3, 0.2)	0.855	0.1 (-0.2, 0.4)	0.388	-0.0 (-0.3, 0.2)	0.985
3. Upfront AI (A) v Tamoxifen (C)	-0.1 (-0.2, 0.0)	0.101	0.0 (-0.1, 0.1)	0.927	-0.1 (-0.2, 0.0)	0.633
4. Switch AI (B) v Tamoxifen (C)	-0.1 (-0.3, 0.1)	0.178	0.0 (-0.2, 0.2)	0.883	-0.1 (-0.3, 0.1)	0.259
5. Upfront AI (A) v Switch AI (B)	0.0 (-0.1, 0.2)	0.752	-0.0 (-0.2, 0.2)	0.922	0.0 (-0.1, 0.2)	0.244
6. AI (A/B) v Tam/nil (C/D)	-0.1 (-0.2, 0.1)	0.381	0.1 (-0.1, 0.2)	0.432	-0.1 (-0.2, 0.1)	0.768

8.6.1.2. HAQ pain visual analogue scale (HAQ VAS)

The HAQ-DI also has a visual analogue scale. The patients were asked: “how much pain have you had because of your illness IN THE PAST WEEK?” The scale was between 0-100. There was good compliance with 72 (94%) completed scales at 12 months.

Baseline data is shown in table 20 and figure 35. Mean baseline HAQ VAS values were less skewed than HAQ-DI scores. Again the Kruskal-Wallis test was used for this analysis. Patients on switch AI, had a low baseline scores. This probably due to the fact that they were over 2 years from initial treatment and thus surgery and radiotherapy effects may have settled. For cohorts A, C and D, pain scores may have been affected by recent treatment. Statistically, A and C’s scores were higher than B and D (p=0.003)

Table 20. Baseline information for HAQ – pain VAS

	A	B	C	D	Overall
N (%)	30 (88.2%)	13 (100%)	22 (100%)	7 (87.5%)	72 (93.5%)
Mean (SD)	18.3 (19.7)	1 (1.5)	22.3 (20.9)	6.6 (6.9)	15.2 (18.9)
Median (IQR)	10.6 (0 to 34.3)	0 (0 to 1)	14.9 (5.6 to 39.3)	5.3 (0 to 12.7)	6.5 (0.4 to 24.7)
Range	0 to 83.7	0 to 4.3	0 to 65.3	0 to 18.7	0 to 83.7

Figure 35 Spread of individual HAQ – pain VAS scores at baseline

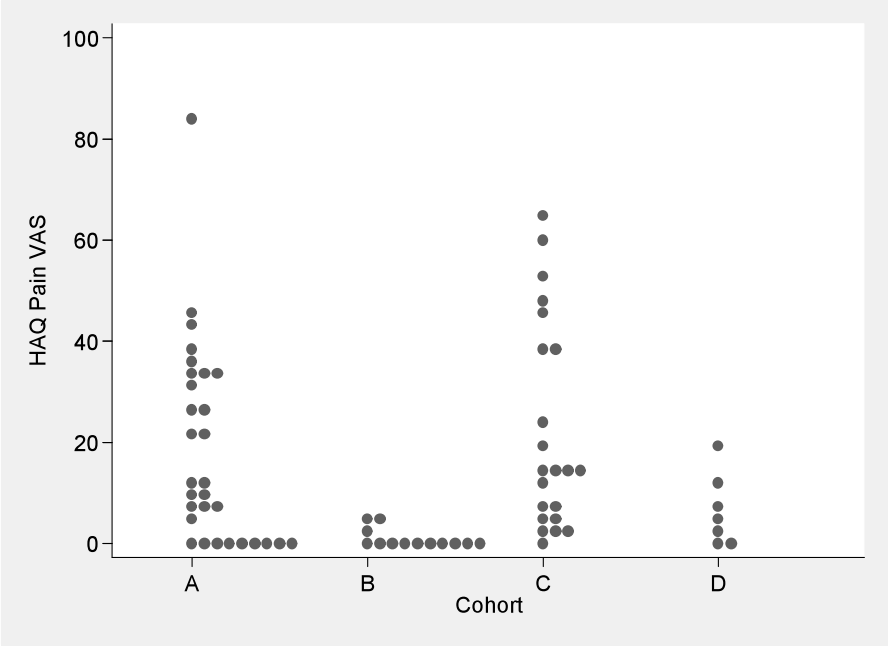


Figure 36 shows the change of HAQ VAS pain score over time. This has revealed some interesting trends. The most clear change has been in those women switching to an AI after tamoxifen. The mean baseline score for this group was 1 (SD 1.5), which had increased to 14.3 (SD 19.5) at 12 months. Likewise a smaller worsening of pain was seen in the upfront AI group, particularly after 6 months. The mean baseline score of 18.3 (SD 19.7) had worsened to 25.2 (SD 28.3) by month 12. The only statistically significant differences were in the averaged mean difference in the A v D comparison (difference of 12 5 (95%CI -6.4-31.4, p=0.021)) and the B v D comparison (difference of 8.4 (-13.4-30.3, p=0.047)) (table 21). These indicate a higher pain score in the AI groups compared to no treatment. This was not, however, seen when compared with the tamoxifen group.

Figure 36. Change in HAQ VAS over time

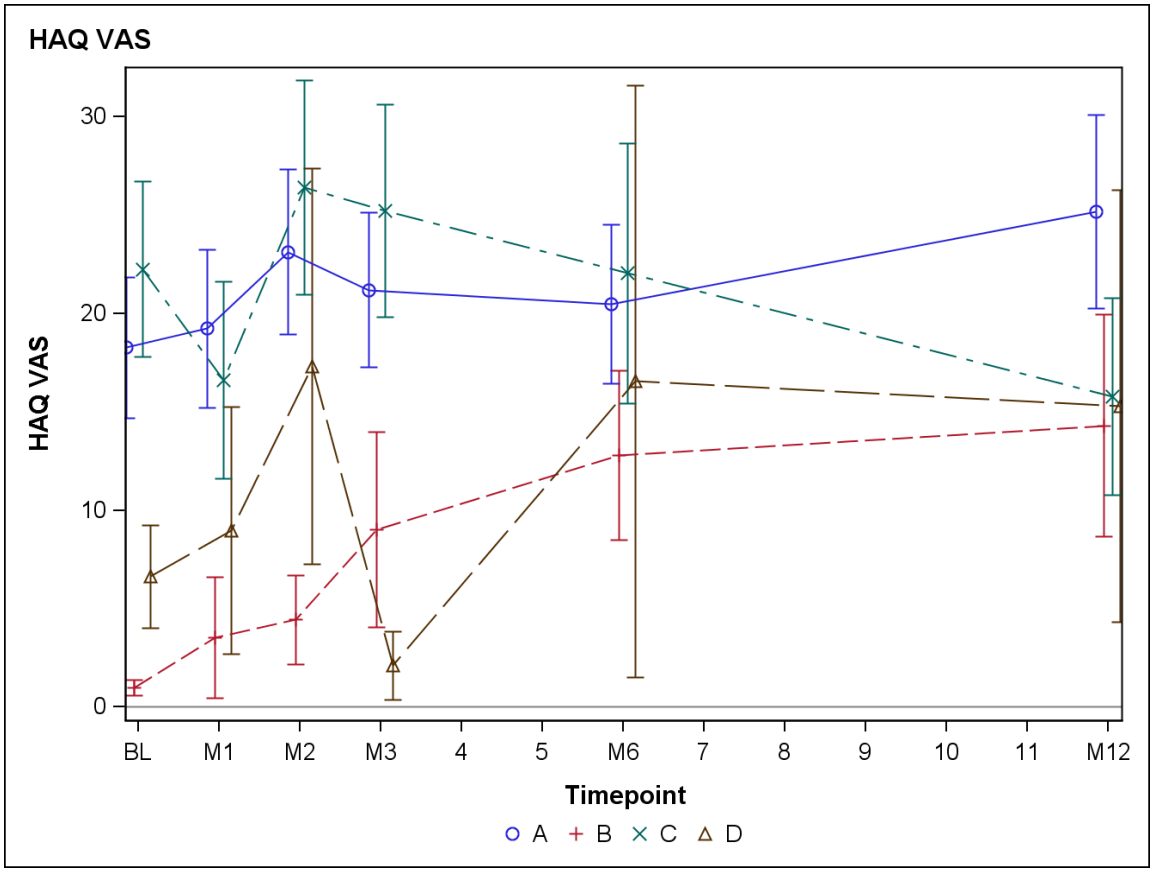


Table 21. Pairwise comparisons showing mean differences of HAQ VAS scores

	Month 3		Month 12		Overall	
	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
1. Upfront AI (A) v No treatment (D)	12.5 (-6.4, 31.4)	0.196	12.9 (-8.8, 34.5)	0.245	12.5 (-6.4, 31.4)	0.021
2. Switch AI (B) v No treatment (D)	8.4 (-13.4, 30.3)	0.450	11.8 (-12.6, 36.1)	0.344	8.4 (-13.4, 30.3)	0.047
3. Upfront AI (A) v Tamoxifen (C)	-1.5 (-12.5, 9.5)	0.794	12.7 (-0.2, 25.6)	0.054	-1.5 (-12.5, 9.5)	0.505
4. Switch AI (B) v Tamoxifen (C)	-5.5 (-23.4, 12.4)	0.547	11.6 (-8.1, 31.3)	0.248	-5.5 (-23.4, 12.4)	0.864
5. Upfront AI (A) v Switch AI (B)	4.0 (-11.9, 19.9)	0.619	1.1 (-16.2, 18.4)	0.902	4.0 (-11.9, 19.9)	0.602
6. AI (A/B) v Tam/nil (C/D)	3.5 (-9.1, 16.1)	0.589	12.2 (-2.0, 26.5)	0.092	3.5 (-9.1, 16.1)	0.108

8.6.1.3. HAQ scores according to Aromatase Inhibitor Arthralgia

Mean scores for both HAQ disability index and visual analogue scales divided by AIA are shown in figures 37 and 38. Differences between these groups start to become apparent compared to the whole group analyses. For the HAQ-DI, although no difference was seen initially, by the end of the study, there has been a small increase in those developing AIA. This difference, however, was less that 0.1. Larger differences were seen in HAQ VAS scores, with worsening in the AIA sufferers from an early stage, which continued to deteriorate as the study progressed.

Figure 37. Actual change in HAQ-DI score from baseline for AIA v No AIA

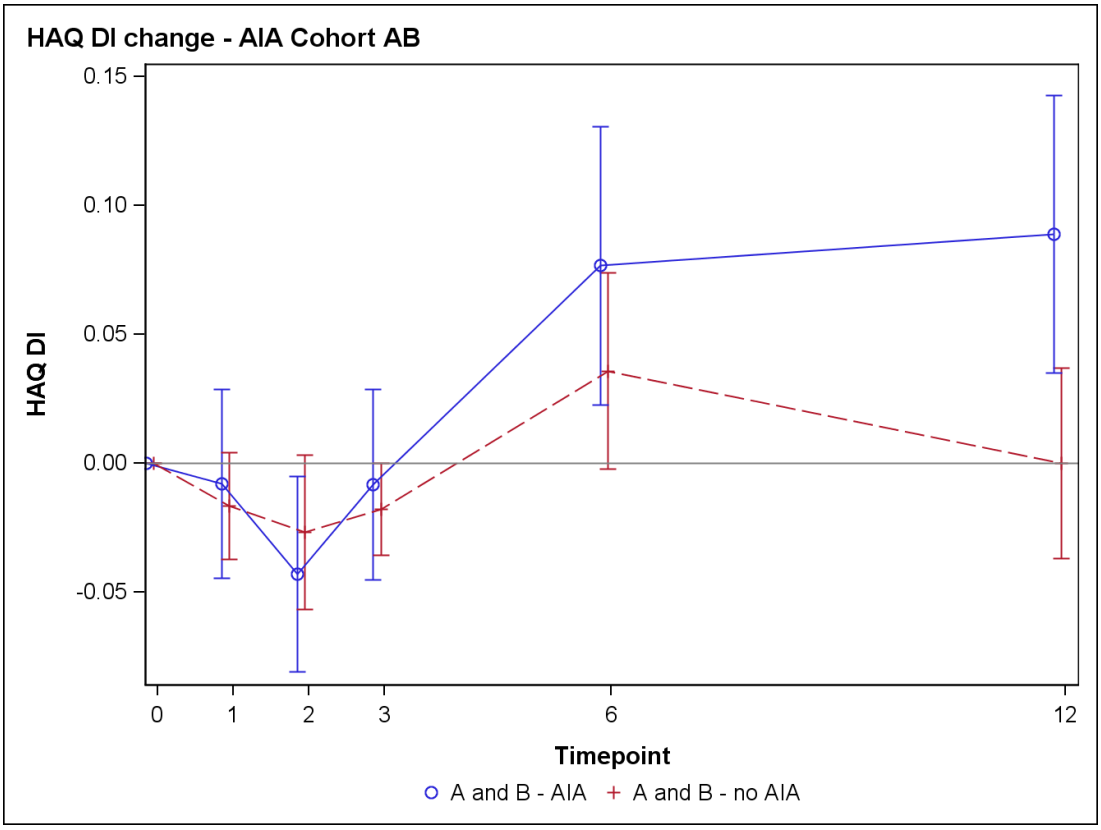
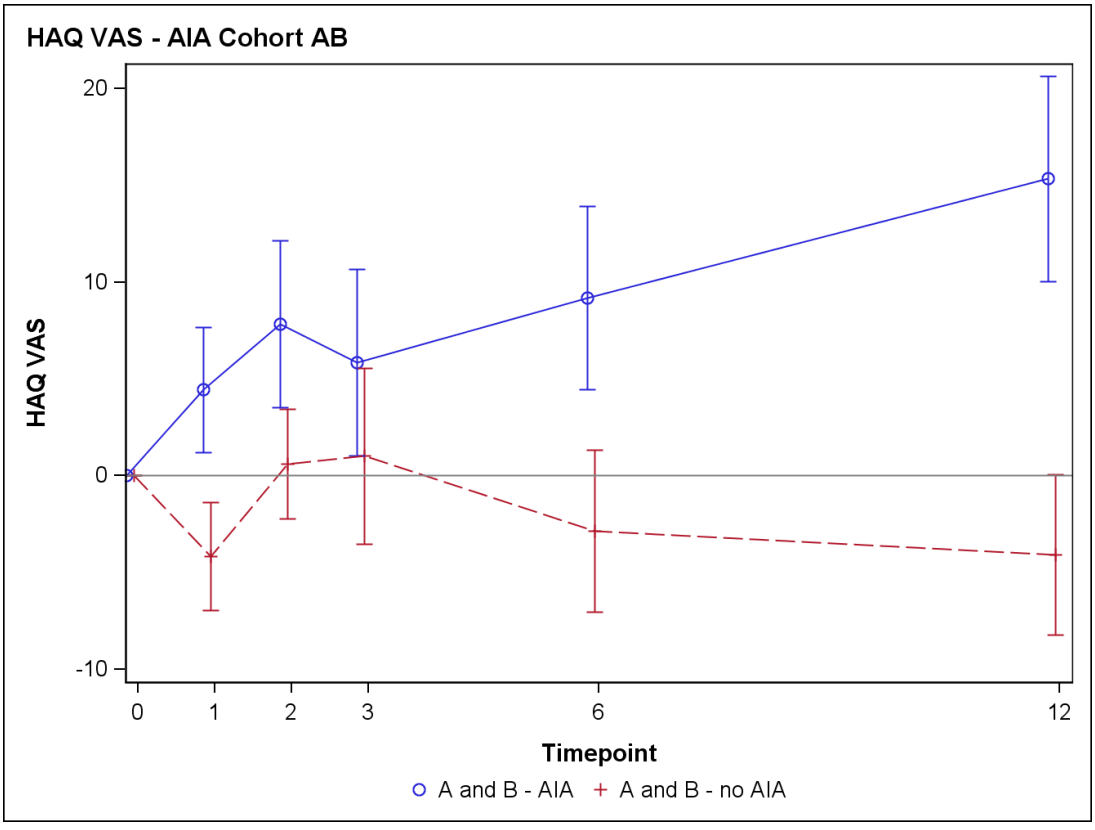


Figure 38. Actual change in HAQ VAS score from baseline for AIA v No AIA



8.6.2. SF-36

The SF-36 is a well validated health questionnaire. Whilst there are 8 domains of health, these lead to 2 total scores, a physical component summary (PCS) and a mental component summary (MCS). The higher the score, the better the health. For the physical component summary, population studies have suggested normal scores between 20 and 58. For the mental component summary, scores between 17 and 62 would be regarded as normal. Of the 8 domains, one is particularly relevant for AIA: bodily pain. This has therefore been analysed separately in addition to the standard summaries.

Questionnaire completion rates were overall very high. By the end of the study, over 90% of questionnaires were completed. The lower number in group D is a result of the study drop outs.

Table 22. Questionnaire completion rates for SF-36v2 over the study period

Timepoint	Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
Baseline	33 (97.1%)	13 (100%)	22 (100%)	8 (100%)	76 (98.7%)
Month 1	34 (100%)	13 (100%)	22 (100%)	8 (100%)	77 (100%)
Month 2	33 (97.1%)	10 (76.9%)	22 (100%)	7 (87.5%)	72 (93.5%)
Month 3	34 (100%)	12 (92.3%)	22 (100%)	7 (87.5%)	75 (97.4%)
Month 6	34 (100%)	12 (92.3%)	22 (100%)	6 (75%)	74 (96.1%)
Month 12	34 (100%)	12 (92.3%)	21 (95.5%)	6 (75%)	73 (94.8%)

Baseline values are shown in table 23. For the PCS, average scores were similar in all groups, but slighter higher in those switching to AI from tamoxifen. This would indicate better general physical health and likely to related to the time from adjuvant treatment. For the MCS, there was a similar pattern for similar reasons. Baseline mean bodily pain health was again better in the switch group than the others. It is likely that there was still a contribution to pain from their recent surgical procedure.

Table 23. SF-36v2 baseline scores for PCS, MCS and bodily pain

Variable	Scoring	Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
Physical component	n (%)	33 (97.1%)	13 (100%)	22 (100%)	8 (100%)	76 (98.7%)
	Mean (SD)	47.2 (8)	53.9 (6.6)	44.7 (11)	43.8 (11.7)	47.3 (9.6)
	Median (IQR)	47.5 (43.3 to 52.5)	55.1 (51.2 to 58.1)	47.3 (35.1 to 53.7)	46.1 (33.4 to 53.9)	49 (42.7 to 54.3)
	Range	29.2 to 60.6	36.4 to 61.6	24 to 62.2	26.1 to 57.4	24 to 62.2
Mental component	n (%)	33 (97.1%)	13 (100%)	22 (100%)	8 (100%)	76 (98.7%)
	Mean (SD)	47.7 (9.6)	53.8 (7.1)	48.8 (9.3)	46.1 (11.9)	48.9 (9.5)
	Median (IQR)	46.9 (40.5 to 56.6)	56 (52.2 to 58)	49.2 (42.7 to 55.8)	45.5 (35.7 to 55.8)	49.2 (40.8 to 57.4)
	Range	28.7 to 61.9	34.5 to 61.5	30.4 to 64	31.7 to 63.4	28.7 to 64
Bodily pain	n (%)	33 (97.1%)	13 (100%)	22 (100%)	8 (100%)	76 (98.7%)
	Mean (SD)	62.4 (22)	89.3 (19.1)	58.4 (24.4)	60.9 (28.5)	65.7 (25)
	Median (IQR)	61 (51 to 80)	100 (84 to 100)	56.5 (41 to 74)	62.5 (36 to 84)	62 (41 to 84)
	Range	22 to 100	41 to 100	22 to 100	22 to 100	22 to 100

Changes in the SF-36 PCS, MCS and bodily pain scores over time are shown in figures 39-41. For women on upfront AI therapy there was no significant change in either PCS, MCS or bodily pain. In the switch AI group, there was no change in the MCS. There was a slight decrease in the mean PCS from 53.9 at baseline to 50.5 at 12 months. The scores for tamoxifen controls were unchanged for the PCS. There was a small increase in MCS 48.8 to 53.5 at 12 months. Mean bodily pain score did improve from 58.4 to 67.9 after one month and stayed at this level for the rest of the study. It is likely that recovery from adjuvant treatment is implicated here. For group D, there was a likewise improvement in PCS and bodily pain, with little change in MCS.

Figure 39. Change in mean SF-36 PCS scores over time

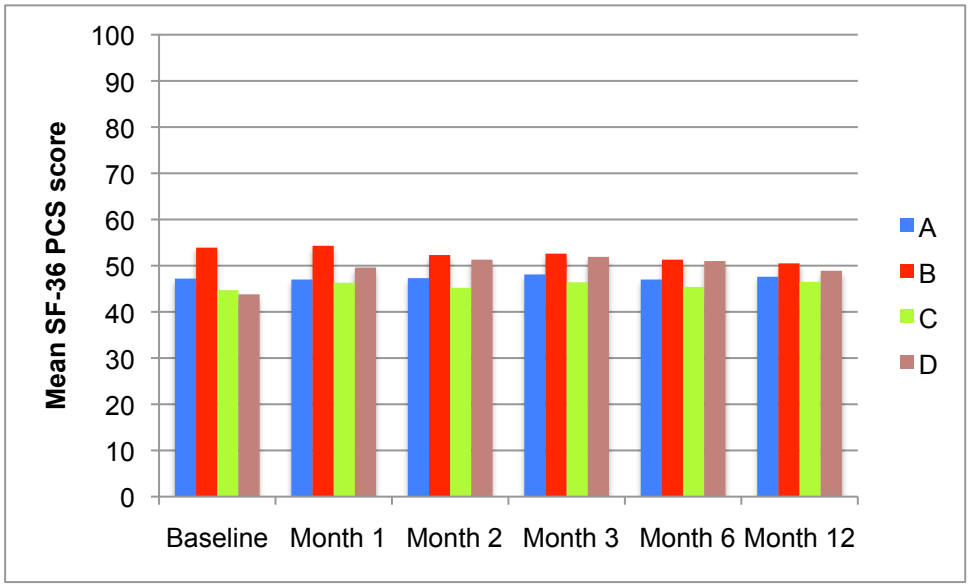


Figure 40. Change in mean SF-36 MCS scores over time

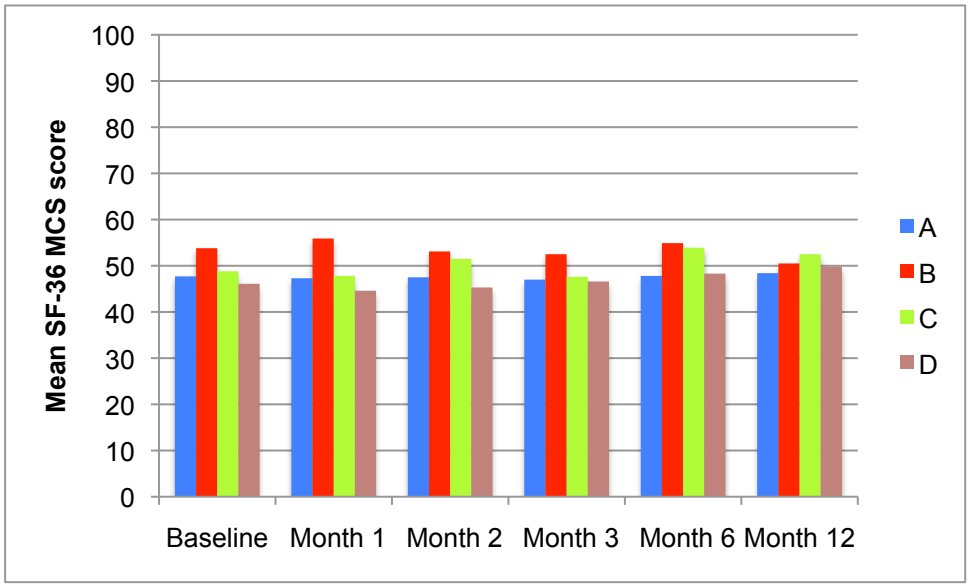
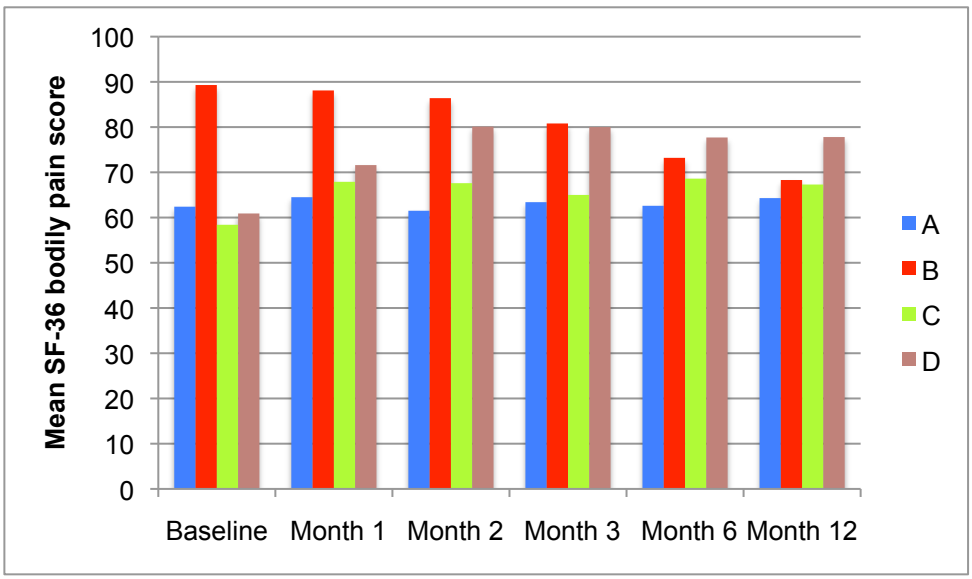


Figure 41. Change in mean SF-36 bodily pain scores over time



In the group wise comparisons, there were no statistically significant differences between the means at 3 months and 12 months for PCS and MCS. For bodily pain, comparison of means at 12 months showed a 22 point lower mean for switch AI compared to no treatment (95%CI -44.6, -0.7, p=0.043). A similar trend was seen at 3 months, but the p value was not significant. This non-significant trend was seen to a lesser extent in the upfront AI groups. The summary of statistical comparisons is shown in table 24.

Table 24 Pairwise comparisons for SF-36 PCS, MCS and bodily pain

		Month 3		Month 12		Overall	
Variable	Comparison	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
Physical component summary	1. Upfront AI (A) v No treatment (D)	-4.9 (-10.4, 0.6)	0.079	-1.8 (-8.0, 4.3)	0.559	-4.9 (-10.4, 0.6)	0.092
	2. Switch AI (B) v No treatment (D)	-5.3 (-12.1, 1.5)	0.126	-4.5 (-12.0, 2.9)	0.233	-5.3 (-12.1, 1.5)	0.123
	3. Upfront AI (A) v Tamoxifen (C)	-0.2 (-3.9, 3.5)	0.907	-0.2 (-4.2, 3.8)	0.920	-0.2 (-3.9, 3.5)	0.853
	4. Switch AI (B) v Tamoxifen (C)	-0.6 (-6.2, 5.1)	0.839	-2.9 (-9.0, 3.1)	0.344	-0.6 (-6.2, 5.1)	0.704
	5. Upfront AI (A) v Switch AI (B)	0.4 (-4.7, 5.4)	0.886	2.7 (-2.5, 7.9)	0.309	0.4 (-4.7, 5.4)	0.732
	6. A/B v C/D	-2.8 (-6.8, 1.3)	0.179	-2.4 (-6.8, 2.0)	0.292	-2.8 (-6.8, 1.3)	0.192
Mental component summary	1. Upfront AI (A) v No treatment (D)	1.2 (-5.0, 7.4)	0.699	-0.6 (-8.2, 7.0)	0.877	1.2 (-5.0, 7.4)	0.541
	2. Switch AI (B) v No treatment (D)	3.6 (-4.1, 11.2)	0.361	-1.8 (-10.9, 7.3)	0.692	3.6 (-4.1, 11.2)	0.145
	3. Upfront AI (A) v Tamoxifen (C)	0.9 (-3.3, 5.1)	0.672	-2.6 (-7.5, 2.4)	0.315	0.9 (-3.3, 5.1)	0.196
	4. Switch AI (B) v Tamoxifen (C)	3.2 (-3.1, 9.6)	0.316	-3.8 (-11.1, 3.5)	0.310	3.2 (-3.1, 9.6)	0.768
	5. Upfront AI (A) v Switch AI (B)	-2.3 (-8.1, 3.4)	0.427	1.2 (-5.2, 7.7)	0.707	-2.3 (-8.1, 3.4)	0.184
	6. A/B v C/D	-2.8 (-6.8, 1.3)	0.179	-2.4 (-6.8, 2.0)	0.292	-2.8 (-6.8, 1.3)	0.192
Bodily pain	1. Upfront AI (A) v No treatment (D)	-12.2 (-27.9, 3.5)	0.128	-10.6 (-28.5, 7.3)	0.246	-12.2 (-27.9, 3.5)	0.305
	2. Switch AI (B) v No treatment (D)	-10.8 (-30.2, 8.6)	0.276	-22.7 (-44.6, -0.7)	0.043	-10.8 (-30.2, 8.6)	0.356
	3. Upfront AI (A) v Tamoxifen (C)	-1.4 (-11.9, 9.1)	0.795	-2.7 (-14.1, 8.7)	0.644	-1.4 (-11.9, 9.1)	0.329
	4. Switch AI (B) v Tamoxifen (C)	-0.0 (-16.4, 16.4)	0.999	-14.8 (-32.5, 3.0)	0.103	-0.0 (-16.4, 16.4)	0.528
	5. Upfront AI (A) v Switch AI (B)	-1.4 (-16.1, 13.4)	0.854	12.1 (-3.7, 27.8)	0.134	-1.4 (-16.1, 13.4)	0.999
	6. A/B v C/D	-6.1 (-17.5, 5.4)	0.297	-12.7 (-25.5, 0.1)	0.052	-6.1 (-17.5, 5.4)	0.223

8.6.3. BPI-SF

This questionnaire has commonly been used in oncological studies, usually those involving metastatic disease. Yet there is little data on what the minimal important difference is. The worst pain score is usually the one of most interest in clinical studies.

The brief pain inventory – short form was completed in 51 (66%) of patients at baseline. At 12 months, 58 (75%) of patients had completed this form. Mathias et al have suggested a 2 point difference as the minimal important difference for worst pain (Mathias et al. 2011).

A comparison of the number completing the questionnaire at all of the study time points is shown in table 25. It is possible that more patients completed the 12 month form in cohorts A and B at 12 months as more had pain to describe.

Table 25. Table showing completed BPI-SF questionnaires at baseline and at each study time point

Timepoint	Scoring	Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
Baseline	N (%)	26 (76.5%)	4 (30.8%)	16 (72.7%)	5 (62.5%)	51 (66.2%)
Month 1	N (%)	27 (79.4%)	7 (53.8%)	16 (72.7%)	6 (75%)	56 (72.7%)
Month 2	N (%)	26 (76.5%)	7 (53.8%)	17 (77.3%)	5 (62.5%)	55 (71.4%)
Month 3	N (%)	27 (79.4%)	9 (69.2%)	14 (63.6%)	5 (62.5%)	55 (71.4%)
Month 6	N (%)	26 (76.5%)	10 (76.9%)	18 (81.8%)	4 (50%)	58 (75.3%)
Month 12	N (%)	29 (85.3%)	9 (69.2%)	17 (77.3%)	3 (37.5%)	58 (75.3%)

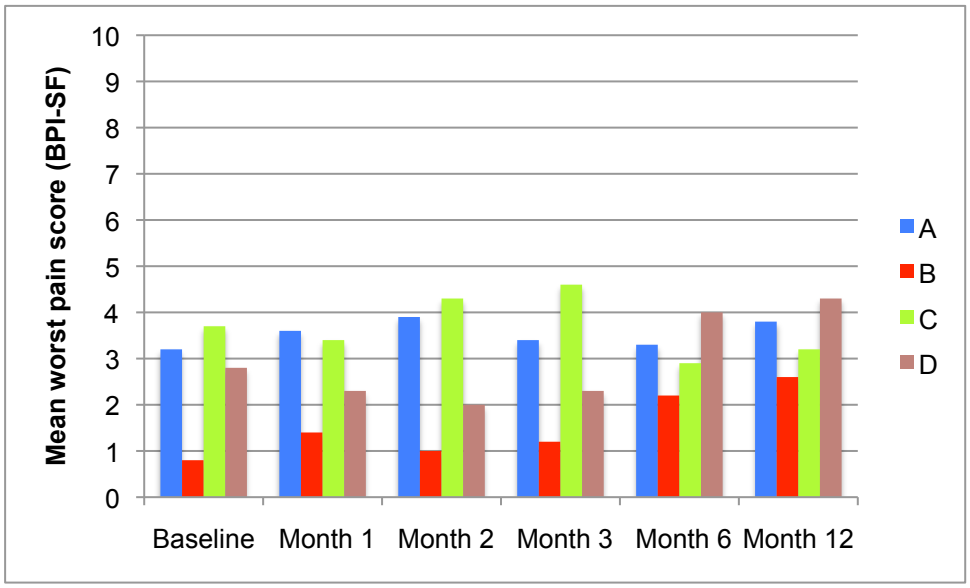
The domains were analysed separately according to worst pain, least pain, average pain and pain now. Interference with daily activities was averaged from scores of general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. Each pain score was rated on a scale of 0-10.

8.6.3.1. Worst pain

Mean worst pain at baseline scores were least for those about to switch to an AI after 2-3 years of tamoxifen. This is consistent with the findings from the HAQ pain VAS and likely to be due to the fact that this group had completed surgery and adjuvant therapy (which are associated with pain) over 2 years previously. The mean scores (with standard deviation) were as follows: A 3.2 (2.9), B 0.8 (1), C 3.7 (2.6), D 2.8 (3.7), overall 3.1 (2.8).

Change of scores over time is shown in figure 42. Mean scores in those on upfront AI stayed relatively constant between 3.2 and 3.8 for the duration of the study. The switch group, had a small but gradual increase from 0.8 to 2.6. Those starting on tamoxifen had fairly stable scores, as did the no treatment controls.

Figure 42. Mean WORST pain scores over time from BPI-SF



Group comparisons revealed some statistically significant differences of the means for these scores. The difference between the groups B and C at 3 months was -3.1 (95% CI -5.5, -0.6, p=0.015), indicating worse pain in those on

tamoxifen. This is partly to the fact that the scores in group B were much lower than the other groups. The scores for group B did worsen over time and by 12 months there was no statistically significant difference in B and C. A small difference was seen at 3 months for worse pain in those on upfront AI versus switch at 3 months, but this had disappeared by 12 months. The averaged difference over the 12 months was still significant (+2.6, p=0.011).

Table 26. Statistical group wise comparisons for BPI-SF WORST pain scores at 3 months, 12 months and overall averaged

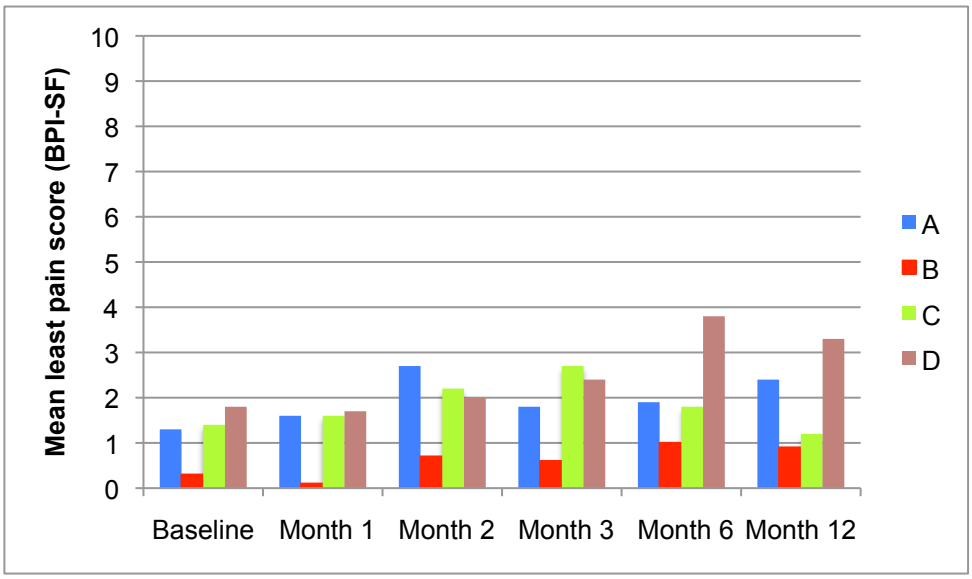
		Month 3		Month 12		Overall	
Variable	Comparison	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
Worst Pain	1. Upfront AI (A) v No treatment (D)	0.6 (-1.5, 2.6)	0.577	-0.2 (-3.4, 3.0)	0.892	0.6 (-1.5, 2.6)	0.251
	2. Switch AI (B) v No treatment (D)	-2.0 (-4.9, 0.9)	0.174	0.2 (-5.2, 5.6)	0.948	-2.0 (-4.9, 0.9)	0.281
	3. Upfront AI (A) v Tamoxifen (C)	-0.5 (-1.8, 0.9)	0.488	0.7 (-0.8, 2.2)	0.365	-0.5 (-1.8, 0.9)	0.733
	4. Switch AI (B) v Tamoxifen (C)	-3.1 (-5.5, -0.6)	0.015	1.1 (-3.4, 5.6)	0.637	-3.1 (-5.5, -0.6)	0.052
	5. Upfront AI (A) v Switch AI (B)	2.6 (0.2, 5.0)	0.036	-0.4 (-4.8, 4.0)	0.859	2.6 (0.2, 5.0)	0.011
	6. AI (A/B) v Tam/no treatment (C/D)	-1.2 (-2.8, 0.4)	0.127	0.4 (-2.4, 3.2)	0.763	-1.2 (-2.8, 0.4)	0.558

8.6.3.2. Least pain

Mean least pain at baseline scores were again lowest for those about to switch to an AI after 2-3 years of tamoxifen. The mean scores (with standard deviation) were as follows: A 1.3 (1.6), B 0.3 (0.5), C1.4 (1.9), D1.8 (4), overall 1.3 (2)

Change of scores over time is shown in figure 43. Mean scores in those on upfront AI stayed showed a small gradual increase over the duration of the study from 1.3 to 2.4. The same was true for cohort D (1.8 to 3.3) The switch group didn't really change. Those starting on tamoxifen had a small rise to 3 months (1.4 to 2.7), but then return to baseline at 12 months (1.2).

Figure 43. Mean LEAST pain scores over time from BPI-SF



Statistical group comparisons revealed two statistically significant differences for the least pain scores. In the upfront AI versus tamoxifen comparison at 12 months, the mean score was 1.4 (95% CI 0.3-2.5, p=0.011) higher, but no statistical difference was seen at 3 months or for the averaged time period. When the mean was averaged over the 12 months, the difference was 0.8 points higher for upfront AI over switch AI (p=0.01). All other comparisons did not meet conventional levels of significance (table 27).

Table 27. Statistical group wise comparisons for BPI-SF LEAST pain scores at 3 months, 12 months and overall averaged

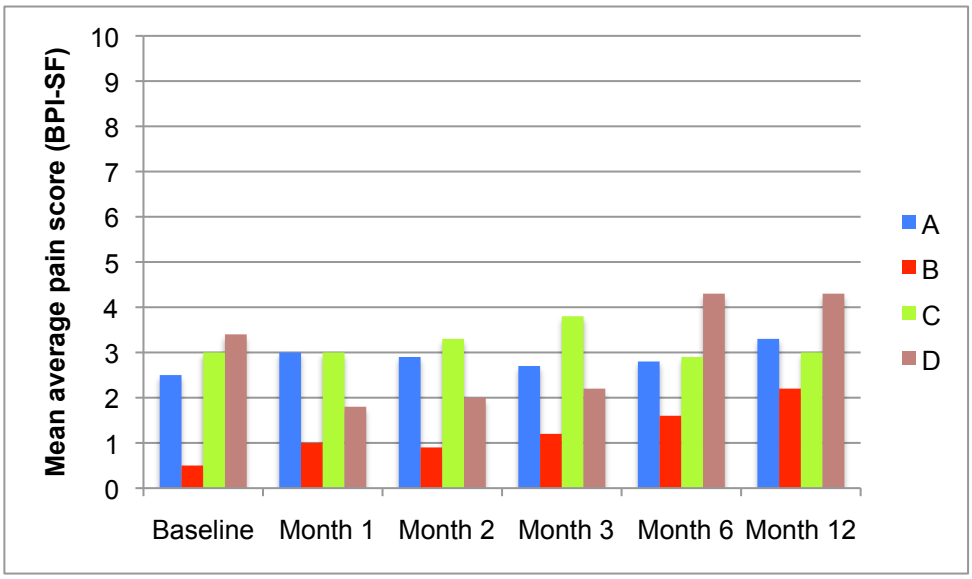
		Month 3		Month 12		Overall	
Variable	Comparison	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
Least Pain	1. Upfront AI (A) v No treatment (D)	-0.2 (-1.9, 1.5)	0.813	0.0 (-2.5, 2.5)	0.997	-0.2 (-1.9, 1.5)	0.120
	2. Switch AI (B) v No treatment (D)	-1.0 (-3.4, 1.4)	0.422	-0.8 (-4.8, 3.2)	0.708	-1.0 (-3.4, 1.4)	0.437
	3. Upfront AI (A) v Tamoxifen (C)	-0.5 (-1.6, 0.6)	0.365	1.4 (0.3, 2.5)	0.011	-0.5 (-1.6, 0.6)	0.523
	4. Switch AI (B) v Tamoxifen (C)	-1.3 (-3.3, 0.7)	0.209	0.7 (-2.6, 3.9)	0.698	-1.3 (-3.3, 0.7)	0.248
	5. Upfront AI (A) v Switch AI (B)	0.8 (-1.2, 2.8)	0.431	0.8 (-2.5, 4.0)	0.641	0.8 (-1.2, 2.8)	0.010
	6. AI (A/B) v Tam/no treatment (C/D)	-0.8 (-2.1, 0.6)	0.269	0.3 (-1.7, 2.4)	0.757	-0.8 (-2.1, 0.6)	0.995

8.6.3.3. Average pain

Mean average pain scores at baseline scores were again least for those about to switch to an AI after 2-3 years of tamoxifen. The mean scores (with standard deviation) were as follows: A 2.5 (2.2), B 0.5 (0.6), C 3 (2.1), D 3.4 (3.8), overall 2.6 (2.3).

Change of scores over time is shown in figure 44. Mean scores in those on upfront AI stayed relatively constant between 2.5 and 3.3 for the duration of the study. The switch group again had a small but gradual increase from 0.5 to 2.2. Those starting on tamoxifen had fairly stable scores. The no treatment controls had a more erratic change that was probably to the small numbers in that group (BL 3.4, month1 1.8, month 6 and 12 4.3).

Figure 44. Mean average pain scores over time from BPI-SF



Statistical group comparisons revealed one statistically significant difference for these scores. Those on an upfront AI had an average pain score 0.3 points higher than control group D (p=0.047). However this is not a clinically relevant difference. All the other comparisons did not meet conventional levels of significance.

Table 28. Statistical group wise comparisons for BPI-SF AVERAGE pain scores at 3 months, 12 months and overall averaged.

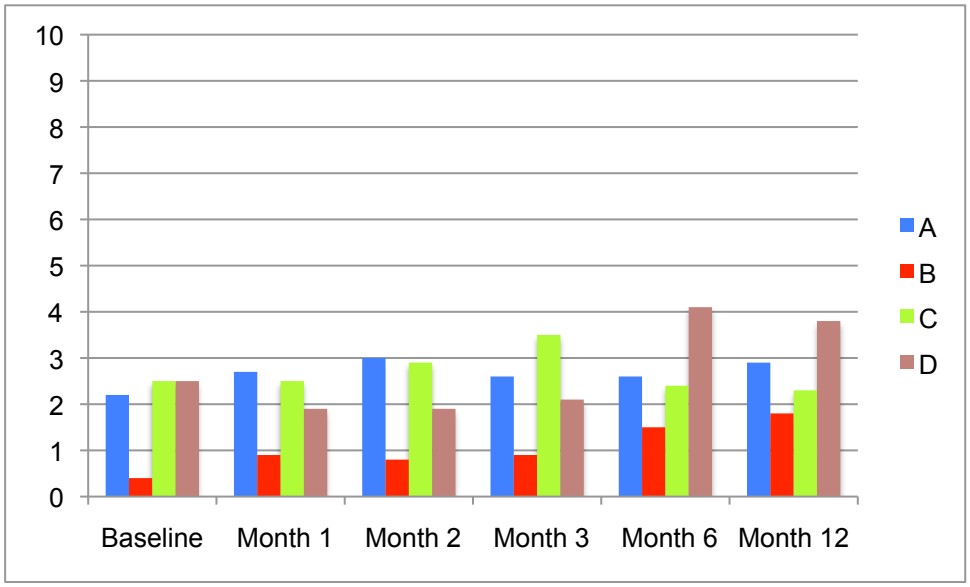
		Month 3		Month 12		Overall	
Variable	Comparison	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
Average Pain	1. Upfront AI (A) v No treatment (D)	0.3 (-1.2, 1.8)	0.704	0.6 (-1.6, 2.8)	0.576	0.3 (-1.2, 1.8)	0.047
	2. Switch AI (B) v No treatment (D)	-0.9 (-3.1, 1.2)	0.395	0.6 (-3.1, 4.3)	0.748	-0.9 (-3.1, 1.2)	0.881
	3. Upfront AI (A) v Tamoxifen (C)	-0.1 (-1.1, 0.8)	0.802	0.5 (-0.4, 1.5)	0.279	-0.1 (-1.1, 0.8)	0.987
	4. Switch AI (B) v Tamoxifen (C)	-1.3 (-3.2, 0.5)	0.152	0.5 (-2.5, 3.5)	0.734	-1.3 (-3.2, 0.5)	0.109
	5. Upfront AI (A) v Switch AI (B)	1.2 (-0.5, 3.0)	0.176	0.0 (-2.9, 3.0)	0.987	1.2 (-0.5, 3.0)	0.078
	6. AI (A/B) v Tam/no treatment (C/D)	-0.5 (-1.7, 0.7)	0.384	0.6 (-1.3, 2.5)	0.556	-0.5 (-1.7, 0.7)	0.921

8.6.3.4. Current pain

Mean current pain at baseline scores were again least for those about to switch to an AI after 2-3 years of tamoxifen. The mean scores (with standard deviation) were as follows: A 1.8 (2.1), B 0 (0), C 1.8 (2.2), D 1.8 (4), overall 1.7 (2.3).

Change of scores over time is shown in figure 45. Mean scores for those on upfront AI stayed relatively constant between 1.8 and 2.6 for the duration of the study. The switch group had a small but gradual increase from 0 to 1.4 by 12 months. Those starting on tamoxifen had fairly stable scores. As before group Ds scores were variable due to small numbers (1.8 - 4.5)

Figure 45. Mean CURRENT pain scores over time from BPI-SF



Statistical group comparisons did not reveal any clinically relevant differences for these scores (table 29).

Table 29. Statistical group wise comparisons for BPI-SF CURRENT pain scores at 3 months, 12 months and overall averaged

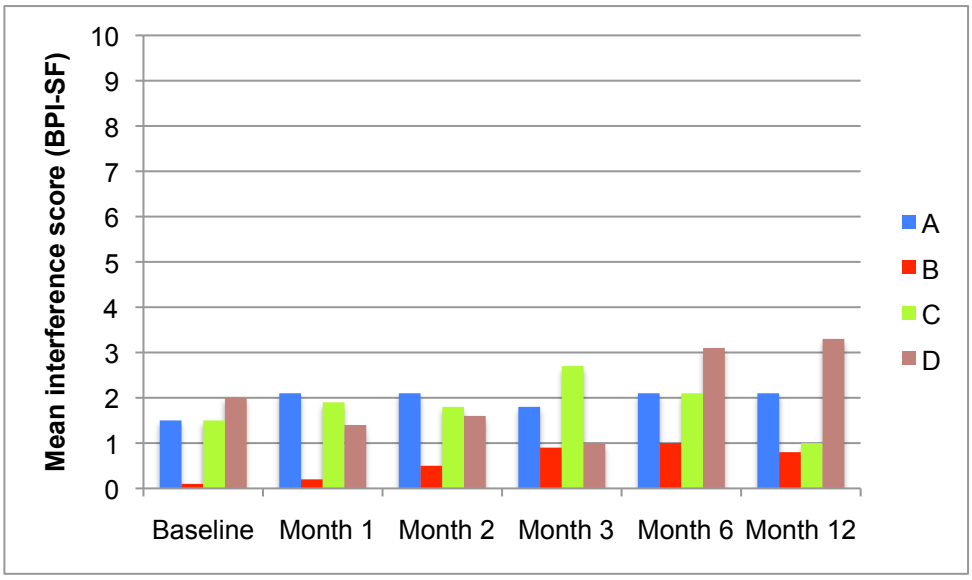
		--Month 3--		--Month 12--		--Overall--	
Variable	Comparison	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
Pain now	1. Upfront AI (A) v No treatment (D)	0.6 (-1.4, 2.6)	0.559	-1.2 (-4.6, 2.2)	0.484	0.6 (-1.4, 2.6)	0.223
	2. Switch AI (B) v No treatment (D)	-0.8 (-3.6, 2.0)	0.566	-0.8 (-6.4, 4.9)	0.792	-0.8 (-3.6, 2.0)	0.953
	3. Upfront AI (A) v Tamoxifen (C)	0.2 (-1.0, 1.5)	0.715	0.5 (-1.0, 2.1)	0.497	0.2 (-1.0, 1.5)	0.513
	4. Switch AI (B) v Tamoxifen (C)	-1.2 (-3.5, 1.2)	0.330	1.0 (-3.7, 5.7)	0.676	-1.2 (-3.5, 1.2)	0.620
	5. Upfront AI (A) v Switch AI (B)	1.4 (-0.9, 3.7)	0.229	-0.5 (-5.1, 4.2)	0.847	1.4 (-0.9, 3.7)	0.209
	6. AI (A/B) v Tam/no treatment (C/D)	-0.3 (-1.8, 1.2)	0.710	-0.1 (-3.0, 2.8)	0.943	-0.3 (-1.8, 1.2)	0.663

8.6.3.5. Interference with lifestyle

As in the previous categories, mean lifestyle interference at baseline scores were lowest for those about to switch to an AI after 2-3 years of tamoxifen. The mean scores (with standard deviation) were as follows: A 1.5 (2.1), B 0.1 (0.1), C 1.5 (2.1), D 2 (2.6), overall 1.4 (2).

Change of scores over time is shown in figure 46. Mean scores for the different cohorts changed very little of the study period.

Figure 46. Mean INTERFERENCE WITH LIFESTYLE scores over time from BPI-SF



Statistical group comparisons revealed 2 significant differences for these scores. The mean scores at month 12 were 1.2 points higher for those on upfront AI compared to tamoxifen controls (p=0.048). The averaged mean difference was 1.4 points higher for upfront AI versus switch AI (p=0.032).

Of note, in the switch versus tamoxifen comparison, the mean difference changed from -2 at 3 month to +1.7 at 12 months. This trend was seen in all BPI analyses, but interesting was most marked in the worst pain section (-3.0 to +1.1).

Table 30. Statistical group wise comparisons for BPI-SF INTERFERENCE WITH LIFESTYLE scores at 3 months, 12 months and overall averaged.

		Month 3		Month 12		Overall	
Variable	Comparison	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
Interference	1. Upfront AI (A) v No treatment (D)	0.7 (-1.2, 2.6)	0.482	-0.1 (-2.7, 2.4)	0.912	0.7 (-1.2, 2.6)	0.388
	2. Switch AI (B) v No treatment (D)	-0.7 (-3.3, 1.9)	0.590	0.4 (-3.8, 4.6)	0.866	-0.7 (-3.3, 1.9)	0.710
	3. Upfront AI (A) v Tamoxifen (C)	-0.6 (-1.5, 0.3)	0.190	1.2 (0.0, 2.4)	0.048	-0.6 (-1.5, 0.3)	0.393
	4. Switch AI (B) v Tamoxifen (C)	-2.0 (-4.1, 0.1)	0.058	1.7 (-1.8, 5.2)	0.339	-2.0 (-4.1, 0.1)	0.242
	5. Upfront AI (A) v Switch AI (B)	1.4 (-0.6, 3.4)	0.172	-0.5 (-3.9, 2.9)	0.772	1.4 (-0.6, 3.4)	0.032
	6. AI (A/B) v Tam/no treatment (C/D)	-0.7 (-2.0, 0.7)	0.347	0.8 (-1.4, 3.0)	0.486	-0.7 (-2.0, 0.7)	0.865

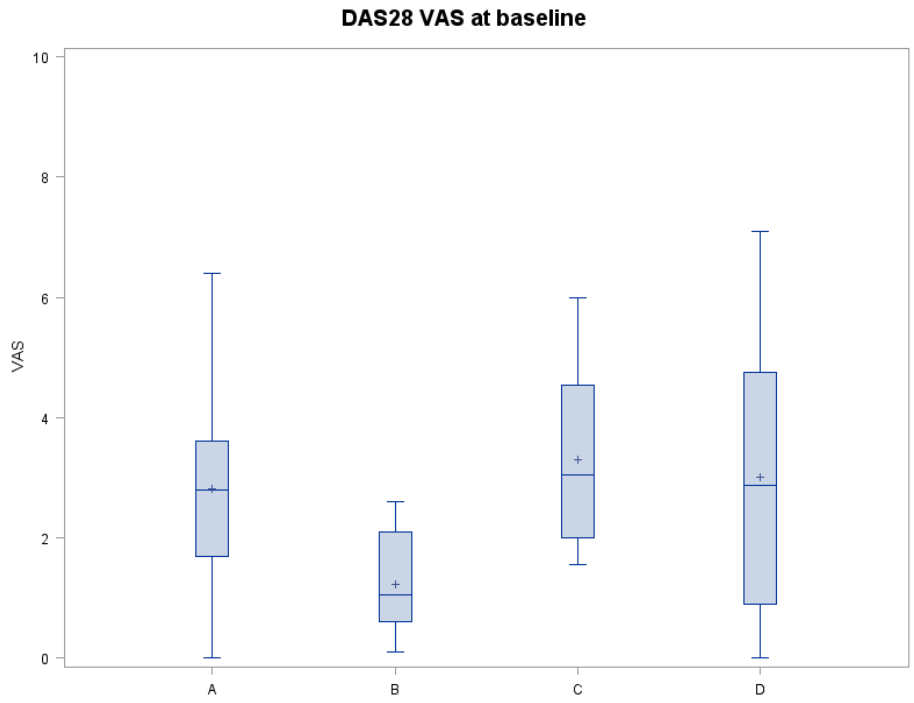
8.7. DISEASE ACTIVITY SCORE (DAS)

8.7.1. General health visual analogue scale (DAS-VAS)

8.7.1.1. Baseline general health visual analogue scale (DAS-VAS)

As part of the DAS-28 score, a general health visual analogue scale was used, with the maximum score being 10. Mean baseline scores (with standard deviation) for cohorts A-D were 2.8 (1.5), 1.2 (0.9), 3.3 (1.4) and 3.0 (2.4). For the whole population, the mean VAS score was 2.7 (1.6). The values of the switch AI group (B) were lower than the other groups and this is probably explained by these patients having had their diagnosis and surgery over 2 years ago. Groups and A, C and D had completed surgery or adjuvant therapy only a few weeks prior to commencing the trial.

Figure 47. Box and whisker plot showing mean baseline general health visual analogue scale



8.7.1.2. Change of general health visual analogue scale (DAS-VAS) over time

The change of general health DAS-VAS score over the twelve months is shown in figure 48. There was little change in mean scores for the upfront AI group. For those on switch AI, lower mean baseline value of 1.2 increased to 1.8 by month 12, indicating a slightly worse health state. The tamoxifen group had a gradual improvement in VAS score from 3.3 to 2.2. Group D controls again were variable with wide confidence intervals.

The prespecifed group comparisons indicated that there were no significant differences between mean scores at month 3, 12 and averaged over the 12 months. The data is displayed in table 31.

Figure 48. Change of general health visual analogue scale (DAS-VAS) over time for cohorts A-D

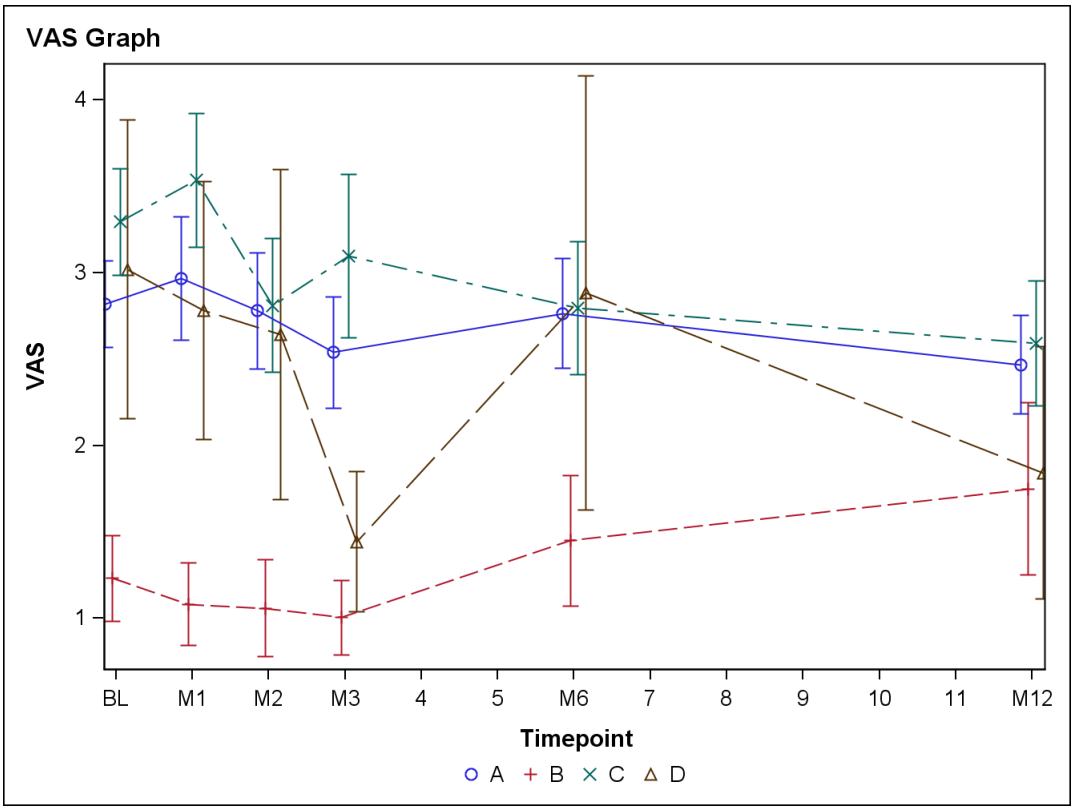


Table 31. Statistical group wise comparisons for general health visual analogue scale (DAS-VAS) at month 3, 12 and averaged

Comparison	Month 3		Month 12		Overall /averaged	
	Mean difference (95% CI)	P	Mean difference (95% CI)	P	Mean difference (95% CI)	P
1. Upfront AI (A) v No treatment (D)	0.9 (-0.4, 2.2)	0.197	0.2 (-1.1, 1.5)	0.804	0.9 (-0.4, 2.2)	0.830
2. Switch AI (B) v No treatment (D)	0.2 (-1.4, 1.8)	0.830	0.6 (-1.0, 2.1)	0.456	0.2 (-1.4, 1.8)	0.758
3. Upfront AI (A) v Tamoxifen (C)	-0.3 (-1.2, 0.6)	0.511	0.1 (-0.8, 0.9)	0.882	-0.3 (-1.2, 0.6)	0.789
4. Switch AI (B) v Tamoxifen (C)	-1.0 (-2.4, 0.4)	0.170	0.5 (-0.8, 1.8)	0.465	-1.0 (-2.4, 0.4)	0.764
5. Upfront AI (A) v Switch AI (B)	0.7 (-0.5, 1.9)	0.272	-0.4 (-1.6, 0.7)	0.470	0.7 (-0.5, 1.9)	0.500
6. AI (A/B) v Tam/no treatment (C/D)	-0.1 (-1.0, 0.9)	0.903	0.3 (-0.6, 1.2)	0.483	-0.1 (-1.0, 0.9)	0.957

8.7.2. Disease Activity Score with CRP (DAS 28 – CRP)

8.7.2.1. Baseline DAS 28 – CRP scores

DAS 28 – CRP incorporated results from the CRP analysis to produce an overall composite score. The score was calculated with the use of an online calculator, which used the following formula:
DAS28 (CRP)=
0.56*√(TJC28) +0.28*√(SJC28)+0.014*GH+0.36*ln(CRP+1)+0.96.
TJC=Tender Joint Count; SJC=Swollen Joint Count; GH=General Health VAS.

The maximum score achievable is 10. At baseline the mean scores were 2 (SD 0.7), 1.6 (SD 0.4), 1.9 (SD 0.5) and 1.6 (0.3) for groups A-D respectively.

8.7.2.2. Change of DAS 28 – CRP over time

The change of mean DAS 28 – CRP over time for the four groups is shown in figure 49. The mean score for the upfront AI group did not change over the 12 month study period. There was a small increase of 0.5 (1.6 to 2.1) for patients receiving switch AI. Scores for the two control groups were largely unchanged.

At 3 months, there were no significant differences between the DAS 28 – CRP scores between the groups in the prespecified comparisons. At 12 months, a difference of +0.7 was seen for switch AI versus tamoxifen (95% CI 0.1-1.2, p=0.019). In addition, there was a smaller difference of means of 0.5 for switch AI compared to upfront AI (95% CI -1.0-0 p=0.032). There were no significant differences in the means when averaged over the study period (table 32).

Figure 49. Change of mean DAS 28 - CRP over time for cohorts A-D

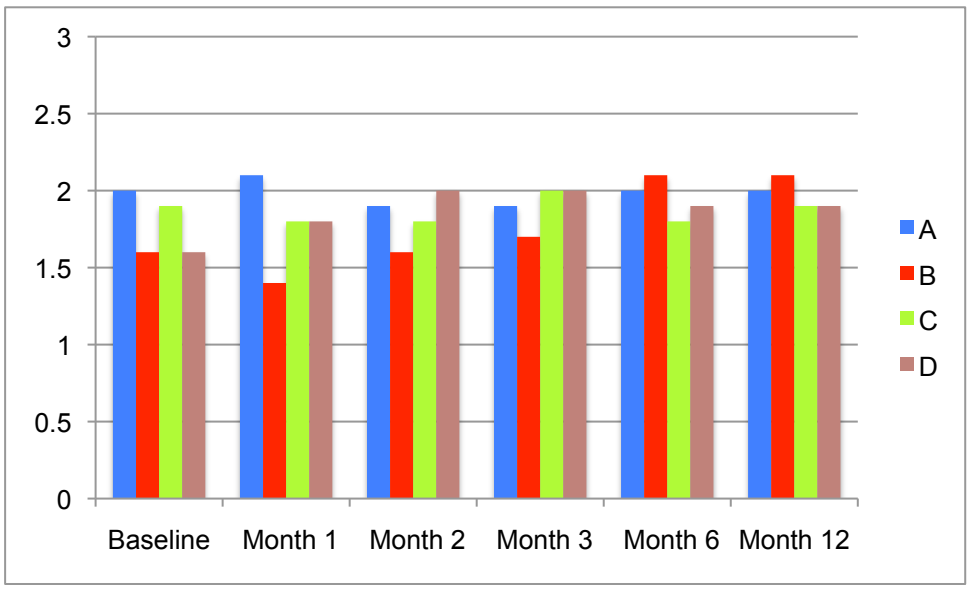


Table 32 Statistical group wise comparisons for DAS 28-CRP at month 3, 12 and averaged

		Month 3		Month 12		Overall	
Variable	Comparison	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
DAS 28-CRP	1. Upfront AI (A) v No treatment (D)	-0.2 (-0.6, 0.2)	0.313	-0.1 (-0.6, 0.4)	0.738	-0.2 (-0.6, 0.2)	0.224
	2. Switch AI (B) v No treatment (D)	-0.1 (-0.6, 0.4)	0.680	0.4 (-0.2, 1.1)	0.194	-0.1 (-0.6, 0.4)	0.915
	3. Upfront AI (A) v Tamoxifen (C)	-0.0 (-0.2, 0.2)	0.966	0.1 (-0.2, 0.5)	0.491	-0.0 (-0.2, 0.2)	0.301
	4. Switch AI (B) v Tamoxifen (C)	0.1 (-0.3, 0.5)	0.626	0.7 (0.1, 1.2)	0.019	0.1 (-0.3, 0.5)	0.060
	5. Upfront AI (A) v Switch AI (B)	-0.1 (-0.4, 0.2)	0.565	-0.5 (-1.0, -0.0)	0.032	-0.1 (-0.4, 0.2)	0.100
	6. AI (A/B) v Tam/no treatment (C/D)	-0.1 (-0.3, 0.2)	0.710	0.3 (-0.1, 0.7)	0.157	-0.1 (-0.3, 0.2)	0.612

9. THE ARIAD STUDY - RESULTS OF BIOCHEMICAL INVESTIGATIONS

9.1. INTRODUCTION

To date, the biochemical investigations tested in this study have been serum oestradiol E2, vitamin D (25 – hydroxyvitamin D) and C-reactive protein (CRP).

By inhibiting the enzyme aromatase, the last step in the enzymatic conversion to oestradiol, very low levels of oestradiol are expected. It is oestrogen deprivation that is implicated as the cause of musculoskeletal symptoms. However, standard assays have a limit to the lowest levels of oestradiol that can be detected. Therefore to accurately quantify levels of oestradiol for women receiving aromatse inhibitors, highly sensitive assays are required to measure levels as low as 5 pg/ml. No studies have monitored such levels in a prospective manner. This remains an important question in the pathogenesis of AIA.

Vitamin D is important for bone health. Low levels can be caused by lack of vitamin D in the diet, often in conjunction with inadequate sun exposure, reduced absorption of vitamin D from the intestine, or inability to process vitamin D due to kidney or liver disease. Insufficiency or deficiency of vitamin D may be characterized by joint pain and stiffness, bone and muscle pain, and muscle weakness. A link between AIA and vitamin D levels has not been confirmed. Vitamin D (25-hydroxyvitamin D) levels are classified as follows:

- normal vitamin D is greater than 30 ng/mL (75 nmol/L).
- Insufficiency is between 20 to 30 ng/mL (50 to 75 nmol/L).
- Deficiency less than 20 ng/mL (50 nmol/L).

CRP was measured to form part of the composite score of DAS-28 CRP. On its own, it is an acute phase protein and can be raised in inflammatory conditions, particularly when synovitis is involved. At the time of study design, there was no clear signal as to whether CRP was an important factor in AIA.

9.2. OESTRADIOL E2

9.2.1. Overall study population

Oestradiol was tested in all patients at the baseline, 3 month, 6 month and 12 month time points. All 77 (100%) of patients had baseline samples tested. At 3 months, 70 (89.7%) patient samples were tested. At 6 and 12 months, 72 (93.5%) and 73 (94.8%) patient samples were tested.

Baseline oestradiol levels were similar in all cohorts. The overall population mean oestradiol level was 13.9pg/ml (SD 6.9). For cohorts A-D, baseline values (with standard deviations) were as follows: A 13.2pg/ml (SD 5.9), B 12.2pg/ml (SD 3.9), 14.6pg/ml (SD 8.2), 17.3pg/ml (SD 9.9). No statistical difference was seen.

Table 33. Baseline Oestradiol levels for all cohorts (pg/ml)

Variable	Timepoint	Scoring	Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
Oestradiol (pg/ml)	Baseline	N (%)	34 (100%)	13 (100%)	22 (100%)	8 (100%)	77 (100%)
		Mean (SD)	13.2 (5.9)	12.2 (3.9)	14.6 (8.2)	17.3 (9.9)	13.9 (6.9)
		Median (IQR)	12 (9.2 to 15)	12.8 (10.9 to 15.3)	12.5 (9.7 to 18.2)	15 (8 to 27.2)	12.3 (9.4 to 16.3)
		Min to Max	5.5 to 30.7	4.9 to 16.5	4.9 to 39.9	7.5 to 31	4.9 to 39.9

Over the 12 month study period, oestradiol levels reduced in cohort A as expected. There was an increase in cohort B. In cohorts C and D levels were fairly static over the 12 months. This is displayed in figure 50.

For the groupwise comparisons of means, there were several statistically significant differences. For women on upfront AI, all comparisons showed lower mean oestradiol values compared with controls, tamoxifen and with switch AI.

Mean oestradiol levels for switch AI group increased and these proved to be significantly higher than levels in groups A, C and D (table 34).

Figure 50. Change in mean Serum Oestradiol over time for cohorts A-D

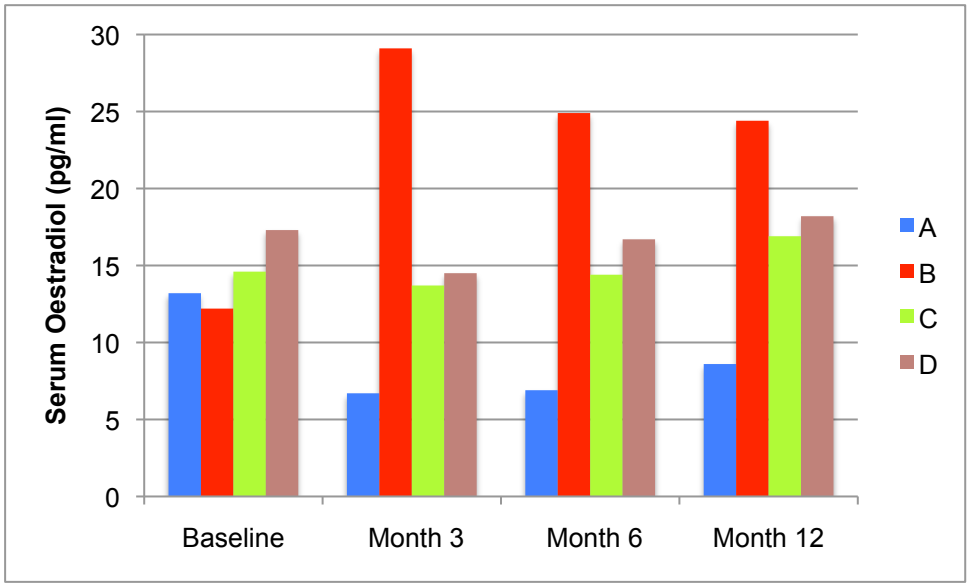


Table 34. Statistical group wise comparisons for serum oestradiol (pg/ml) at month 3, 12 and averaged

		--Month 3--		--Month 12--		--Overall--	
Variable	Comparison	Mean (95% CI) at 3 months	p (month 3)	Mean (95% CI) at 12 months	p (month 12)	Mean (95% CI) overall	p (overall)
Oestradiol	1. Upfront AI (A) v No treatment (D)	-7.5 (-11.8, -3.2)	<.001	-8.4 (-12.9, -3.9)	<.001	-7.5 (-11.8, -3.2)	<.001
	2. Switch AI (B) v No treatment (D)	14.4 (9.1, 19.7)	<.001	7.0 (1.6, 12.4)	0.011	14.4 (9.1, 19.7)	<.001
	3. Upfront AI (A) v Tamoxifen (C)	-6.5 (-9.0, -4.0)	<.001	-7.6 (-10.5, -4.7)	<.001	-6.5 (-9.0, -4.0)	<.001
	4. Switch AI (B) v Tamoxifen (C)	15.4 (11.2, 19.6)	<.001	7.8 (3.5, 12.2)	<.001	15.4 (11.2, 19.6)	<.001
	5. Upfront AI (A) v Switch AI (B)	-21.9 (-25.6,-18.2)	<.001	-15.4 (-19.2,-11.6)	<.001	-21.9 (-25.6,-18.2)	<.001
	6. AI (A/B) v Tam/no treatment (C/D)	3.9 (0.9, 7.0)	0.011	-0.3 (-3.5, 2.9)	0.861	3.9 (0.9, 7.0)	0.360

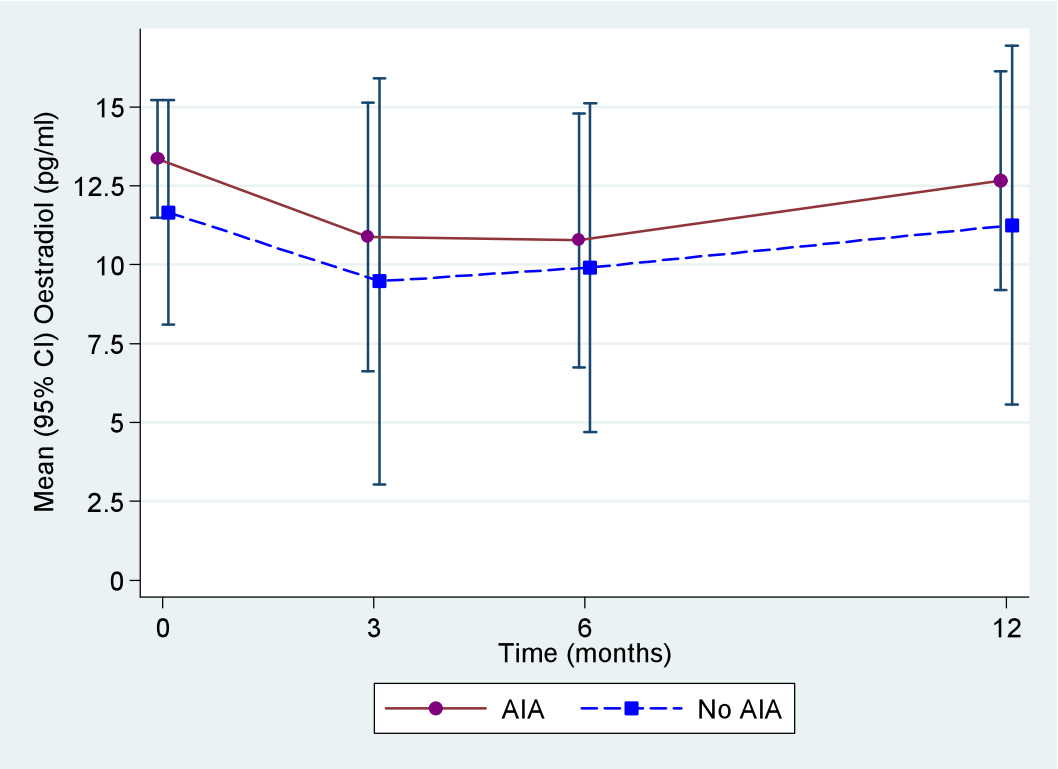
9.2.2. Comparison according to Aromatase Inhibitor Arthralgia (AIA)

For those on an aromatase inhibitor, the data with respect to patients developing the arthralgia syndrome were then evaluated. An important hypothesis has been that oestrogen deprivation may be implicated in the cause of the joint problems. The figures for oestradiol E2 are presented and displayed graphically below. Overall there is no clear evidence of a difference of oestradiol levels between AIA and non-AIA. There was a small, non-statistically significant increased ostradiol in AIA compared with non-AIA, which prevailed over the course of the study.

Table 35. Comparison of mean Oestradiol E2 levels (pg/ml) according to AIA versus Non AIA sufferers. Mean difference tested for significance with the t-test.

	AIA		No AIA		Comparison	
Month	n	Mean (SD)	n	Mean (SD)	Mean difference (95% CI)	p-value
0	32	13.4 (5.2)	15	11.7 (6.5)	1.7 (-1.8, 5.2)	0.339
3	31	10.9 (11.6)	13	9.5 (10.7)	1.4 (-6.2,9.0)	0.711
6	30	10.8 (10.8)	14	9.9 (9.1)	0.9 (-5.9,7.6)	0.797
12	32	12.7 (9.6)	15	11.3 (10.3)	1.4 (-4.8, 7.6)	0.648

Figure 51. Mean Oestradiol E2 levels with 95% Confidence Intervals (pg/ml) for AIA and Non AIA over the study period



Further exploratory analyses were undertaken by the study statistician. It was noted above that there were differences in oestradiol levels in cohorts A and B. As the AIA v non-AIA comparison may be masking cohort differences, further analyses were undertaken in which AIA (yes/no) were compared in an analysis of variance model in which cohort (A/B) was a covariate. Doing so made no material difference as is shown in table 36; the adjusted differences between AIA and non-AIA were similar to the unadjusted differences.

Table 36. Comparison of unadjusted and adjusted mean Oestradiol E2 levels (pg/ml) for AIA versus Non-AIA (p values derived from analysis of covariance)

	Unadjusted comparison (AIA vs non-AIA)		Adjusted comparison (AIA vs non-AIA)	
Month	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
0	1.7 (-1.8, 5.2)	0.339	1.7 (-1.8, 5.3)	0.336
3	1.4 (-6.2,9.0)	0.711	-0.3 (-4.4,3.8)	0.888
6	0.9 (-5.9,7.6)	0.797	0.5 (-3.3,4.2)	0.798
12	1.4 (-4.8, 7.6)	0.648	0.1 (-4.2, 4.1)	0.965

9.3. 25 HYDROXYVITAMIN D

9.3.1. Overall study population

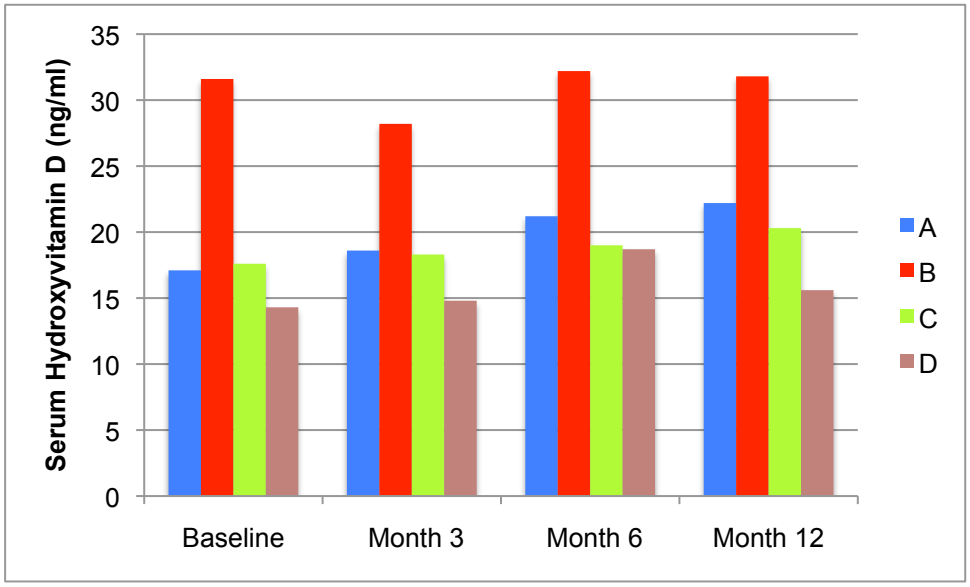
Vitamin D was tested in all patients at the baseline, 3 month, 6 month and 12 month time points. The overall population mean was 19.4ng/ml (SD 12.4), which falls on the border between deficiency and insufficiency. The cohort mean baseline values (with standard deviations) were as follows: A 17.1ng/ml (SD 9.8), B 31.6ng/ml (SD 16.1), C 17.6ng/ml (SD 10.1) and D 14.3ng/ml (SD 11.3). Cohort B had significantly higher baseline values than the other cohorts. Table 37 summarises the baseline features.

Table 37. Baseline 25 Hydroxyvitamin D characteristics (ng/ml)

Variable	Timepoint	Scoring	Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
Vitamin D (ng/ml)	Baseline	N (%)	34 (100%)	13 (100%)	22 (100%)	8 (100%)	77 (100%)
		Mean (SD)	17.1 (9.8)	31.6 (16.1)	17.6 (10.1)	14.3 (11.3)	19.4 (12.4)
		Median (IQR)	16.2 (10.1 to 20.3)	30.4 (24.7 to 40.7)	17.7 (8.3 to 23.5)	11.2 (6.8 to 17.2)	16.9 (9.1 to 27.4)
		Min to Max	3.4 to 47.2	6.7 to 66.5	3.4 to 41	4.5 to 39.2	3.4 to 66.5

Over time there was little change in Vitamin D levels. The whole group mean increased slightly from 19.4ng/ml to 22ng/ml. Levels increased mostly in cohort A from 17.1ng/ml to 22.2ng/ml. This may have been due to Calcium/Vitamin D use. For the other groups, levels were fairly static for the study duration.

Figure 52. Change in mean Serum Hydroxyvitamin D over time for cohorts A-D



In the group comparisons, there were no statistically significant changes noted either at 3 months, 12 month or averaged over the 12 months. This is summarised in table 38.

Table 38. Group comparisons for differences in mean vitamin D levels (ng/ml) at 3 months, 12 months and averaged over the 12 months

		--Month 3--		--Month 12--		--Overall--	
Variable	Comparison	Mean (95% CI) at 3 months	p (month 3)	Mean (95% CI) at 12 months	p (month 12)	Mean (95% CI) overall	p (overall)
Vitamin D ng/ml	1. Upfront AI (A) v No treatment (D)	1.0 (-4.2, 6.1)	0.711	4.9 (-1.6, 11.4)	0.143	1.0 (-4.2, 6.1)	0.121
	2. Switch AI (B) v No treatment (D)	-1.1 (-7.6, 5.5)	0.748	6.5 (-1.9, 14.8)	0.127	-1.1 (-7.6, 5.5)	0.551
	3. Upfront AI (A) v Tamoxifen (C)	-0.4 (-3.4, 2.6)	0.793	1.6 (-2.6, 5.8)	0.462	-0.4 (-3.4, 2.6)	0.276
	4. Switch AI (B) v Tamoxifen (C)	-2.5 (-7.7, 2.8)	0.356	3.2 (-3.7, 10.0)	0.361	-2.5 (-7.7, 2.8)	0.795
	5. Upfront AI (A) v Switch AI (B)	2.1 (-2.6, 6.7)	0.391	-1.6 (-7.6, 4.4)	0.600	2.1 (-2.6, 6.7)	0.817
	6. AI (A/B) v Tam/no treatment (C/D)	-0.7 (-4.4, 3.0)	0.697	4.0 (-0.8, 8.9)	0.103	-0.7 (-4.4, 3.0)	0.342

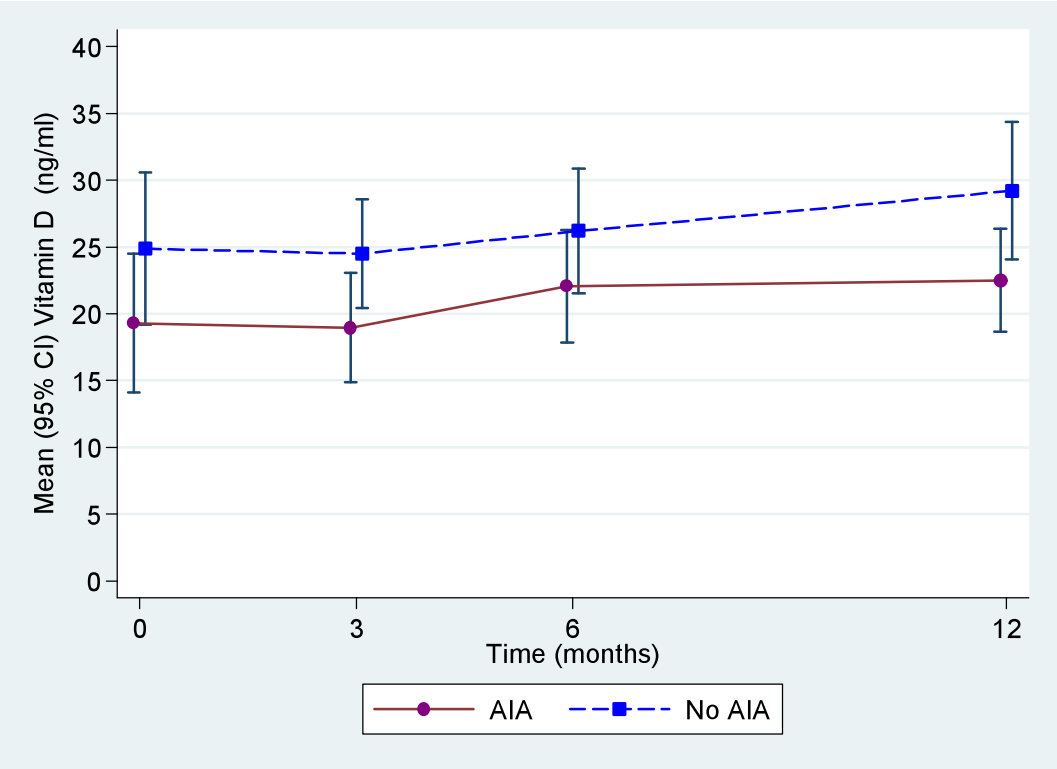
9.3.2. Comparison according to Aromatase Inhibitor Arthralgia (AIA)

The differences in vitamin D levels were then explored according to patients developing the AIA syndrome. As indicated previously, low vitamin D levels can be associated with musculoskeletal symptoms. Overall, there was no statistically significant difference between then means between AIA and non-AIA sufferers. Over the course of the study, mean vitamin D levels were consistently (but non significantly) lower in those developing AIA. However, at 12 months, the difference did meet conventional levels of significance. It is worth noting here that the use of exogenous calcium and vitamin D may have influenced these values. These data are shown in table 39 and figure 53.

Table 39. Comparison of mean 25 Hydroxyvitamin D levels (ng/ml) according to AIA versus non-AIA sufferers. Mean difference tested for significance with the t-test.

	AIA		No AIA		Comparison	
Month	n	Mean (SD)	n	Mean (SD)	Mean difference (95% CI)	p-value
0	32	19.3 (14.4)	15	24.9 (10.3)	-5.6 (-13.9, 2.8)	0.186
3	31	19.0 (11.2)	13	24.5 (6.8)	-5.5 (-12.3,1.2)	0.107
6	30	22.1 (11.3)	14	26.2 (8.2)	-4.1 (-10.9,2.7)	0.228
12	32	22.5 (10.8)	15	29.2 (9.4)	-6.7 (-13.2, 0.2)	0.044

Figure 53. Mean 25 Hydroxyvitamin D levels with 95% Confidence Intervals (ng/ml) for AIA and Non AIA over the study period



9.4. C – REACTIVE PROTEIN

9.4.1. Overall Study Population

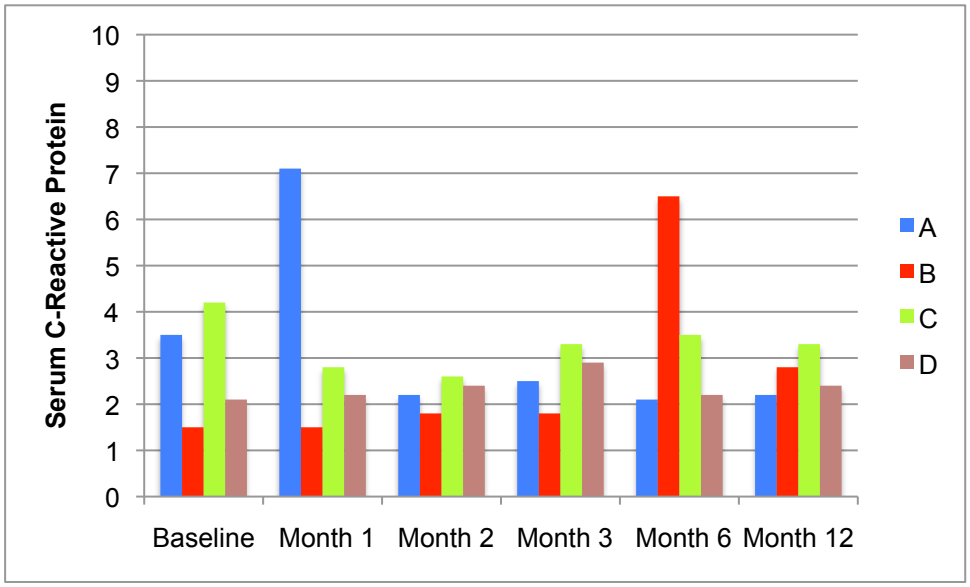
CRP was tested in all patients as part of the DAS 28 – CRP assessment. It was therefore assessed at baseline, month 1, month 2, month 3, month 6 and month 12. At baseline, 76/77 (99%) of samples were available for testing. At 12 months, 73/77 (95%) were still available for testing. The overall population mean CRP level at baseline was low at 3.2. Across the cohorts, baseline values were similar and low as shown in table 40.

Table 40. Baseline C-Reactive Protein level characteristics.

Variable	Timepoint	Scoring	Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
CRP	Baseline	N (%)	34 (100%)	12 (92.3%)	22 (100%)	8 (100%)	76 (98.7%)
		Mean (SD)	3.5 (4.4)	1.5 (1.3)	4.2 (6.2)	2.1 (2)	3.2 (4.6)
		Median (IQR)	1.8 (0.7 to 4.7)	1.1 (0.5 to 2.1)	2.3 (1 to 3.5)	1.3 (0.9 to 3.1)	1.7 (0.7 to 3.7)
		Min to Max	0.3 to 21.1	0.3 to 4	0.3 to 23.3	0.3 to 5.8	0.3 to 23.3

Over the study period, there was little change in CRP levels for all the cohorts as shown in figure 54. On the whole, levels stayed well within the normal laboratory reference range. Although two peaks are seen for cohort A at month 1 and Cohort B at month 6, the standard error was wide at 21 and 14 respectively. Median values were low throughout.

Figure 54. Change in mean C-Reactive Protein over time for cohorts A-D



9.4.2. Comparison of CRP according to Aromatase Inhibitor Arthralgia

When cohorts A and B were combined and evaluated according to the presence of joint symptoms, it was clear that CRP values were highly skewed, as shown in figure 55. Therefore, to avoid giving undue weight to the high values and produce a more symmetrical distribution, a logarithmic transformation was applied prior to analysis.

Figure 55. Distribution of individual CRP values for cohorts A and B combined for both unadjusted (left) and logarithmic (right)

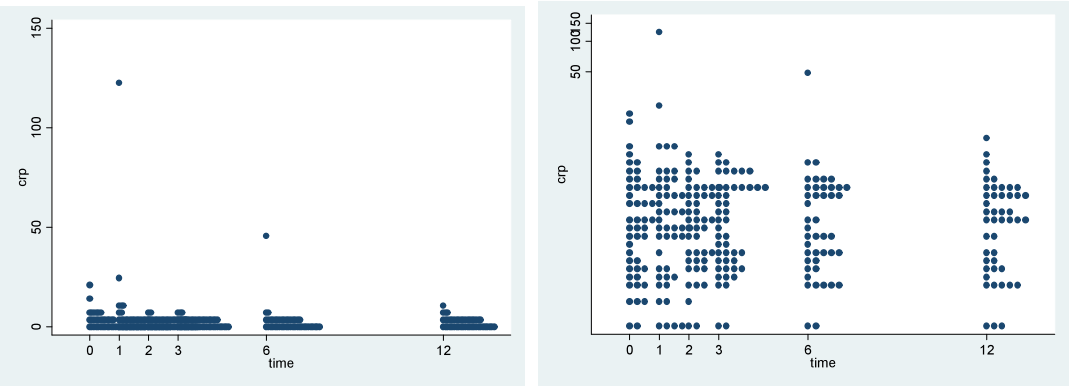


Table 41 shows the mean (SD) CRP values between AIA and non-AIA sufferers for both unadjusted and logarithmic values. For the comparison of values, only the logarithmic levels were taken and thus giving differences in geometric mean ratios. These data therefore confirm that no significant difference in CRP was seen according to the presence of AIA. Log transforming of the data suggested mean values if anything were slightly lower for patients developing AIA adding weight to the hypothesis that AIA is not associated with systemic inflammatory features. This is also shown graphically for both analysis types in figures 56 and 57 below.

Table 41. Comparison of CRP levels according to AIA and non-AIA with log transforming of the data. P values derived from the t test using the log transformed data.

	AIA		No AIA		Comparison	
Month	n	Mean (SD)	n	Mean (SD)	Ratio of means (95% CI)	p-value
0 Original Log	32	2.5 (3.0) 0.29 (1.19)	14	4.0 (5.4) 0.77 (1.12)	0.62 (0.29,1.32)	0.207
1 Original Log	31	6.5 (21.6) 0.47 (1.49)	15	3.6 (6.2) 0.57 (1.16)	0.91 (0.38,2.20)	0.834
2 Original Log	29	2.1 (1.8) 0.31 (1.02)	14	2.2 (1.7) 0.50 (0.87)	0.83 (0.43,1.57)	0.551
3 Original Log	32	2.0 (1.7) 0.30 (0.99)	14	2.9 (2.3) 0.65 (1.05)	0.70 (0.37,1.35)	0.282
6 Original Log	30	3.3 (8.0) 0.32 (1.18)	14	2.6 (1.9) 0.59 (0.97)	0.76 (0.37,1.59)	0.463
12 Original Log	32	2.3 (2.2) 0.40 (1.03)	14	2.4 (2.1) 0.36 (1.17)	1.04 (0.52,2.09)	0.902

Figure 56. Change of mean CRP levels over time for AIA and non-AIA sufferers

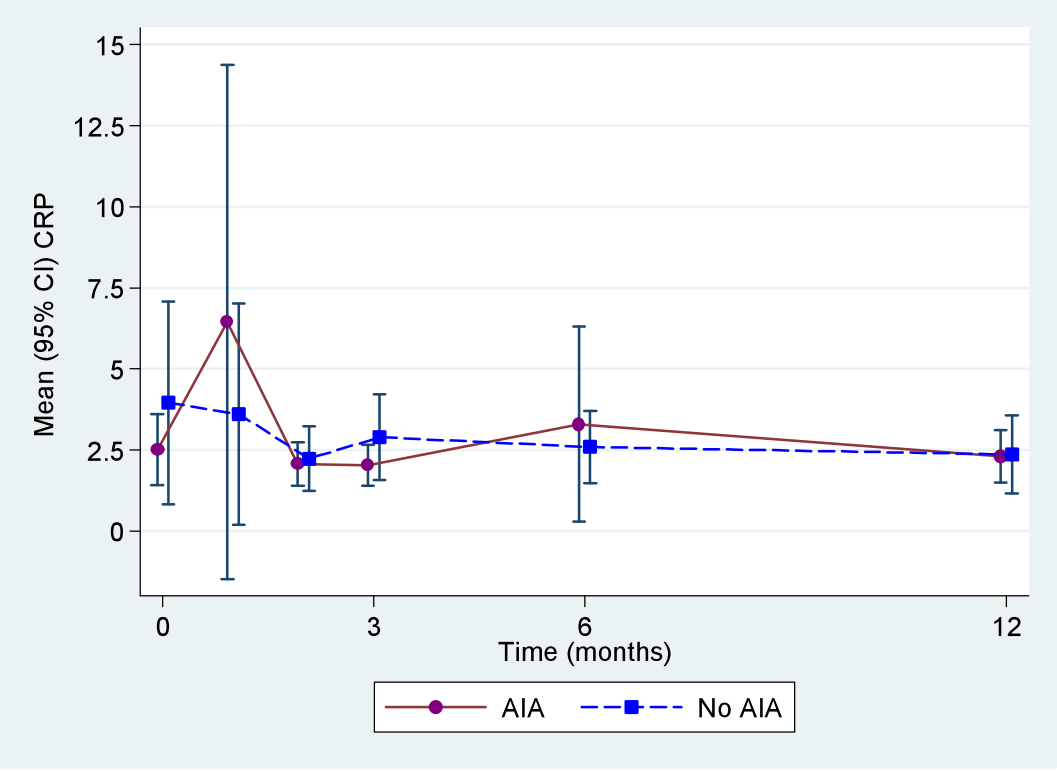
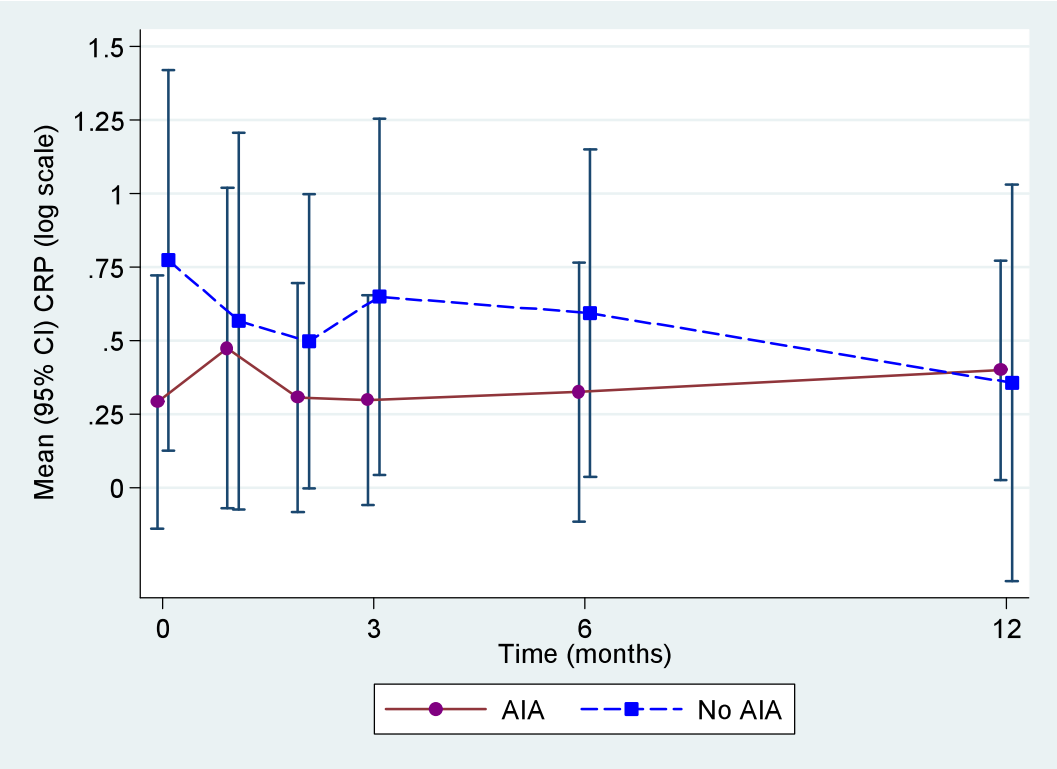


Figure 57. Change of mean log transformed CRP levels over time for AIA and non-AIA sufferers



10. THE ARIAD STUDY - RESULTS OF RADIOLOGICAL INVESTIGATIONS

10.1. INTRODUCTION

Given the unknown aetiological mechanism behind aromatase inhibitor induced arthralgia (AIA), it was felt that a variety of musculoskeletal radiological investigations may provide insight.

At the time of study design, there were only 2 radiological studies that had provided insight into the aetiological mechanism of this syndrome. The first by Morales et al (Morales et al 2008, Morales et al 2007), had demonstrated intra-articular and tenosynovial changes on hand and wrist MRI scanning. These changes had also been correlated with grip strength. No other study had reported or indeed investigated these findings.

The second radiological study that had given insight into the pathological mechanism behind AIA, had been presented in abstract only. Alegre-Sancho et al showed that in 7 patients referred to rheumatology for investigation of AIA, all had a clinical diagnosis of bilateral trigger thumb (Alegre-Sancho et al. 2008). 6/7 had carpal tunnel syndrome and 2/7 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.

Since then, others studies have been set up to investigate this further with both ultrasound and MRI imaging.

In the ARIAD study, ultrasound, which was performed on all patients, was specifically looking for synovitis, osteoarthritis, tenosynovitis and median nerve swelling. MRI imaging, which was performed on selected patients in cohorts A and D, assessed these with the addition of bone erosions and oedema, though not the median nerve. Specific scoring systems were used to aid statistical comparison, as have already been described in the methods chapter.

The more novel investigation here was hand bone mineral density, which no arthralgia study had previously performed. In rheumatoid arthritis, periarticular osteoporosis has been shown to occur. An association with lowering of hand bone mineral density has been demonstrated in such a condition. Hand DXA was performed at baseline and 12 months as previously described.

10.2. HAND BONE MINERAL DENSITY (BMD)

10.2.1. Baseline Values

Of the 77 patients entering into the study, all (100%) had their baseline DXA scan. There were no significant differences in baseline hand BMD between all cohorts (global test $F(3,73)=0.25$, $p=0.86$). All groups had mean values of between 0.36 and 0.37g/cm^2. The baseline group statistics are shown in table 42.

Table 42. Baseline hand BMD characteristics

Variable	Timepoint	Scoring	Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
DXA Average BMD	Baseline	N (%)	34 (100%)	13 (100%)	22 (100%)	8 (100%)	77 (100%)
		Mean (SD)	0.371 (0.059)	0.376 (0.038)	0.361 (0.054)	0.365 (0.038)	0.368 (0.052)
		Median (IQR)	0.365 (0.327 to 0.418)	0.380 (0.344 to 0.384)	0.359 (0.313 to 0.397)	0. 359 (0.349 to 0.394)	0.363 (0.331 to 0.411)
		Min to Max	0.248 to 0.469	0.317 to 0.440	0.293 to 0.498	0.298 to 0.416	0.248 to 0.498

10.2.2. Change in hand BMD over time

71 out 77 patients had 12 month DXA scans. Mean percentage change in hand BMD is indicated in table 43. All 4 cohorts had an overall reduction. With increasing bone age, bone density falls by 1% per year (Reid DM 2008). Percentage reductions in cohorts A-D were -2.5% (range -9.4 to +3.8), -3.6%

(range -5.8 to -1.4), -0.3% (range -1.7 to +1.1) and -2.1% (range -3.3 to -1.2) respectively.

When compared with tamoxifen controls, there was a significant reduction in hand BMD for groups A ($p=0.004$) and B ($p<0.001$) (table 44). The difference may have been enhanced because of the bone protective effect of tamoxifen.

Figure 58. Mean percentage change in Hand BMD for cohorts A-D

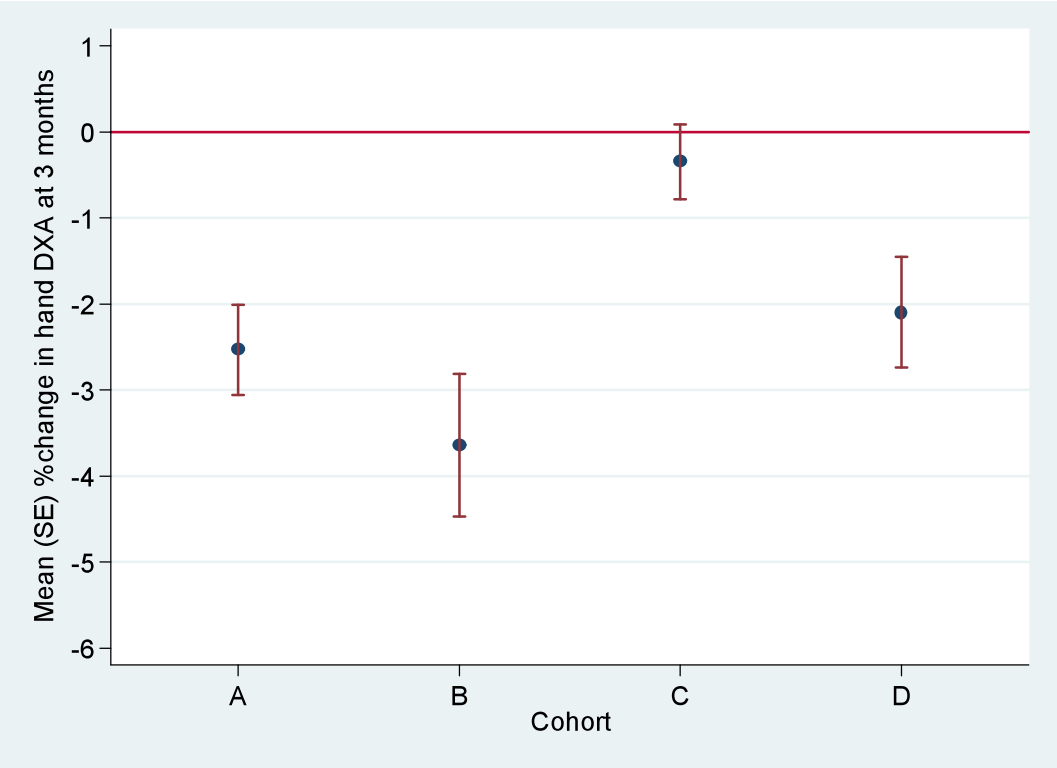


Table 43. Percentage change of hand BMD at 12 months

		A	B	C	D	Overall
Percentage DXA Average BMD	N (%)	32 (97%)	12 (100%)	21 (100%)	6 (100%)	71 (98.6%)
	Mean (SD)	-2.5 (3)	-3.6 (2.9)	-0.3 (2)	-2.1 (1.6)	-2 (2.8)
	Median (IQR)	-2.5 (-4.3 to -0.4)	-2.9 (-5.8 to -1.4)	-0.2 (-1.7 to 1.1)	-2.1 (-3.3 to -1.2)	-2 (-3.8 to 0)
	Min to Max	-9.4 to 3.8	-9.7 to -0.3	-4.2 to 3.8	-4 to 0.2	-9.7 to 3.8

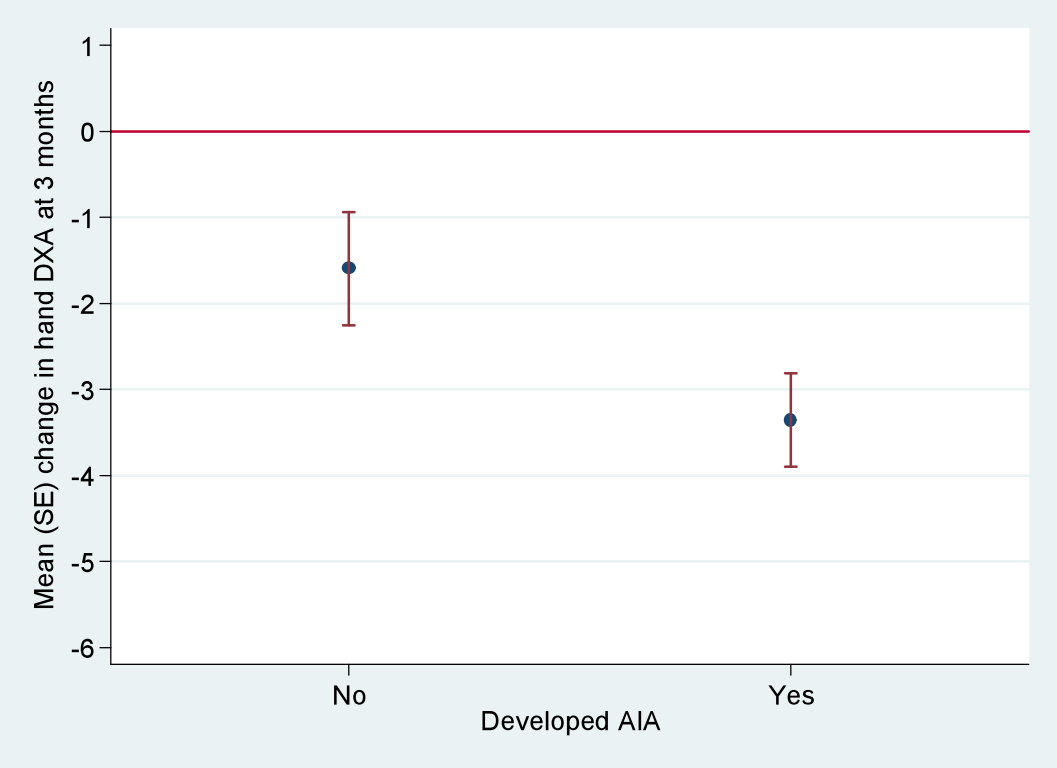
Table 44. Statistical group comparisons for change in hand BMD at 12 months

Comparison of DXA change at 12 months	**p value** (from post-ANOVA linear contrast)
1. Upfront AI (A) v No treatment (D)	0.706
2. Switch AI (B) v No treatment (D)	0.238
3. Upfront AI (A) v Tamoxifen (C)	0.004
4. Switch AI (B) v Tamoxifen (C)	<0.001
5. Upfront AI (A) v Switch AI (B)	0.212
6. AI (A/B) v Tam/no treatment (C/D)	0.015

10.2.3. Change in hand BMD for those developing AIA

For those patients on an aromatase inhibitor who developed the AIA syndrome, the changes in hand BMD are summarised in Figure 59. These data show that for women on aromatase inhibitors, loss of hand bone density may be associated with the development of the AIA syndrome. This was not statistically significant, but the p value approached conventional levels of significance (p=0.069).

Figure 59. Percentage change of Hand BMD for those developing AIA



Test of AIA v non-AIA : p=0.069 (two sample t-test)

10.3. HAND ULTRASOUND

Data was available for all 77 (100%) patients at baseline, for all the joint and tendon evaluations. The scan was repeated at 3 months. At this point, 73 (94.8%) patients had this form of imaging. In total, 150 scans were used for analysis. This is summarised in table 45 below.

Table 45. Numbers (and percentages) of patients undergoing ultrasound assessment at baseline and 3 months

	A	B	C	D	Total
Baseline	34 (100%)	13 (100%)	22 (100%)	8 (100%)	77 (100%)
Month 3	33 (97.1%)	11 (84.6%)	22 (100%)	7 (87.5%)	73 (94.8%)

10.3.1. Flexor Tenosynovitis

At baseline, the numbers of patients having ultrasound evidence of flexor tenosynovitis was significant. Overall 30/77 (39%) patients had evidence of any grade abnormality at this time point. For each patient, scores were totalled for the ten digits, giving a maximum possible score of 30 (10 digits with maximum grade of 3) for grey scale and power Doppler. Therefore the maximum score was 60 per patient. In reality, grades of up to 2 were seen, but not grade 3. Therefore scores have been divided according to the number of patients with a total score greater than or equal to 3. So for the whole population, 11/77 (14%) patients had a baseline score ≥3. The scores for the four cohorts are shown in table 46 below.

Table 46. Summary of baseline tenosynovitis scores for cohorts A-D

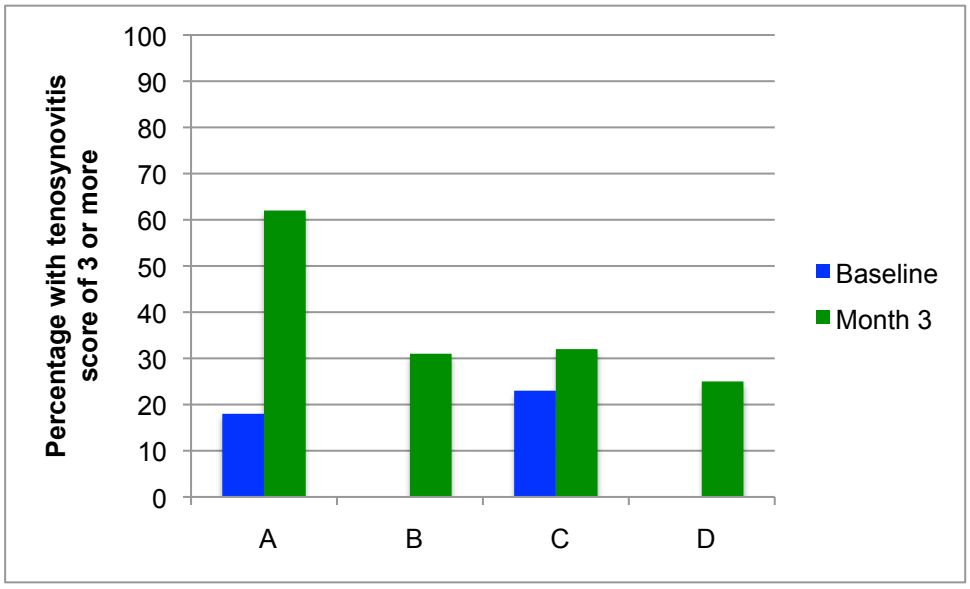
Score	A n=34	B n=13	C n=22	D n=8	Total n=77
<3	27 (80%)	11 (84%)	17 (78%)	7 (89%)	62 (81%)
≥3	6 (18%)	0	5 (23%)	0	11 (14%)
Unclassified	1 (3%)	2 (15%)	0	1 (13%)	4 (5%)

At the 3 month time point, the overall number with any grade of abnormality had increased to 54/77 (70%). The number with a total score ≥3 had also increased significantly to 34/77 (44%). The totals here are given out of 77 so as not to overestimate any effect. The summary for the individual cohorts is shown in table 47 below. All groups have shown an increase the proportion with scores above or equal to 3. However this effect appeared more marked in the two AI groups. For those on an upfront AI, the proportion went up from 18% to 62% at 3 months. For those who had switched to an AI, there were no scores above or equal to three at baseline, but 4 (31%) changed to meet this criterion at 3 months (figure 60).

Table 47. Summary of Month 3 tenosynovitis scores for cohorts A-D

Score	A n=34	B n=13	C n=22	D n=8	Total n=77
<3	12 (35%)	7 (54%)	15 (68%)	5 (63%)	39 (51%)
≥3	21 (62%)	4 (31%)	7 (32%)	2 (25%)	34 (44%)
Unclassified	1 (3%)	2 (15%)	0	1 (13%)	4 (5%)

Figure 60. Percentage of patients with an ultrasound tenosynovitis score of ≥3 at baseline and 3 months.



A score of 3 was used to define the group of patients with what may represent a more clinically meaningful score. When the scores were analysed according to any change, it was the upfront AI group which contained the highest proportion with worsening scores. Sixty five percent in this group had evidence of deterioration. Of note, significant numbers in groups B, C and D also had worsening scores (table 48).

Table 48. Change in tenosynovitis score at 3 month ultrasound by cohort.

Change of score	A n=34	B n=13	C n=22	D n=8
Improved	4 (12%)	2 (15%)	5 (23%)	1 (13%)
Unchanged	7 (21%)	3 (23%)	8 (36%)	2 (25%)
Worsened	22 (65%)	6 (46%)	9 (41%)	4 (50%)
Unclassified	1 (3%)	2 (15%)	0 (0%)	1 (13%)

Mean and median scores were also analysed. The distribution was heavily skewed as the majority of scores were zero, so this was less helpful. Median ultrasound grey scale scores at baseline (and interquartile range) for A-D respectively were: 0 (0-2), 1 (0-1), 0 (0-1), 0 (0-0.5). At 3 months, the score were little different, except for in group A: 4 (1-5), 1 (0-3), 1 (0-3), 1 (0-3). Power Doppler scores were mostly zero in the whole population, both for baseline and 3 months. Hence this method of evaluation was largely non-contributory.

Table 49 shows the statistical group comparisons using the Mann Whitney U test for non-parametric data. There was a statistically significant difference between women receiving upfront AI as compared to tamoxifen (p=0.029) and also for the whole AI group (A and B) compared the tamoxifen /control (C and D) (p=0.033). The same was not seen for the switch AI group, though numbers were smaller in this group. This adds weight to the hypothesis that AI usage is associated with ultrasound determined tenosynovial changes.

Table 49. Statistical group comparisons for ultrasound tenosynovitis. P values derived from Mann Whitney U test

Comparisons	P
1. Upfront AI (A) v No treatment (D)	0.144
2. Switch AI (B) v No treatment (D)	0.746
3. Upfront AI (A) v Tamoxifen (C)	0.029
4. Switch AI (B) v Tamoxifen (C)	0.506
5. Upfront AI (A) v Switch AI (B)	0.291
6. AI (A/B) v Tam/no treatment (C/D)	0.033

However, table 50 shows tenosynovitis scores when subdivided according to the presence or absence of AIA for women receiving AIs. This did not confirm a statistically significant difference. In fact it did show numerically more patients showing evidence of worsening tenosynovial score in women with features of AIA (69%) versus non-AIA (40%).

Table 50. Change in ultrasound wrist tenosynovitis score according to AIA and Non-AIA subdivision. P value derived from Mann Whitney U test

Flexor tenosynovitis - month 3	**No AIA (N=15)**	**Developed AIA (N=32)**
Reduced	2 (13%)	4 (13%)
Unchanged	4 (27%)	6 (19%)
Increased	6 (40%)	22 (69%)
Missing	3 (20%)	0
AIA v non-AIA	p=0.215	

10.3.2. Synovitis

10.3.2.1. Wrist Synovitis

Wrist synovitis was scored at each of 3 joints per wrist, with a maximum score of 3 per joint. The maximum overall score was therefore 18 for grey scale and 18 for power Doppler. These were combined to a total out of 36. However, most of the power Doppler scores were zero. It was noted that the number of patients with baseline grey scale abnormalities was significant in this postmenopausal population. The numbers of patients in the whole study cohort scoring 3 or above was 18/77 (23%). For each cohort, the numbers with these scores were as follows: A 21%, B 23%, C 32%, D 13%. The baseline data for cohorts A-D are summarised in table 51.

Table 51. Summary of Baseline wrist synovitis scores for cohorts A-D

Score	A n=34	B n=13	C n=22	D n=8	Total n=77
<3	26 (76%)	8 (62%)	13 (64%)	6 (75%)	53 (69%)
≥3	7 (21%)	3 (23%)	7 (32%)	1 (13%)	18 (23%)
Unclassified	1 (3%)	2 (15%)	2 (15%)	1 (13%)	6 (8%)

After 3 months of follow up, there was very little change in the proportions having wrist synovitis scores of three or more. The overall population with this score was 22/77 (29%). For each cohort the scores were as follows: A 29%, B 23%, C 41%, D 0. The summary scores at 3 months are shown in table 52 and figure 61. Of note, mean and median scores were 2 or less.

Table 52. Summary of Month 3 wrist synovitis scores for cohorts A-D

Score	A n=34	B n=13	C n=22	D n=8	Total n=77
<3	23 (68%)	8 (62%)	13 (64%)	7 (88%)	51 (66%)
≥3	10 (29%)	3 (23%)	9 (41%)	0	22 (29%)
Unclassified	1 (3%)	2 (15%)	0	1 (13%)	4 (5%)

Figure 61. Percentage of patients with an ultrasound wrist synovitis score of ≥3 at baseline and 3 months.

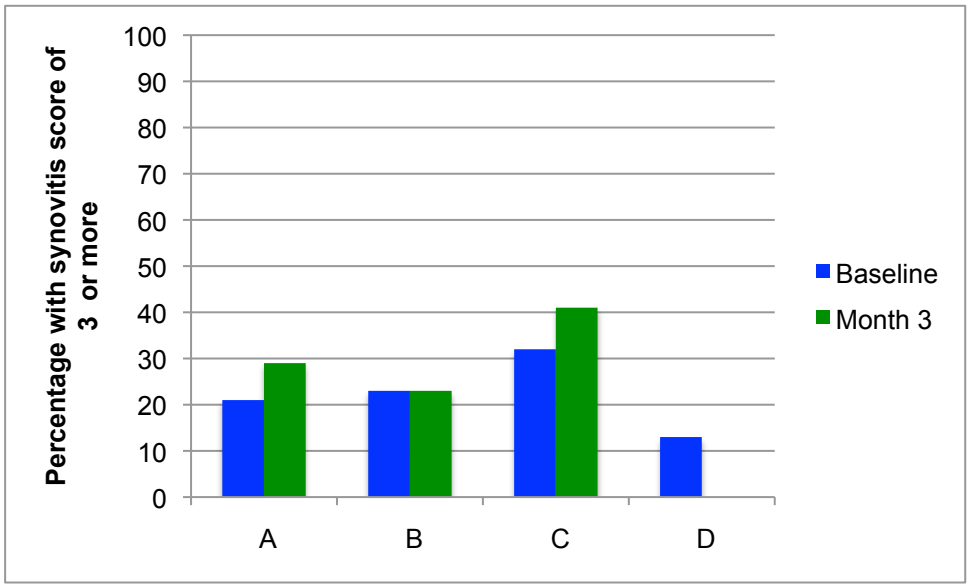


Table 53 shows the data for the proportion in each group where there was any change in overall wrist synovitis score from baseline to 3 months. There was no clear signal here of any significant differences between the groups.

Table 53. Change in overall wrist synovitis score at 3 month ultrasound by cohort

Change	A n=34	B n=13	C n=22	D n=8
Reduced	13 (38%)	1 (8%)	7 (32%)	1 (13%)
Unchanged	6 (18%)	7 (54%)	7 (32%)	2 (25%)
Increased	14 (41%)	3 (23%)	8 (36%)	4 (50%)
Missing	1 (3%)	2 (15%)	0 (0%)	1 (13%)

Table 54 shows the group statistical comparisons using the Mann Whitney U test. There was no statistically significant association between wrist synovitis and endocrine therapy received.

Table 54. Statistical group comparisons for ultrasound wrist synovitis. P values derived from Mann Whitney U test

Comparisons	P
1. Upfront AI (A) v No treatment (D)	0.678
2. Switch AI (B) v No treatment (D)	0.354
3. Upfront AI (A) v Tamoxifen (C)	0.814
4. Switch AI (B) v Tamoxifen (C)	0.780
5. Upfront AI (A) v Switch AI (B)	0.825
6. AI (A/B) v Tam/no treatment (C/D)	1.000

A similar finding of no association was also seen when AIA and Non-AIA sufferers were compared (table 55).

Table 55. Change in ultrasound wrist synovitis score according to AIA and Non-AIA subdivision. P value derived from Mann Whitney U test

Overall wrist synovitis - month 3	**No AIA (N=15)**	**AIA (N=32)**
Reduced	4 (27%)	10 (31%)
Unchanged	4 (27%)	9 (28%)
Increased	4 (27%)	13 (41%)
Missing	3 (20%)	0
AIA v non-AIA	p=0.925	

10.3.2.2. PIP (proximal interphalangeal joint) / MCP (metacarpophalangeal joint) Synovitis

Small joint synovitis was scored as above at each of 10 joints per hand, with a maximum score of 3 per joint. The maximum overall score was therefore 60 per patient, each for grey scale and power Doppler. Therefore the overall maximum score was 120. The numbers of patients in the whole study cohort scoring 3 or above was 11/77 (14%). This was relatively lower than the corresponding values for wrist synovitis. For each cohort, the numbers with these scores were as follows: A 21%, B 0%, C 18%, D 0. The baseline data for cohorts A-D are summarised in table 56. Mean and median scores for each group for both baseline and month 3 were all equal to 2 or less.

Table 56. Summary of Baseline PIP/MCP synovitis scores for cohorts A-D

Score	A n=34	B n=13	C n=22	D n=8	Total n=77
<3	26 (76%)	11 (85%)	18 (82%)	7 (88%)	62 (81%)
≥3	7 (21%)	0	4 (18%)	0	11 (14%)
Unclassified	1 (3%)	2 (15%)	0	1 (13%)	4 (5%)

After 3 months of follow up, there was no real change in the proportions having PIP/MCP synovitis scores of three or more. The overall population with this score was 10/77 (13%). For each cohort the scores were as follows: A 24%, B 0%, C 5%, D 13%. Overall these scores remained low and unchanged over the 3 month study period. The summary scores at 3 months are shown in table 57 and figure 62.

Table 57. Summary of Month 3 PIP/MCP synovitis scores for cohorts A-D

Score	A n=34	B n=13	C n=22	D n=8	Total n=77
<3	25 (74%)	11 (85%)	21 (95%)	6 (75%)	63 (82%)
≥3	8 (24%)	0	1 (5%)	1 (13%)	10 (13%)
Unclassified	1 (3%)	2 (15%)	0	1 (13%)	4 (5%)

Figure 62. Percentage of patients with an ultrasound PIP/MCP synovitis score of ≥3 at baseline and 3 months.

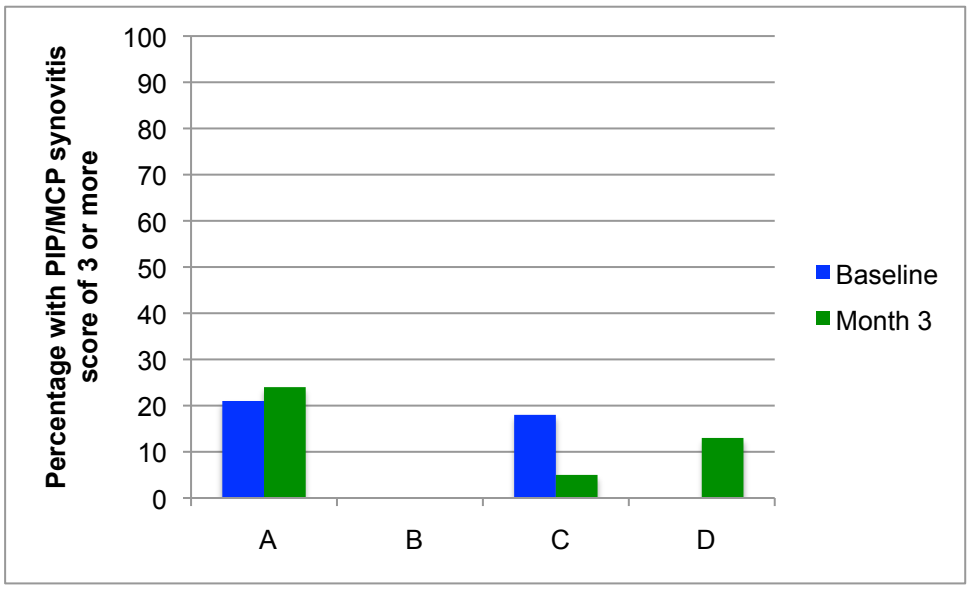


Table 58 shows the data for the proportion in each group where there was any change in overall wrist synovitis score from baseline to 3 months. Again, like with wrist synovitis, there was no evidence here of any significant differences between the groups.

Table 58. Change in overall PIP/MCP synovitis score at 3 month ultrasound by cohort

Change	A n=34	B n=13	C n=22	D n=8
Reduced	8 (24%)	0 (0%)	5 (23%)	0(0%)
Unchanged	15 (44%)	10 (77%)	14 (64%)	5(63%)
Increased	10 (29%)	1 (8%)	3 (14%)	2(25%)
Missing	1 (3%)	2 (15%)	0 (0%)	1(13%)

Table 59 shows the group comparisons for this assessment. There was no statistically significant association between type of endocrine therapy received and MCP/PIP synovitis. In addition, when subdivided according to AIA or not, there was no statistically significant difference noted (table 60).

Table 59. Statistical group comparisons for ultrasound MCP/PIP synovitis. P values derived from Mann Whitney U test

Comparisons	P
1. Upfront AI (A) v No treatment (D)	0.350
2. Switch AI (B) v No treatment (D)	0.236
3. Upfront AI (A) v Tamoxifen (C)	0.570
4. Switch AI (B) v Tamoxifen (C)	0.355
5. Upfront AI (A) v Switch AI (B)	0.976
6. AI (A/B) v Tam/no treatment (C/D)	0.833

Table 60. Change in ultrasound MCP/PIP synovitis score according to AIA and Non-AIA subdivision. P value derived from Mann Whitney U test

Overall MCP PIP - month 3	No AIA (N=15)	AIA (N=32)
Reduced	0	8 (25%)
Unchanged	9 (60%)	16 (50%)
Increased	3 (20%)	8 (25%)
Missing	3 (20%)	0
AIA v non-AIA	p=0.327	

10.3.3. Median Nerve

10.3.3.1. Overall study population

Median nerve cross-sectional area was measured as an indicator of carpal tunnel syndrome. A larger area, indicating swelling of the nerve, has been correlated with the syndrome. Thus measurements were taken of both sides and an average recorded in cm^2.

At baseline, the mean cross-sectional area values in cm^2 were as follows: A (0.11), B (0.11), C (0.11), D (0.12). Table 61 shows the change from baseline to month 3. Overall the changes were small. Figure 63 shows the mean percentage change in cross-sectional area at 3 months. Again these values were small with standard errors that crossed zero. Only group B had a modest increase of just under 2%. The groupwise comparisons showed that none of these changes were statistically significant (table 62).

Table 61. Baseline and Month 3 characteristics for Median Nerve cross-sectional area (cm^2)

Timepoint	Scoring	Cohort A (N=34)	Cohort B (N=13)	Cohort C (N=22)	Cohort D (N=8)	Total (N=77)
Baseline	N (%)	34 (100%)	12 (92.3%)	22 (100%)	8 (100%)	76 (98.7%)
	Mean (SD)	0.11 (0.02)	0.11 (0.03)	0.11 (0.03)	0.12 (0.03)	0.11 (0.03)
	Median (IQR)	0.11 (0.10 to 0.13)	0.11 (0.09 to 0.12)	0.11 (0.09 to 0.13)	0.11 (0.09 to 0.14)	0.11 (0.10 to 0.13)
	Min to Max	0.06 to 0.17	0.06 to 0.19	0.08 to 0.16	0.09 to 0.16	0.06 to 0.19
Month 3	N (%)	33 (97.1%)	11 (84.6%)	22 (100%)	7 (87.5%)	73 (94.8%)
	Mean (SD)	0.12 (0.03)	0.11 (0.02)	0.12 (0.04)	0.12 (0.03)	0.11 (0.03)
	Median (IQR)	0.11 (0.09 to 0.13)	0.11 (0.09 to 0.13)	0.11 (0.10 to 0.14)	0.11 (0.19 to 0.14)	0.11 (0.10 to 0.13)
	Min to Max	0.07 to 0.19	0.07 to 0.16	0.08 to 0.19	0.09 to 0.16	0.06 to 0.20

Figure 63. Mean percentage change in Median Nerve cross-sectional area at 3 months

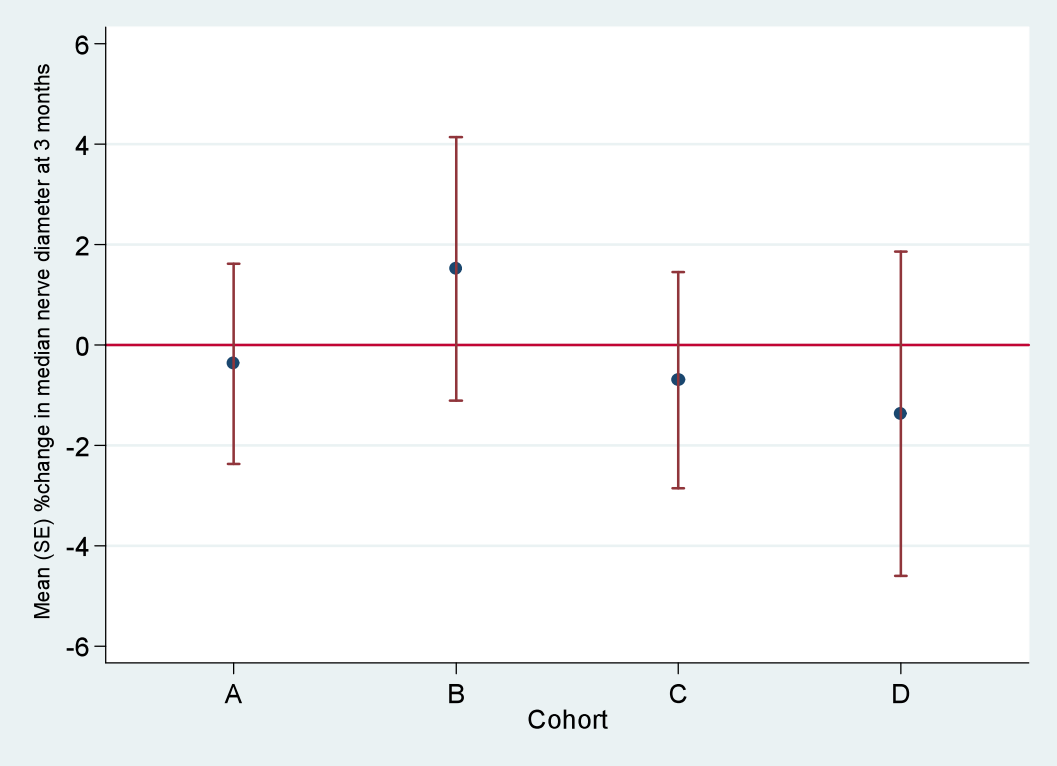


Table 62. Statistical group comparisons for percentage change in Median Nerve cross-sectional area at 3 months

Comparison of %median nerve change at 3 months	p value (post-ANOVA linear contrast)
1. Upfront AI (A) v No treatment (D)	0.733
2. Switch AI (B) v No treatment (D)	0.939
3. Upfront AI (A) v Tamoxifen (C)	0.796
4. Switch AI (B) v Tamoxifen (C)	0.931
5. Upfront AI (A) v Switch AI (B)	0.773
6. AI (A/B) v Tam/no treatment (C/D)	0.847

The data was also analysed for the number of patients that had a cross-sectional diameter of greater than or equal to 0.13cm^2. This value represents one that would be considered in keeping with moderate carpal tunnel syndrome. These data provide further evidence for a lack of change in median nerve diameter during the follow up of this study.

Table 63. Number (and percentage) of patients with a Median Nerve cross-sectional diameter of greater than or equal to 0.13cm^2

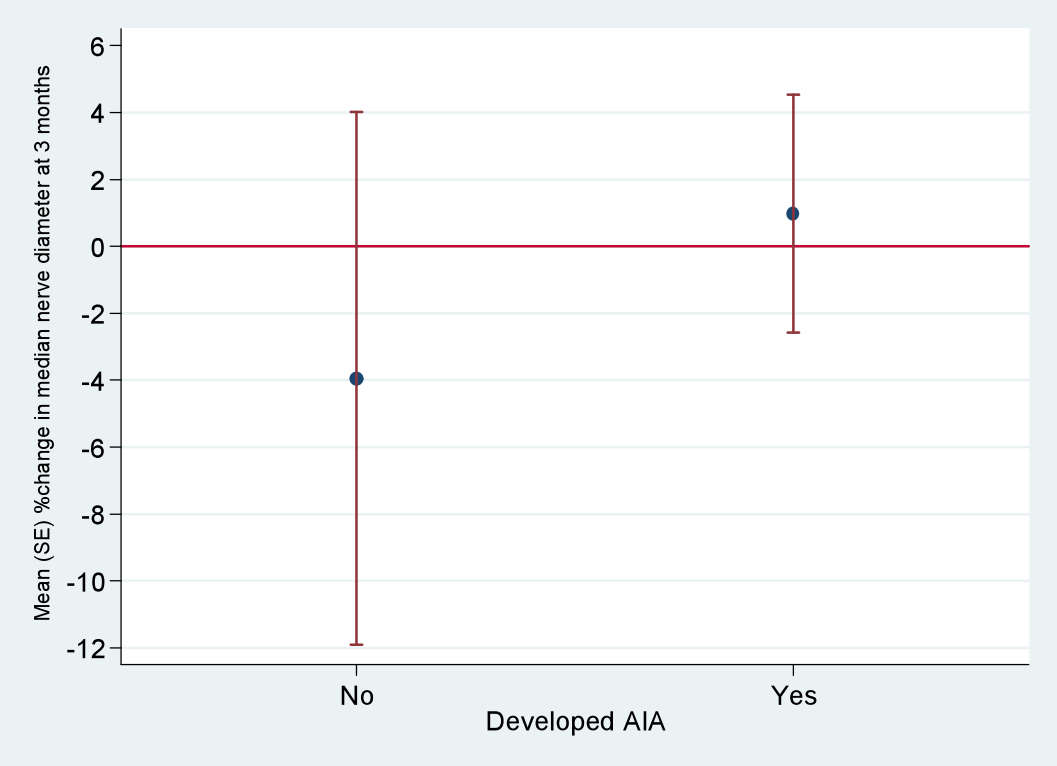
	A n=34	B n=13	C n=22	D n=8
Baseline	8 (24%)	2 (15%)	5 (22%)	3 (38%)
Month 3	6 (18%)	2 (15%)	5 (22%)	2 (25%)

Clinical carpal tunnel syndrome was defined as the presence of both positive Tinel's and Phalen's signs. At baseline, this was present in one patient in group D and stayed positive throughout the study. Three patients developed both positive signs: two in group A and one in group D. For those in group A the cross-sectional area went from 0.13cm^2 to 0.2cm^2 (60% increase) and 0.10cm^2 to 0.14cm^2 (33% increase). For the patient in group D who developed signs of CTS, diameters increased from 0.16cm^2 to 0.19cm^2 (23% increase).

10.3.3.2. Median Nerve according to AIA

The change in the characteristics of the Median Nerve were also evaluated for women developing aromatase inhibitor joint symptoms. Figure 64 shows the mean percentage change of the nerve area at 3 months for those developing AIA and the group that didn't. Statistical testing suggests no difference between these two groups (p=0.517).

Figure 64. Mean percentage change in Median Nerve cross-sectional area at 3 months for patients developing AIA



Test of AIA v non-AIA : p=0.517 (two sample t-test)

10.4. HAND MRI

In total, 36 patients had MRI imaging of hand and wrist contralateral to breast surgery. 33 were in cohort A (upfront AI) and 3 were in group D (no treatment controls). In A, a total of 30 baseline scans and 27 month 3 scans were suitable for analysis. In D, 3 baseline and 2 month 3 scans were available for analysis. In total 62 scans were available for analysis. As discussed earlier, there were two reporting radiologists who independently reported the scans.

10.4.1. Tenosynovitis

10.4.1.1. Cohort A and D

The scores for overall tenosynovitis are summarised in table 64. The maximum scores were for each hand were 30, as 10 tendons were evaluated for each hand (grade 0-3). As with the ultrasound, these scores were skewed to the majority of tendons having a score of zero. Nevertheless, the median scores did show a small increase from 1 to 1.8 for those on upfront AI. Little information could be gained from cohort D as only a few scans were performed and all scores were zero. The analysis was therefore more focussed on cohort A and the comparison of AIA versus non-AIA.

Table 64. Summary of characteristics for overall tenosynovitis at Baseline and Month 3

Timepoint	Scoring	Cohort A	Cohort D
Baseline	Mean (SD)	1.1 (1)	0
	Median (IQR)	1 (0.5 to 1.5)	0
	Min to Max	0 to 4	0
Month 3	Mean (SD)	2.2 (2)	0
	Median (IQR)	1.8 (0.5 to 2.5)	0
	Min to Max	0 to 8	0

10.4.1.2. Cohort A subdivided by AIA

The scores for MR tenosynovitis were also divided according to the development of clinical AIA. Table 65 below shows the summary scores for the two radiologists. Using the Mann Whitney U test, no difference in tenosynovitis scores was seen between those developing AIA versus non-AIA. The same was true for both radiologists. However, radiologist 1 scored far more patients having a worsening of MRI score (88% and 65%, No AIA vs AIA) than radiologist 2 (14% for AIA and non-AIA). For cohort A as a whole, there appeared to be more patients who had a deterioration in their score over the 3 months than an improvement, raising the possibility of an association.

Table 65. MRI tenosynovitis score according to AIA and radiologist

	No AIA (N=11)	**Developed AIA (N=23)**
Radiologist 1 (MRI)		
Overall tenosynovitis - month 3		
Change		
Reduced	0	3 (18%)
Unchanged	1 (13%)	3 (18%)
Increased	7 (88%)	11 (65%)
AIA v non-AIA	p=0.698	
Radiologist 2 (RAMRIS)		
Overall tenosynovitis - month 3		
Change		
Reduced	0	0
Unchanged	6 (86%)	12 (86%)
Increased	1 (14%)	2 (14%)
AIA v non-AIA	p=1.000	

10.4.2. Synovitis

10.4.2.1. Wrist synovitis (A and D)

The overall scores for wrist synovitis are summarised in table 66. At baseline, median values were low and similar for cohorts A and D with values of 8.5 and 7 respectively.

By 3 months, there was little change in median values with A and D scoring 10.5 and 6.5 respectively.

Table 66. . Summary of characteristics for overall wrist synovitis at Baseline and Month 3.

Timepoint	Scoring	Cohort A	Cohort D
Baseline	Mean (SD)	11.4 (7.5)	6.7 (4.5)
	Median (IQR)	8.5 (6 to 17)	7 (2 to 11)
	Min to Max	2 to 27.5	2 to 11
Month 3	Mean (SD)	13.3 (7.9)	6.5 (4.9)
	Median (IQR)	10.5 (7 to 19)	6.5 (3 to 10)
	Min to Max	2 to 29	3 to 10

10.4.2.2. Wrist Synovitis (Cohort A according to AIA)

The results here were similar to the tenosynovitis data. Both radiologists scored no difference between those developing AIA or not. Again radiologist 1 scored a high proportion with worsening scores (75% and 84%). Radiologist 2 scored a lower proportion having deteriorating synovitis scores (33% and 32%). Nevertheless, there were significant number of patients overall who had deteriorating wrist synovitis scores over the 3 month study period.

Table 67. MRI wrist synovitis score according to AIA and radiologist

	No AIA (N=11)	Developed AIA (N=23)
Radiologist 1 (MRI)		
Overall wrist synovitis - month 3		
Change		
Reduced	1 (13%)	2 (11%)
Unchanged	1 (13%)	1 (5%)
Increased	6 (75%)	16 (84%)
AIA v non-AIA	p=0.686	
Radiologist 2 (RAMRIS)		
Overall wrist synovitis - month 3		
Change		
Reduced	4 (44%)	5 (26%)
Unchanged	2 (22%)	8 (42%)
Increased	3 (33%)	6 (32%)
AIA v non-AIA	p=0.666	

10.4.2.3. Metacarpal synovitis (A and D)

Overall metacarpal synovitis is shown in table 68. At baseline, median scores were 1.5 (A) and 0 (D). By month 3, these scores were 2.5 (A) and 0.5 (D).

Table 68. Summary of characteristics for overall metacarpal synovitis at Baseline and Month 3

Timepoint	Scoring	Cohort A (N=34)	Cohort D (N=8)
Baseline	Mean (SD)	2 (2.3)	0.3 (0.6)
	Median (IQR)	1.5 (0 to 2.5)	0 (0 to 1)
	Min to Max	0 to 8.5	0 to 1
Month 3	Mean (SD)	2.7 (2.6)	0.5 (0.7)
	Median (IQR)	2.5 (0.5 to 3.5)	0.5 (0 to 1)
	Min to Max	0 to 10	0 to 1

10.4.2.4. MCP Synovitis (Cohort A according to AIA)

Synovitis scores of the metacarpophalangeal joints for cohort A divided by AIA are shown in table 69. For radiologist 1, there were no differences between scores according to the presence of AIA. For radiologist 2, there was a significant difference with worsening scores seen in the non-AIA population as compared to the AIA population - the opposite of what one may expect. Overall, significant numbers of patients appeared to have deteriorating scores over the 3 months, whether or not they developed the clinical syndrome (table 69).

Table 69. MRI MCP synovitis score according to AIA and radiologist

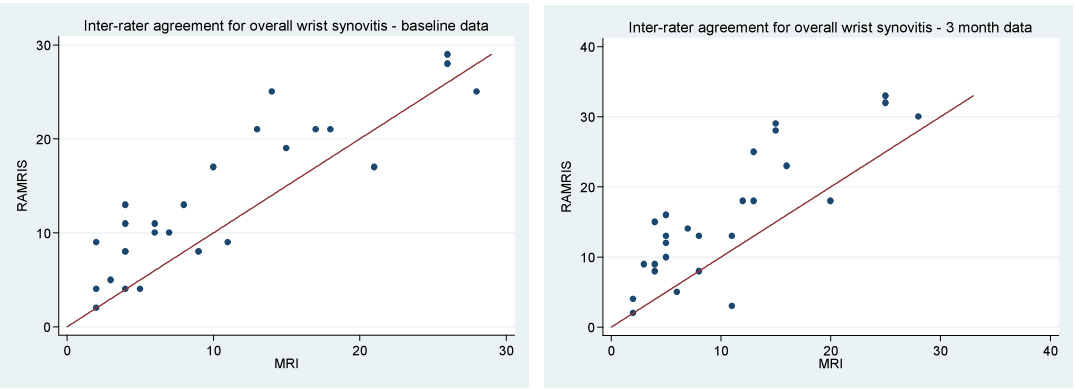
	No AIA (N=11)	Developed AIA (N=23)
Radiologist 1 (MRI)		
Overall MCP synovitis - month 3		
Change		
Reduced	1 (14%)	1 (5%)
Unchanged	3 (43%)	8 (42%)
Increased	3 (43%)	10 (53%)
AIA v non-AIA	p=0.807	
Radiologist 2 (RAMRIS)		
Overall MCP synovitis - month 3		
Change		
Reduced	0	3 (16%)
Unchanged	5 (55%)	15 (79%)
Increased	4 (44%)	1 (5%)
AIA v non-AIA	p=0.016	

10.4.3. Agreement between Radiologists

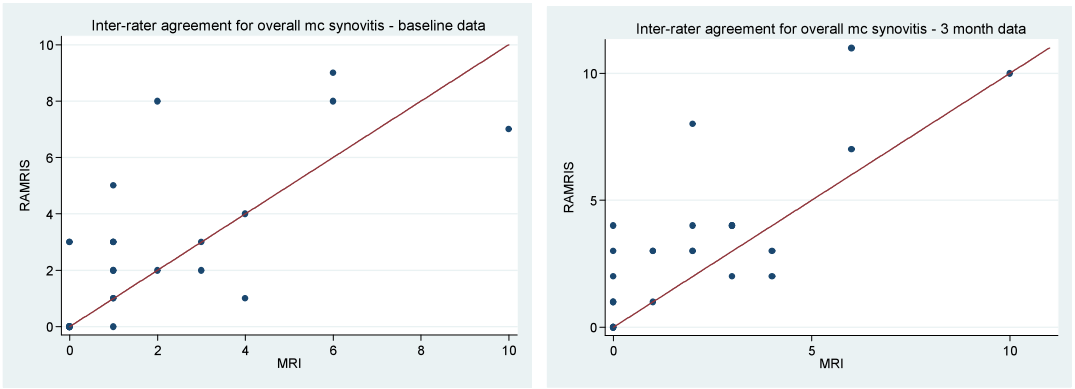
As shown above, there was a degree of disagreement between radiologists. This was examined further by analysing the scores with the use of scatter plot diagrams (figure 65). Radiologist 1 (MRI) and radiologist 2 (RAMRIS) seemed to have the closest agreement in relation to wrist synovits. This was less clear for MCP synovitis and tenosynovitis scores.

Figure 65. Scatter plot diagrams for all MRI scores at baseline and at 3 months; (A) Wrist Synovitis, (B) MCP Synovitis, (C) Tenosynovitis

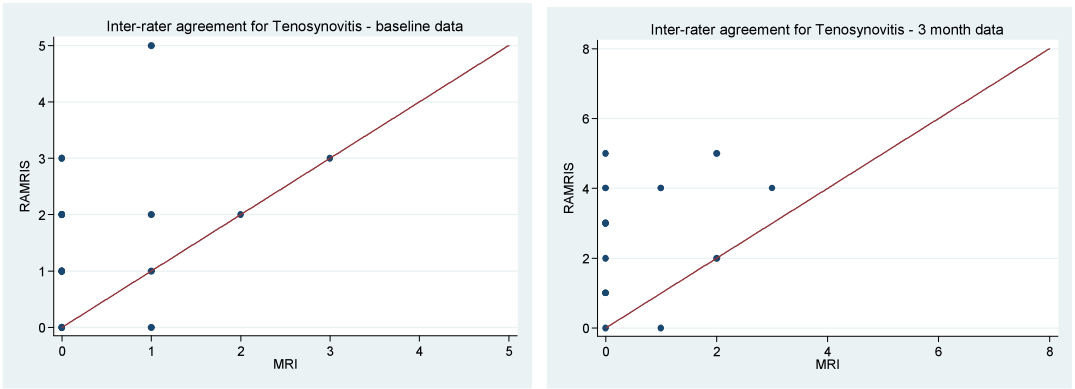
A



B



C



11. DISCUSSION

In this thesis, a variety of potential causes of the musculoskeletal effects of aromatase inhibitors have been investigated. The results are discussed for the ARIAD trial and followed by potential future research directions.

11.1. GRIP STRENGTH

The overall results of the study have shown that grip strength using the Jamar dynamometer has not been a useful tool in assessing arthralgia due to aromatase inhibitors. The conclusions here are somewhat limited by sample size of particularly the switch AI group and the no treatment control group, which may have affected the statistical comparisons. In addition, despite, adjusting the power calculation for the reduced sample size, to 80%, the required number of participants of 22 in each group could not be achieved within the time constraints of this study. Thus smaller statistically significant changes may not have been picked up.

Despite the slight differences in age between the groups, the baseline grip strength did not differ significantly. A difference might have been expected in the switch AI group. This group have a lower median age of 51 years compared to the study median of 61 years. In addition, this group had a higher proportion previously receiving chemotherapy and a lower mean baseline duration of morning stiffness (1 minute compared to overall mean of 7 minutes). As mentioned previously, some of these differences may have been explained by the time from initial breast caner treatment being longer in group B, as these patients had already taken at least two years of tamoxifen. According to the normative grip strength data from the manufacturers, the grip strength for the study population should be around 22kg, which is similar to the study mean and median.

The adjusted mean changes in grip strength overall were relatively small for 3 months and 12 months. Most mean changes were less than 5%, which is far lower than the 20% reported differences in the literature for women on AI therapy. These changes were neither statistically significant or clinically

relevant. Important differences may have been diluted by the study design of examining differences compared with controls from the start of AI therapy, rather than investigating women who had already developed symptoms from their aromatase inhibitor. However, even when describing findings according to a clinical arthralgia syndrome (AIA), grip strength was still no different. Women on an AI who developed arthralgia, had similar grip strength those on an AI who weren't classified as such. Thus there seems to be little clinical utility of grip strength as shown by this study. Other studies have used different methods of grip strength assessment such as a modified sphygmomanometer. It is unclear how accurate and reproducible such methods are. The Jamar dynamometer has been considered the gold standard in rheumatological studies in the past. As this study has been one of the largest to date and is one of the few to have control groups, the findings provide important insight into the usefulness of grip strength in the design of future studies investigating AIA.

11.2. JOINT PAIN

The results have shown that a significant number of patients in this population have a degree of joint pain at baseline. At least 20% had pain described as grade 2 or more. Nearly a third gave a history of osteoarthritis. It is therefore important to note that when studying the typical postmenopausal population taking aromatase inhibitors, joint pains are already prevalent, so a longitudinal design for treatment emergent symptoms is important.

The findings in this study agree with others that joint pain increases over time in women receiving aromatase inhibitors (Henry et al 2012). By month 12, approximately 50% had treatment emergent pain. It is also important to note that similar findings were also seen in the tamoxifen population. Tamoxifen has not been considered an important cause of joint pain. However, even in the large trials of adjuvant AIs, the incidence of joint pain for women on tamoxifen was signficant. For example, in the ATAC study, joint symptoms were reported in 35% of women taking anastrozole compared to 30% receiving tamoxifen. Whlist this may have been assumed to be the background effect of a

postmenopausal population, this study raises the suspicion that tamoxifen may also be associated with worsening joint pain. Although the control population D was small, the same trend was not seen as in the tamoxifen group. Recent data from the IBIS II breast cancer prevention study, showed that the incidence of joint pain was similar with anastrozole (51%) and placebo (46%) in a non breast cancer postmenopausal population. Whilst this was statistically higher for the anastrozole group, it showed that the incidence of arthralgia on placebo was high. Interestingly, in the ARIAD study, the only statistical differences were when AI group was compared to placebo, but not with tamoxifen as control. It is worth bearing in mind that joint pain results here are measured by investigator determined CTC toxicity criteria, which may or may not be the most sensitive method of determining the effect of interest. Patient reported outcomes are an alternative and the results from the questionnaire assessments in the ARIAD study are discussed below.

11.3. QUESTIONNAIRES

The large adjuvant trials of aromatase inhibitor use were unable to provide detailed patient reported outcome data on joint pain. Whilst quality of life assessments were used, joint pain was not assessed in a systematic way. The choice of questionnaires used in the ARIAD was carefully considered and opinions were sought from experts in rheumatology and breast cancer.

The HAQ-DI had a good overall completion rate with 94% of questionnaires completed at 12 months. Whilst the baseline distribution was skewed at baseline, mean scores were consistent with the general population scores (Bruce and Fries 2003). As seen in figure 33, there were a proportion of patients with HAQ-DI scores above 1, particularly in groups A and C, which indicates moderate to severe difficulty. This may have been related to recent breast cancer surgery, adjuvant chemotherapy or radiotherapy. Notably, a common theme that was seen with most of the questionnaires, was that baseline scores in group B were generally lower. Again this was probably related to the time lag of at least two years between primary breast cancer treatment and enrolment into ARIAD study. The HAQ-DI did not show

significant changes that would indicate worsening disability in any of the groups. This was a little unexpected as previous studies had shown that the hands were commonly affected by AIA and thus a functional difference may be picked out the questions asked in the HAQ form. However, these analyses were exploratory, so small statistically significant differences may not have been detected. These assessments were also done on the whole study group. Given that only a proportion of patients develop significant arthralgia, the detection of these may have been diluted out by the rest of the study population.

The HAQ visual analogue scale for pain demonstrated a similar trend in the baseline scores. The median baseline score for the switch group was 0, compared to 10 in group A, 15 in group C and 5 in group D. This was similar to the CTC graded pain scores (figure 27), which demonstrated less pain in group B. Both of these pain assessments showed a clear worsening in pain for the switch AI group, though changes were less dramatic in the other groups. Over the course of the study, significant but small changes were seen in the upfront and switch groups compared to no treatment controls (table 21). Group B was most interesting here as pain was so low at baseline. Figure 36 clearly shows deterioration in pain scores at around 2 to 3 months, which gradually deteriorated up to 12 months. Changes were, however, less marked in the upfront A users. These findings were similar to CTC joint pain assessments. The main difference was that group C tamoxifen users showed little change with HAQ VAS, but with CTC grading, there was an increase in pain.

Changes started to became more apparent when considering the AIA syndrome, as defined by this study. As in figure 37, HAQ-DI scores started to deteriorate after 3 months and were slightly worse compared to those on AIs not developing these symptoms. The mean difference was just short of the minimal important change of 0.1. A similar trend was seen for the HAQ-VAS pain score, confirming AIA sufferers have worse pain than those who do not get these symptoms. Again the differences start to become more apparent after 3 months. This is an important finding and suggests that the AIA criteria used for this study were relevant.

The SF-36 provided information on general health and again showed little difference between the groups. The bodily pain sub score did show a gradual deterioration for group B, though little changes in the other groups. These findings either suggest that this questionnaire is of limited value in the assessment of AI musculoskeletal symptoms or that overall health is little affected be this treatment.

For the Brief Pain Inventory, completion rates were generally lower (50-75%). This may have been because if patients were not in pain, they did not complete the questionnaire. Worst pain is the most commonly reported score in clinical studies. Again, lower scores were demonstrated at baseline for the switch group (mean 0.8), compared with the others and overall (3.1). As discussed, this remains a consistent finding and likely to be related to the time from adjuvant treatment. During the course of the study, the mean worst pain scores did not change much for groups A, C and D. However, for group B, with the lower baseline value, scores increased gradually from month 3 onwards. The overall increase in pain was generally small. However, in the comparisons, the differences tended to come from the fact that scores were still lower for group B for the majority of the study, with the gap closing by month 12.

It would be reasonable to conclude here that the impact of AI therapy, from the patients' perspective, appears greatest when a switch AI strategy is used. The fact that these patients are over two years from initial treatment and thus have better quality of life scores is a significant factor. It may be that for the other groups, the relatively recent breast cancer treatment may have a confounding effect, making small changes in pain more difficult to pick up. In addition, the limited numbers of patients in the study may also be important here. However, other studies have not reported patient reported outcomes in such detail and thus the results of this study are an important addition to the AIA literature.

11.4. DISEASE ACTIVITY SCORE (DAS)

Similar findings were seen with the DAS–VAS and DAS-CRP. Lower baseline scores were seen for the switch group, with no clinically significant changes

over the study period. This provided supportive evidence that AIA does not appear to be an inflammatory arthropathy. These findings are consistent with the CIRAS study, which investigated the effects of AIs on DAS and ESR scores. No significant differences were demonstrated (Shanmugam et al 2012).

11.5. BIOCHEMICAL INVESTIGATIONS

It was important that oestradiol levels were evaluated by a sensitive assay, as oestrogen deprivation has long since felt to be the most likely association of AIA. Over 90% of samples were available for analysis. Baseline levels were similar in all groups at around 12pg/ml. As expected, serum oestradiol reduced in cohort A and was stable in cohorts C and D. How an interesting finding was an increase of oestradiol in the switch AI group, but levels were still in the postmenopausal range. This may be because some of these patients may not have been fully postmenopausal. There was one patient in the group B who regained menses after switching from tamoxifen to an AI and her very high oestradiol levels skewed the distribution.

A key finding of this study, in an exploratory analysis, was that there was no difference in mean oestradiol levels according whether the AIA syndrome developed or not. In fact, mean oestradiol levels were non-significantly lower in those not developing the syndrome as defined in this study. This finding throws in to question whether oestrogen deprivation is a key causative factor for AIA. To date, this is the largest evaluation of the role of oestradiol in AIA in a prospective manner and is an important addition to the current knowledge relating to this syndrome. As discussed in the section below on future work, more detailed evaluation is required with regard to oestradiol. This important negative finding may inform others to continue investigating for others causes and not to assume oestrogen deprivation is the cause.

Vitamin D levels were more or less unchanged during the study period, suggesting a lack of association. For women receiving AI therapy, mean levels of 25OH vitamin D were on the border of deficient and insufficient. This could have been a confounding factor as low levels of vitamin D can be associated

with joint and muscle pain. Women with AIA had a lower vitamin D level than those not developing AIA and this reached statistical significance by the 12 month time point. The use of vitamin D supplementation may be a confounding factor although levels remained low throughout the study time period.

Low overall CRP levels were seen throughout the study, both at baseline and follow up. The same was true for those developing AIA. This is consistent with other trials suggesting women with joint pain due to aromatase inhibitors are not developing a systemic inflammatory arthropathy.

11.6. RADIOLOGICAL INVESTIGATIONS

The variety of radiological investigations have provided an insight into the aetiological mechanisms of AIA. The ARIAD study was the first study to investigate hand BMD in this syndrome. As demonstrated in the results section, hand bone density assessments were performed in virtually all patients participating in the ARIAD study. As expected, BMD fell more in the AI population compared to controls. This is consistent with the knowledge of AI associated bone loss at the hip and spine. The findings were statistically significant in comparison with tamoxifen. An important finding was that women developing AIA had a lower hand bone density than those who did not. This nearly reached statistical significance and certainly requires further investigation. This is the first study to demonstrate a possible link between AIA and hand bone density.

The use of hand ultrasound produced some interesting findings. Previous studies had reported higher rates of MRI tenosynovitis and associated it with a reduction in grip strength. At baseline, there was a significant prevalence of any radiological tenosynovitis (39%) and when limited to those with an ultrasound score of 3 or more (14%). These values had changed by 3 months to 70% and 44% respectively. The main contribution to this change was from groups A and B and to a lesser extent group D (though small number on this group). These data confirm the hypothesis that ultrasound detected tenosynovits may be important in AIA. Inflammatory synovitis seemed to be less important with little

change in these scores across the cohorts. Ultrasound was also investigated by Henry et al in a subset of the ELPh study (Henry et al 2010). The study design was prospective with serial use of ultrasound over a 12 month period. Both this study and ARIAD detected a high number of baseline tendon and joint abnormalities in this postmenopausal population. Both studies repeated ultrasound after 3 months and demonstrated a potential increase in ultrasound abnormalities. Henry et al demonstrated a possible association between baseline ultrasound abnormalities and the development of AIA. The definition of AIA in this study and others differed significantly. This is an ongoing problem for the reporting of AIA trials, as no uniform definition has been agreed.

Median nerve cross-sectional area was investigated, as increasing area has been associated with carpal tunnel syndrome. In the ARIAD study, no change was seen in the first three months. Whether with longer follow up a difference would be seen is unknown. However, those patients developing both clinical signs of carpal tunnel syndrome had a corresponding increase in median nerve swelling. Of those receiving an upfront AI, 6% developed these signs, which is slightly higher than the UK annual incidence of approximately 1-2%.

The evaluation of MRI in this study was limited by the small numbers of patients in the control group agreeing to this investigation. Nevertheless the median score for MR tenosynovial change nearly doubled after 3 months. There were minor increases in median scores for synovitis in addition, raising the possibility of localised joint inflammation in the pathogenesis of AIA. There were similarities between this study and that of Morales et al, both showing an increase in MR detected tenosynovial changes. However, both studies had relatively small numbers and thus any conclusions are limited (Morales et al 2007, 2008).

11.7. STUDY LIMITATIONS

Despite being a well conducted detailed prospective evaluation with two control groups, there were some inherent limitations to the findings presented. For the primary endpoint, the both the original and revised power calculation were not

reached. This may have impacted on the ability of this study to identify smaller statistically different changes. There were two main reasons for this. Firstly, the time taken to design a study and successfully gain all the regulatory approvals was significant. This impacted on recruitment time, which had to be stopped as the time for the clinical fellowship was limited. The recruitment graphs showed that the recruitment rate was acceptable and the target numbers may have been reached with more time. However, the switch group and the no treatment controls were more difficult to identify and recruit to.

Whilst the overall number of patients in this study was small, it was as large as any other study that has investigated aromatase inhibitor joint symptoms prospectively. The study was also limited by the fact that the study sonogragher was a trained oncologist rather than a radiologist or a rheumatologist. In addition, the ultrasounds were not blinded; the investigator knew which patients were on which hormone treatment. This may have introduced some bias in the results. For the MRI reporting, the radiologists knew that MRIs were paired, but were unaware of the treatment group. Analysis by radiologist has shown differences in the reporting of bone and joint changes.

Nevertheless, overall there was a good compliance rate for study attendance, questionnaire completion and radiological investigations.

11.8. FUTURE WORK

Whilst this study has provided important positive and negative findings, there is still more to learn about the syndrome of AIA. So far, there is no universal definition, clinical or radiological. It will be important for future studies to adopt a standard definition so results can be reproduced and compared. An important finding from this study was that there was a significant baseline incidence of joint problems in postmenopausal women. In addition, there was a suggestion that joint problems were also worse for women on tamoxifen. Thus having control groups is vitally important in future study design.

Larger studies are needed to evaluate the ultrasound and MRI changes and correlation with oestradiol and vitamin D levels. Mean vitamin D levels were low in this study and confounding effects would need to be taken into account. The underlying biochemical mechanisms are still not fully understood. The use of novel inflammatory mediators and markers of cartilage breakdown such as CTX-II may provide useful data. In addition, the role of hand DXA warrants further investigation.

Ultimately, the goal would be to identify strategies to predict those at risk of AIA and to circumvent it. Further investigation of non-pharmacological methods and phamrmacological interventions are needed. Studies are already underway evaluating exercise programs, acupuncture and herbal remedies such as glucosamine and chondroitin sulphate. Other studies are evaluating the role of Vitamin D3, omega 3 fatty acids, pregabalin and duloxetine. Patient reported outcomes remain an important factor for such studies. It is still not clear which tools are the best way of assessing AIA. Pain scores as assessed by CTC grading or visual analogue scale are clearly useful. The BPI-SF questionnaire picked up modest differences. Future studies may need to look at which assessment tools are most useful for AIA and consider whether new assessment methods can be designed that are more specific for this condition.

AIA remains an important study question as many thousands of women receive this therapy. If compliance is to be maintained, strategies to circumvent AIA are desperately needed.

11.9. CONCLUSION

The questionnaire to UK breast cancer clinicians confirmed that AIA is seen as an important clinical problem. In the ARIAD study, no association was seen between grip strength and the use of AI therapy versus controls. A link between AIA and oestradiol levels was not demonstrated. Important tenosynovial changes were demonstrated on ultrasound with some evidence of worsening on MRI. However, no clear evidence of an inflammatory arthropathy was seen, as

was demonstrated by the use of HAQ-DI, DAS-28 and CRP. Furthers studies are required to assess the tenosynovial and synovial changes and the role of hand DXA. Future investigation still needs to evaluate underlying mechanisms with a view to determining strategies to maintain compliance.

12. REFERENCES

Alegre-Sancho, J. J., S. Olmos-Anton, et al. (2008). "Trigger thumb in patients with breast cancer and hand pain associated with aromatase inhibitors." Ann Rheum Dis **67(Suppl II)**.

Allen, K. D., R. F. DeVellis, et al. (2007). "Validity and factor structure of the AUSCAN Osteoarthritis Hand Index in a community-based sample." Osteoarthritis Cartilage **15**(7): 830-6.

Avis, N., P. Kaufert, et al. (2004). Baillere's Clinical Endocrinology and Metabolism London, Bailliere Tindall.

Azria, D., P. Lamy, et al. (2007). "Letrozole induced arthralgia: results of a multicentric prospective trial exploring clinical parameters and plasma biomarkers." ASCO Breast Cancer Symposium: 228.

Backhaus, M., G. R. Burmester, et al. (2001). "Guidelines for musculoskeletal ultrasound in rheumatology." Ann Rheum Dis **60**(7): 641-9.

Basch, E., A. Iasonos, et al. (2006). "Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study." Lancet Oncol **7**(11): 903-9.

Blair, S. J., E. McCormick, et al. (1987). "Evaluation of impairment of the upper extremity." Clin Orthop Relat Res(221): 42-58.

Bocca, C., F. Bozzo, et al. (2011). "Antiproliferative effects of COX-2 inhibitor celecoxib on human breast cancer cell lines." Mol Cell Biochem **350**(1-2): 59-70.

Boccardo, F., A. Rubagotti, et al. (2006). "Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial." Ann Oncol **17 Suppl 7**: vii10-4.

Bonneterre, J., B. Thurlimann, et al. (2000). "Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study." J Clin Oncol **18**(22): 3748-57.

Briot, K., M. Tubiana-Hulin, et al. (2010). "Effect of a switch of aromatase inhibitors on musculoskeletal symptoms in postmenopausal women with hormone-receptor-positive breast cancer: the ATOLL (articular tolerance of letrozole) study." Breast Cancer Res Treat **120**(1): 127-34.

Bruce, B. and J. F. Fries (2003). "The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation." J Rheumatol **30**(1): 167-78.

Brufsky, A., N. Bundred, et al. (2008). "Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole." Oncologist **13**(5): 503-14.

Bundred, N. J., I. D. Campbell, et al. (2008). "Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results." Cancer **112**(5): 1001-10.

Burstein, H. J. (2007). "Aromatase inhibitor-associated arthralgia syndrome." Breast **16**(3): 223-34.

Buzdar, A. (2006). "Clinical features of joint symptoms observed in the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial." J Clin Oncol, 2006 ASCO Annual Meeting Proceedings **24**(18S): 551.

Buzdar, A., A. Howell, et al. (2006). "Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial." Lancet Oncol **7**(8): 633-43.

Buzdar, A. U., R. C. Coombes, et al. (2007). "Summary of aromatase inhibitor clinical trials in postmenopausal women with early breast cancer." Cancer **112**(S3): 700-709.

Campos, S. M. (2004). "Aromatase inhibitors for breast cancer in postmenopausal women." Oncologist **9**(2): 126-36.

Cecil, R. L. and B. H. Archer (1925). "Arthritis of the menopause." JAMA **84**: 75-9.

Cella, D., L. Fallowfield, et al. (2006). "Quality of life of postmenopausal women in the ATAC ("Arimidex", tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for early breast cancer." Breast Cancer Res Treat **100**(3): 273-84.

Chlebowski, R. T. and M. L. Geller (2006). "Adherence to endocrine therapy for breast cancer." Oncology **71**(1-2): 1-9.

Christensen, A. F., T. Lottenburger, et al. (2009). "Differential association of the N-propeptide of collagen IIA (PIIANP) and collagen II C-telopeptide (CTX-II) with synovitis and erosions in early and longstanding rheumatoid arthritis." Clin Exp Rheumatol **27**(2): 307-14.

Christiansen, A. V., H. Paalum, et al. (1997). "Quantitative determination of thapsigargins in roots and fruits from Thapsia gymnesica." Planta Med **63**(6): 565-7.

ClinicalTrials.gov. (2009). Retrieved 7th July 2009, from http://clinicaltrials.gov/ct2/results?term=breast+cancer+AND+arthralgia.

Coates, A. S., A. Keshaviah, et al. (2007). "Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98." J Clin Oncol **25**(5): 486-92.

Coleman, R. E., W. W. Bolten, et al. (2008). "Aromatase inhibitor-induced arthralgia: clinical experience and treatment recommendations." Cancer Treat Rev **34**(3): 275-82.

Coombes, R. C., E. Hall, et al. (2004). "A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer." N Engl J Med **350**(11): 1081-92.

Coombes, R. C., L. S. Kilburn, et al. (2007). "Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial." Lancet **369**(9561): 559-70.

Crew, K. D., J. Capodice, et al. (2009). "Randomized, blinded, placebo-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer." Journal of Clinical Oncology, 2009 ASCO Annual Meeting Procedings (post-meeting edition) **27**(15s): 571.

Crew, K. D., H. Greenlee, et al. (2007). "Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer." J Clin Oncol **25**(25): 3877-83.

Cuzick, J., I. Sestak, et al. (2008). "Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: a retrospective analysis of the ATAC trial." Lancet Oncol **9**(12): 1143-8.

Cvoro, A., D. Tatomer, et al. (2008). "Selective estrogen receptor-beta agonists repress transcription of proinflammatory genes." J Immunol **180**(1): 630-6.

Dawson-Basoa, M. and A. R. Gintzler (1997). "Involvement of spinal cord delta opiate receptors in the antinociception of gestation and its hormonal simulation." Brain Res **757**(1): 37-42.

Dawson-Basoa, M. and A. R. Gintzler (1997). "Nociceptin (Orphanin FQ) abolishes gestational and ovarian sex steroid-induced antinociception and induces hyperalgesia." Brain Res **750**(1-2): 48-52.

Dawson-Basoa, M. and A. R. Gintzler (1998). "Gestational and ovarian sex steroid antinociception: synergy between spinal kappa and delta opioid systems." Brain Res **794**(1): 61-7.

Dawson-Basoa, M. B. and A. R. Gintzler (1993). "17-Beta-estradiol and progesterone modulate an intrinsic opioid analgesic system." Brain Res **601**(1-2): 241-5.

Dawson-Basoa, M. E. and A. R. Gintzler (1996). "Estrogen and progesterone activate spinal kappa-opiate receptor analgesic mechanisms." Pain **64**(3): 608-15.

Dawson-Basoa, M. E. and A. R. Gintzler (1996). "Estrogen and progesterone activate spinal kappa-opiate receptor analgesic mechanisms." Pain **64**(1): 169-77.

Dent, S., T. DiValentin, et al. (2006). "Long term toxicities in women with early stage breast cancer treated with aromatase inhibitors: data from a tertiary care center." San Antonio Breast Caner Symposium: 4057.

Dent, S. F., S. Hopkins, et al. (2007). Adjuvant aromatse inhibitors in early breast cancer - toxicity and adherence. Important observations in clinical practice. San Antonio Breast Cancer Symposium, San Antonio, Texas.

di Salle, E., G. Ornati, et al. (1992). "Exemestane (FCE 24304), a new steroidal aromatase inhibitor." J Steroid Biochem Mol Biol **43**(1-3): 137-43.

Dietrich, W., A. Haitel, et al. (2006). "Estrogen receptor-beta is the predominant estrogen receptor subtype in normal human synovia." J Soc Gynecol Investig **13**(7): 512-7.

Din, O. S., D. Dodwell D, et al. (2010). “Aromatase inhibitor-induced arthralgia in early breast cancer: what do we know and how can we find out more?” Breast Cancer Res Treat **120**(3): 525-38.

Dizdar, O., L. Ozcakar, et al. (2009). "Sonographic and electrodiagnostic evaluations in patients with aromatase inhibitor-related arthralgia." J Clin Oncol **27**(30): 4955-60.

Donnellan, P. P., S. L. Douglas, et al. (2001). "Aromatase inhibitors and arthralgia." J Clin Oncol **19**(10): 2767.

Dowsett, M. and P. E. Lonning (1997). "Anastrozole--a new generation in aromatase inhibition: clinical pharmacology." Oncology **54 Suppl 2**: 11-4.

Dugan, S. A., L. H. Powell, et al. (2006). "Musculoskeletal pain and menopausal status." Clin J Pain **22**(4): 325-31.

Eastell, R., J. E. Adams, et al. (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): 1051-7.

EBCTCG (2005). "Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials." Lancet **365**(9472): 1687-717.

Ellis, G. K., H. G. Bone, et al. (2008). "Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer." J Clin Oncol **26**(30): 4875-82.

Fallowfield, L. (2008). "There's many a slip twixt cup and lip: adherence issues in cancer therapy." Nat Clin Pract Oncol **5**(3): 118-9.

Fallowfield, L., D. Cella, et al. (2004). "Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial." J Clin Oncol **22**(21): 4261-71.

Fallowfield, L. J., J. M. Bliss, et al. (2006). "Quality of life in the intergroup exemestane study: a randomized trial of exemestane versus continued tamoxifen after 2 to 3 years of tamoxifen in postmenopausal women with primary breast cancer." J Clin Oncol **24**(6): 910-7.

Felson, D. T. (2008). "Comparing the prevalence of rheumatic diseases in China with the rest of the world." Arthritis Res Ther **10**(1): 106.

Fraenkel, L., P. Shearer, et al. (2000). "Improving the selective use of plain radiographs in the initial evaluation of shoulder pain." J Rheumatol **27**(1): 200-4.

Fries, J. F., P. Spitz, et al. (1980). "Measurement of patient outcome in arthritis." Arthritis Rheum **23**(2): 137-45.

Galantino, M. L., K. Desai, et al. (2012). "Impact of yoga on functional outcomes in breast cancer survivors with aromatase inhibitor-associated arthralgias." Integr Cancer Ther **11**(4): 313-20.

Garg, M., J. S. Lubel et al (2012). “Review article: vitamin D and inflammatory bowel disease – established concepts and future directions.” Aliment Pharmacol **36**: 324-344.

Ghasemi-Rad, M., E. Nosair et al (2014). “A handy review of carpal tunnel syndrome: From anatomy to diagnosis and treatment.” World J Radiol **28**;6(6): 284-300.

Goss, P. E., J. N. Ingle, et al. (2003). "A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer." N Engl J Med **349**(19): 1793-802.

Greendale, G. A., N. P. Lee, et al. (1999). "The menopause." Lancet **353**(9152): 571-80.

Greenspan, S. L., A. Brufsky, et al. (2008). "Risedronate prevents bone loss in breast cancer survivors: a 2-year, randomized, double-blind, placebo-controlled clinical trial." J Clin Oncol **26**(16): 2644-52.

Haavardsholm, E. A., M. Ostergaard, et al. (2007). "Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study." Ann Rheum Dis **66**(9): 1216-20.

Haavardsholm, E. A., M. Ostergaard, et al. (2005). "Reliability and sensitivity to change of the OMERACT rheumatoid arthritis magnetic resonance imaging score in a multireader, longitudinal setting." Arthritis Rheum **52**(12): 3860-7.

Hadji, P., D. G. Kieback, et al. (2012). "Correlation of treatment-emergent adverse events and clinical response to endocrine therapy in early breast cancer: a retrospective analysis of the German cohort of TEAM." Ann Oncol **23**(10): 2566-72.

Hammer, H. B., E. A. Haavardsholm, et al. (2007). "Ultrasonographic measurement of the median nerve in patients with rheumatoid arthritis without symptoms or signs of carpal tunnel syndrome." Ann Rheum Dis **66**(6): 825-7.

Harkonen, R., R. Harju, et al. (1993). "Accuracy of the Jamar dynamometer." J Hand Ther **6**(4): 259-62.

Haugeberg, G., M. J. Green, et al. (2007). "Hand bone densitometry: a more sensitive standard for the assessment of early bone damage in rheumatoid arthritis." Ann Rheum Dis **66**(11): 1513-7.

Haugeberg, G., M. J. Green, et al. (2006). "Hand bone loss in early undifferentiated arthritis: evaluating bone mineral density loss before the development of rheumatoid arthritis." Ann Rheum Dis **65**(6): 736-40.

Henry, N. L., *P. Charles*, et al. (2008). A distinct inflammatory marker pattern in patients with aromatase inhibitor (AI)-induced musculoskeletal symptoms. SABCS, San Antonio, Texas.

Henry, N. L., J. T. Giles, et al. (2008). "Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors." Breast Cancer Res Treat **111**(2): 365-72.

Henry, N. L., J. A. Jacobson, et al. (2010). "A prospective study of aromatase inhibitor-associated musculoskeletal symptoms and abnormalities on serial high-resolution wrist ultrasonography." Cancer **116**(18): 4360-7.

Henry, N. L., F. Azzouz et al (2012). “Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early stage breast cancer.” J Clin Oncol **30**(9): 936-42.

Hershman, D. L. (2008). "Getting a grip on aromatase inhibitor-associated arthralgias." J Clin Oncol **26**(19): 3120-1.

Holick, M. F., Binkley N. C. et al (2011). “Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline.” J Clin Endocrinol Metab **96**: 1911–30.

Howell, A., J. Cuzick, et al. (2005). "Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer." Lancet **365**(9453): 60-2.

Huang, C., P. D. Ross, et al. (1997). "Factors associated with joint pain among postmenopausal women." Int J Obes Relat Metab Disord **21**(5): 349-54.

Hunter, D. J., J. Li, et al. (2007). "Cartilage markers and their association with cartilage loss on magnetic resonance imaging in knee osteoarthritis: the Boston Osteoarthritis Knee Study." Arthritis Res Ther **9**(5): R108.

Jakesz, R., R. Greil, et al. (2007). "Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a." J Natl Cancer Inst **99**(24): 1845-53.

Jakesz, R., W. Jonat, et al. (2005). "Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial." Lancet **366**(9484): 455-62.

Jaque, J., H. Macdonald, et al. (2013). "Deficiencies in immunoassay methods used to monitor serum Estradiol levels during aromatase inhibitor treatment in postmenopausal breast cancer patients." Springerplus **2**(1): 5.

Jorgensen, L., H. Willumsen, et al. (1987). "The effect of parenteral emepronium bromide (Cetiprin) on postoperative vesical tenesms after transurethral resection of the prostate. A randomized, placebo-controlled study." Int Urol Nephrol **19**(1): 87-90.

Kanematsu, M., M. Morimoto, et al. (2011). "The time since last menstrual period is important as a clinical predictor for non-steroidal aromatase inhibitor-related arthralgia." BMC Cancer **11**: 436.

Katz, J. N. and B.P. Simmons . (2002). “Clinical practice. Carpal tunnel syndrome.” N Engl J Med **346**: 1807–1812.

Khan, Q. J., P. S. Reddy, et al. (2009). "Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer." Breast Cancer Res Treat.

Khanduri, S. and D. J. Dodwell (2007). "Aromatase inhibitors and musculoskeletal symptoms." Breast.

Kong, S. Y., T. V. Stabler, et al. (2006). "Diurnal variation of serum and urine biomarkers in patients with radiographic knee osteoarthritis." Arthritis Rheum **54**(8): 2496-504.

Kubo, M., H. Onishi, et al. (2012). "Short-term and low-dose prednisolone administration reduces aromatase inhibitor-induced arthralgia in patients with breast cancer." Anticancer Res **32**(6): 2331-6.

Landewe, R. (2007). "Predictive markers in rapidly progressing rheumatoid arthritis." J Rheumatol Suppl **80**: 8-15.

Laroche, M., S. Borg, et al. (2007). "Joint pain with aromatase inhibitors: abnormal frequency of Sjogren's syndrome." J Rheumatol **34**(11): 2259-63.

Lassen, M. R., L. C. Borris, et al. (1998). "Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty--the Danish Prolonged Prophylaxis (DaPP) Study." Thromb Res **89**(6): 281-7.

Le Bail, J., B. Liagre, et al. (2001). "Aromatase in synovial cells from postmenopausal women." Steroids **66**(10): 749-57.

Lester, J. E., D. Dodwell, et al. (2008). "Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer." Clin Cancer Res **14**(19): 6336-42.

Lintermans, A. and P. Neven (2011). "Pharmacology of arthralgia with estrogen deprivation." Steroids **76**(8): 781-5.

Lintermans, A., B. Van Calster, et al. (2011). “Aromatase inhibitor-induced loss of grip strength is body mass index dependent: hypothesis-generating findings for its pathogenesis.” Ann Oncol **22**(8):1763-9.

Lintermans, A., K. Van Asten, et al. (2014). “A prospective assessment of musculoskeletal toxicity and loss of grip strength in breast cancer patients receiving adjuvant aromatase inhibitors and tamoxifen, and relation with BMI.” Breast Cancer Res Treat **146**: 109-116.

Liuba, P., E. Pesonen, et al. (2003). "Co-infection with Chlamydia pneumoniae and Helicobacter pylori results in vascular endothelial dysfunction and enhanced VCAM-1 expression in apoE-knockout mice." J Vasc Res **40**(2): 115-22.

Machin, D., M. J. Campbell, et al. (1997). Sample Size Tables for Clinical Studies. Oxford, Blackwell Science.

Mao, J. J., D. W. Bruner, et al. (2009). "Feasibility trial of electroacupuncture for aromatase inhibitor--related arthralgia in breast cancer survivors." Integr Cancer Ther **8**(2): 123-9.

Mao, J. J., C. Stricker, et al. (2009). "Patterns and risk factors associated with aromatase inhibitor-related arthralgia among breast cancer survivors." Cancer **115**(16): 3631-9.

Mathias, S. D., R. D. Crosby, et al. (2011). "Estimating minimally important differences for the worst pain rating of the Brief Pain Inventory-Short Form." J Support Oncol **9**(2): 72-8.

Mathiowetz, V., K. Weber, et al. (1984). "Reliability and validity of grip and pinch strength evaluations." J Hand Surg [Am] **9**(2): 222-6.

McAlindon, T. E., P. W. Wilson, et al. (1999). "Level of physical activity and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: the Framingham study." Am J Med **106**(2): 151-7.

Medina, V. M., M. E. Dawson-Basoa, et al. (1993). "17 beta-estradiol and progesterone positively modulate spinal cord dynorphin: relevance to the analgesia of pregnancy." Neuroendocrinology **58**(3): 310-5.

Mendoza, T., T. Mayne, et al. (2006). "Reliability and validity of a modified Brief Pain Inventory short form in patients with osteoarthritis." Eur J Pain **10**(4): 353-61.

Morales, L., S. Pans, et al. (2007). "Debilitating musculoskeletal pain and stiffness with letrozole and exemestane: associated tenosynovial changes on magnetic resonance imaging." Breast Cancer Res Treat **104**(1): 87-91.

Morales, L., S. Pans, et al. (2007). "A prospective study to assess short term intra-articular and tenosynovial changes in the aromatase inhibitor-associated arthralgia syndrome." San Antonio Breast Caner Symposium: 3053.

Morales, L., S. Pans, et al. (2008). "Prospective study to assess short-term intra-articular and tenosynovial changes in the aromatase inhibitor-associated arthralgia syndrome." J Clin Oncol **26**(19): 3147-52.

Morel, B., H. Marotte, et al. (2007). "Will steroidal aromatase inhibitors induce rheumatoid arthritis?" Ann Rheum Dis **66**(4): 557-8.

Mouridsen, H., M. Gershanovich, et al. (2003). "Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group." J Clin Oncol **21**(11): 2101-9.

Nabholtz, J. M., A. Buzdar, et al. (2000). "Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group." J Clin Oncol **18**(22): 3758-67.

Nakamichi, K and S. Tachibana. (1993). “The use of ultrasonography in detection of synovitis in carpal tunnel syndrome.” J Hand Surg Br **18**: 176–179.

Nevitt, M. C., D. T. Felson, et al. (2001). "The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: The Heart and Estrogen/Progestin Replacement Study, a randomized, double-blind, placebo-controlled trial." Arthritis Rheum **44**(4): 811-8.

Nielsen, R. H., C. Christiansen, et al. (2008). "Oestrogen exhibits type II collagen protective effects and attenuates collagen-induced arthritis in rats." Clin Exp Immunol.

Niravath, P. (2013). "Aromatase inhibitor-induced arthralgia: a review." Ann Oncol **24**(6): 1443-9.

Njar, V. C. and A. M. Brodie (1999). "Comprehensive pharmacology and clinical efficacy of aromatase inhibitors." Drugs **58**(2): 233-55.

Oestergaard, S., B. C. Sondergaard, et al. (2006). "Effects of ovariectomy and estrogen therapy on type II collagen degradation and structural integrity of articular cartilage in rats: implications of the time of initiation." Arthritis Rheum **54**(8): 2441-51.

Ostergaard, M., J. Edmonds, et al. (2005). "An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas." Ann Rheum Dis **64 Suppl 1**: i3-7.

Pacala, S. W. and A. P. Dobson (1988). "The relation between the number of parasites/host and host age: population dynamic causes and maximum likelihood estimation." Parasitology **96 (Pt 1)**: 197-210.

Pfeilschifter, J., R. Koditz, et al. (2002). "Changes in proinflammatory cytokine activity after menopause." Endocr Rev **23**(1): 90-119.

Presant, C. A., L. Bosserman, et al. (2007). "Aromatase inhibitor-associated arthralgia and/ or bone pain: frequency and characterization in non-clinical trial patients." Clin Breast Cancer **7**(10): 775-8.

Prieto-Alhambra, D., M. K. Javaid, et al. (2010). "Vitamin D threshold to prevent aromatase inhibitor-induced arthralgia: a prospective cohort study." Breast Cancer Res Treat **125**(3): 869-78.

Pritchard, K. I. (2008). "Endocrine symptoms to predict risk of recurrence?" Lancet Oncol **9**(12): 1117-9.

Rao, G. N., D. W. Banick, et al. (1997). "Particle size distribution of a suspension aerosol using Andersen and Marple-Miller cascade impactors." Pharm Res **14**(9): 1272-4.

Reid, D. M., J. Doughty, et al. (2008). "Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group." Cancer Treat Rev **34 Suppl 1**: S3-18.

Renshaw, L., M. McHugh, et al. (2007). "Comparison of joint problems as reported by patients in a randomised adjuvant trial of anastrozole and letrozole." San Antonio Breast Caner Symposium: 2072.

Richette, P., M. Corvol, et al. (2003). "Estrogens, cartilage, and osteoarthritis." Joint Bone Spine **70**(4): 257-62.

Riley, J. L., 3rd, M. E. Robinson, et al. (1999). "A meta-analytic review of pain perception across the menstrual cycle." Pain **81**(3): 225-35.

Robidoux, A., E. Rich, et al. (2011). "A prospective pilot study investigating the musculoskeletal pain in postmenopausal breast cancer patients receiving aromatase inhibitor therapy." Curr Oncol **18**(6): 285-94.

Sand-Jespersen, T., J. Paaske, et al. (2007). "Kondo-enhanced Andreev tunneling in InAs nanowire quantum dots." Phys Rev Lett **99**(12): 126603.

Santen, R. J., L. Demers, et al. (2007). "Superiority of gas chromatography/tandem mass spectrometry assay (GC/MS/MS) for estradiol for monitoring of aromatase inhibitor therapy." Steroids **72**(8): 666-71.

Sasano, H., M. Uzuki, et al. (1997). "Aromatase in human bone tissue." J Bone Miner Res **12**(9): 1416-23.

Sautner, J., I. Andel, et al. (2004). "Development of the M-SACRAH, a modified, shortened version of SACRAH (Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands)." Rheumatology (Oxford) **43**(11): 1409-13.

Sautner, J., I. Andel, et al. (2009). "A Comparison of the Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands and the Australian/Canadian Osteoarthritis Hand Index in Hand Osteoarthritis Patients." International Journal of Rheumatology: 1-7.

Schmidt, W. A. (2007). "Technology Insight: the role of color and power Doppler ultrasonography in rheumatology." Nat Clin Pract Rheumatol **3**(1): 35-42; quiz 59.

Sestak, I. and J. Cuzick (2007). "Risk factors for joint symptoms in the ATAC trial." San Antonio Breast Caner Symposium: 2071.

Sestak, I., J. Cuzick, et al. (2008). "Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis." Lancet Oncol **9**(9): 866-72.

Sestak, I., F. Sapunar, et al. (2009). "Aromatase inhibitor-induced carpal tunnel syndrome: results from the ATAC trial." J Clin Oncol **27**(30): 4961-5.

Shanmugam, V. K., J. McCloskey, et al. (2012). "The CIRAS study: a case control study to define the clinical, immunologic, and radiographic features of aromatase inhibitor-induced musculoskeletal symptoms." Breast Cancer Res Treat **131**(2): 699-708.

Singh, S., J. Cuzick, et al. (2012). "Effect of baseline serum vitamin D levels on aromatase inhibitors induced musculoskeletal symptoms: results from the IBIS-II, chemoprevention study using anastrozole." Breast Cancer Res Treat **132**(2): 625-9.

Singh, S., A. Howell, et al. (2006). "Vit D levels among patients with arthralgia: results from IBIS-II breast cancer prevention study." San Antonio Breast Caner Symposium: 1068.

Sniekers, Y. H., H. Weinans, et al. (2008). "Animal models for osteoarthritis: the effect of ovariectomy and estrogen treatment - a systematic approach." Osteoarthritis Cartilage **16**(5): 533-41.

Stahl, K., J. E. Andersen, et al. (2009). "Structures of strontium diformate and strontium fumarate. A synchrotron powder diffraction study." Acta Crystallogr B **65**(Pt 4): 481-7.

Szoeke, C. E., F. M. Cicuttini, et al. (2008). "The relationship of reports of aches and joint pains to the menopausal transition: a longitudinal study." Climacteric **11**(1): 55-62.

Tan, A. L. and P. Emery (2008). "Role of oestrogen in the development of joint symptoms?" Lancet Oncol **9**(9): 817-8.

Tan, A. L., R. J. Wakefield, et al. (2003). "Imaging of the musculoskeletal system: magnetic resonance imaging, ultrasonography and computed tomography." Best Pract Res Clin Rheumatol **17**(3): 513-28.

Thorne, C. (2007). "Management of arthralgias associated with aromatase inhibitor therapy." Curr Oncol **14 Suppl 1**: S11-9.

Thurlimann, B., A. Keshaviah, et al. (2005). "A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer." N Engl J Med **353**(26): 2747-57.

Toesca, A., A. Pagnotta, et al. (2008). "Estrogen and progesterone receptors in carpal tunnel syndrome." Cell Biol Int **32**(1): 75-9.

Tulli, G., G. Vignali, et al. (1992). "[Hypoxia and oxygen content during dialysis]." Minerva Anestesiol **58**(3): 77-81.

Uhlen, M., E. Bjorling, et al. (2005). "A human protein atlas for normal and cancer tissues based on antibody proteomics." Mol Cell Proteomics **4**(12): 1920-32.

van de Velde, C. J., D. Rea, et al. (2011). "Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial." Lancet **377**(9762): 321-31.

van Gestel, A. M., C. J. Haagsma, et al. (1998). "Validation of rheumatoid arthritis improvement criteria that include simplified joint counts." Arthritis Rheum **41**(10): 1845-50.

Wad, G., H. E. Andersen, et al. (1969). "The Vodskov project. I. Introduction." Dan Med Bull **16**(8): 225-6.

Wagner, A. M., P. Cloos, et al. (2008). "Posttranslational Protein Modifications in Type 1 Diabetes - Genetic Studies with PCMT1, the Repair Enzyme Protein Isoaspartate Methyltransferase (PIMT) Encoding Gene." Rev Diabet Stud **5**(4): 225-31.

Wakefield, R. J., P. V. Balint, et al. (2005). "Musculoskeletal ultrasound including definitions for ultrasonographic pathology." J Rheumatol **32**(12): 2485-7.

Whelan, T. J., P. E. Goss, et al. (2005). "Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women." J Clin Oncol **23**(28): 6931-40.

Wild, N., J. Karl, et al. (2008). "Diagnosis of rheumatoid arthritis: multivariate analysis of biomarkers." Biomarkers **13**(1): 88-105.

Williams, F. M. and T. D. Spector (2008). "Biomarkers in osteoarthritis." Arthritis Res Ther **10**(1): 101.

Xu, J., M. Bartoces, et al. (2005). "Natural history of menopause symptoms in primary care patients: a MetroNet study." J Am Board Fam Pract **18**(5): 374-82.

Yager, J. D. and N. E. Davidson (2006). "Estrogen carcinogenesis in breast cancer." N Engl J Med **354**(3): 270-82.

13. APPENDICES

13.1. HEALTH ASSESSMENT QUESTIONNAIRE – DISABILITY INDEX (HAQ-DI)

The STANFORD HEALTH ASSESSMENT QUESTIONNAIRE©
Stanford University School of Medicine, Division of Immunology & Rheumatology

HAQ Disability Index:
In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty [0]	With SOME difficulty [1]	With MUCH difficulty [2]	UNABLE to do [3]
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
-Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐
-Lift a full cup or glass to your mouth?	☐	☐	☐	☐
-Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	☐	☐	☐	☐
-Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Cane
- ☐ Walker
- ☐ Crutches
- ☐ Wheelchair
- ☐ Devices used for dressing (button hook, zipper pul long-handled shoe horn, etc.)
- ☐ Built up or special utensils
- ☐ Special or built up chair
- ☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Dressing and Grooming
- ☐ Arising
- ☐ Eating
- ☐ Walking

Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY difficulty [0]	With SOME difficulty [1]	With MUCH difficulty [2]	UNABLE to do [3]
HYGIENE				
Are you able to:				
-Wash and dry your body?	☐	☐	☐	☐
-Take a tub bath?	☐	☐	☐	☐
-Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
-Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars which have been previously opened?	☐	☐	☐	☐
-Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
-Run errands and shop?	☐	☐	☐	☐
-Get in and out of a car?	☐	☐	☐	☐
-Do chores such as vacuuming or yardwork	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

☐ Raised toilet seat
☐ Bathtub seat
☐ Jar opener (for jars previously opened)
☐ Bathtub bar
☐ Long-handled appliances for reach
☐ Long-handled appliances in bathroom
☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

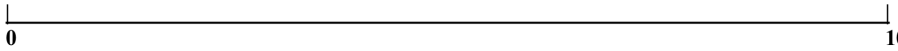
☐ Hygiene
☐ Reach
☐ Gripping and opening things
☐ Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN

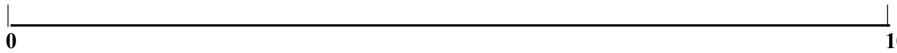
No Pain — **Severe Pain**



0 — **100**

Considering all the ways that your arthritis affects you, rate how you are doing on the following scale by placing a vertical mark on the line.

Very Well — **Very Poor**



0 — **100**

13.2. SF-36 VERSION 2

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking more than a mile	☐ 1	☐ 2	☐ 3
h	Walking several hundred yards	☐ 1	☐ 2	☐ 3
i	Walking one hundred yards	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Had difficulty performing the the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time <u>during the past 4 weeks</u>…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f	Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i	Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

13.3. BRIEF PAIN INVENTORY – SHORT FORM (BPI-SF)

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

Date: ____ / ____ / ____ Time: _____

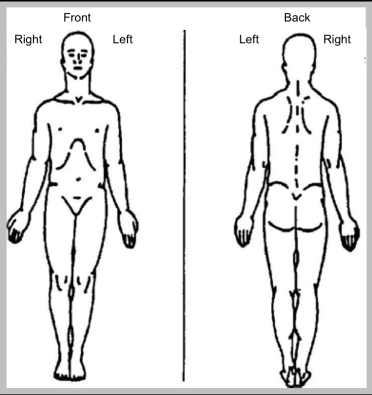
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Date: _ _ _ / _ _ _ _ / _ _ _ _ Time: _____

Name: _____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

13.4. ARIAD STUDY ASSESSMENT FORM

ARIAD assessment form

Patient Initials |__|__|__| Study number|__|__|__| Visit No |__|

DAS Observer name _____ Date **|___|___|___|**

Morning Stiffness
Duration of morning stiffness **|__|__|__|** minutes

DAS 28
Overall well-being – please indicate on the scale below

Best imaginable health state — Worst imaginable health state

		Left		Right	
		Swollen	**Tender**	**Swollen**	**Tender**
Shoulder					
Elbow					
Wrist					
MCP	**1**				
	2				
	3				
	4				
	5				
PIP	**1**				
	2				
	3				
	4				
	5				
Knee					
Subtotal					

VAS

Ht (m)	
Wt (kg)	

Total swollen

Total tender

Grip strength

Measurement	**Left**	**Right**
1	**kg**	**kg**
2	**kg**	**kg**
3	**kg**	**kg**

WHO Performance status	✓
0 Fully active, able to carry on all pre-disease performance without restriction	
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work	
2 Ambulatory and capable of self care but unable to carry out any work activities: up and about more than 50% of waking hours	
3 Capable of only limited self care, confined to bed or chair more than 50% of waking hours	
4 Completely disabled, cannot carry on any self care, totally confined to bed or chair	

ARIAD assessment form

Rheumatology assessment

Date of assessment **|___|___|___|**

Arthralgia grade (CTC)	✓
0 none	
1 mild pain not interfering with function	
2 moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	
3 severe pain: pain or analgesics severely interfering with activities of daily living	
4 disabling	

Ability to work	✓
Able to work	
Retired	
In work	
Impaired	
Job lost due to arthralgia	

History

Psoriasis	**Yes No**
Raynauds	**Yes No**

Examination

Heberden's nodes	**Yes No**
Bouchard's nodes	**Yes No**
Carpometacarpal joint arthrosis	**Yes No**
Inflammatory Synovitis	**Yes No**
Hand stiffness	**Yes No**
Hand pain	**Yes No**
Triggering finger/thumb	**Yes No**
Flexor tendon nodules	**Yes No**
Gout	**Yes No**
Psoriasis	**Yes No**
Psoriatic nail change	**Yes No**
Dupuytren's/contractures	**Yes No**

Carpal tunnel

tinel's	**+ve -ve**
phalen's	**+ve -ve**
sensory change	**Yes No**
motor change	**Yes No**

13.5. ARIAD STUDY HAND ULTRASOUND ASSESSMENT FORM

Ultrasound Form for ARIAD Study

Patient Initials |__|__|__| **Study number** |__|__|__| **Visit** |_____|

Date of ultrasound |___|___|___|

Right						Left				
ICJ		UCJ		RCJ		RCJ		UCJ		ICJ
					Wrist GS (0-3)					
					Wrist PD (0-3)					
					Wrist erosions					
					Wrist osteophytes					
5	4	3	2	1		1	2	3	4	5
					MCP GS (0-3)					
					MCP PD (0-3)					
					MCP erosions					
					MCP osteophytes					
					PIP GS (0-3)					
					PIP PD (0-3)					
					PIP erosions					
					PIP osteophytes					
					Flexor tenosynovitis GS (see below)					
					Flexor tenosynovitis PD (0-3)					
					Median N X-sectional area (cm2)					

Grade 0 (normal): no peritendinous effusion or synovial proliferation with enhancement
Grade 1: <2mm peritendinous effusion and/or synovial proliferation with enhancement
Grade 2: ≥2mm and < 5mm peritendinous effusion and/or synovial proliferation with enhancement
Grade 3: ≥5mm peritendinous effusion and/or synovial proliferation with enhancement

13.6. MRI RAMRIS SCORING SHEETS

Score sheet for the OMERACT RAMRIS

using the EULAR-OMERACT RA MRI reference image atlas

MCP JOINTS

MRI ID: _____ **Scorer's name:** _____

Centre where MRI was performed: _____

Image set (e.g. baseline or follow-up): _____

Sequences scored: _____

Scoring of synovitis

	MCP-joints			
	2	3	4	5
Synovitis (0-3)				

Scoring of bone erosion and bone oedema

Bone erosion is scored 0-10, according to the proportion (in increments of 10%) of bone involved:
0: 0%, 1: 1-10%, 2: 11-20 %, ……., 10: 91-100%

Bone oedema is scored 0-3, according to the proportion (in increments of 33%) of bone involved:
0: 0%, 1: 1-33%, 2: 34-66 %, 3: 67-100%

Score from the articular surface (or its best estimated position if absent) to a depth of 1 cm.

		MCP joints			
		2	3	4	5
Bone erosion 0-10	**Proximal**				
	Distal				
Bone oedema 0-3	**Proximal**				
	Distal				

Score sheet for the OMERACT RAMRIS

using the EULAR-OMERACT RA MRI reference image atlas

WRIST JOINTS

MRI ID: _____ **Scorer's name:** _____

Centre where MRI was performed: _____

Image set (e.g. baseline or follow-up): _____

Sequences scored: _____

Scoring of synovitis

	Distal radio-ulnar joint	Radio-carpal joint	Intercarpal-CMCJ
Synovitis (0-3)			

Scoring of bone erosion and bone oedema

Bone erosion is scored 0-10, according to the proportion (in increments of 10%) of bone involved: 0: 0%, 1: 1-10%, 2: 11-20 %, ……., 10: 91-100%

Bone oedema is scored 0-3, according to the proportion (in increments of 33%) of bone involved: 0: 0%, 1: 1-33%, 2: 34-66 %, 3: 67-100%

For carpal bones, score the whole bone. For long bones, score from the articular surface (or its best estimated position if absent) to a depth of 1 cm.

	Base of metacarpal				
	1	2	3	4	5
Bone erosion (0-10)					
Bone oedema (0-3)					

	Trapezium	Trapezoid	Capitate	Hamate
Bone erosion (0-10)				
Bone oedema (0-3)				

	Scaphoid	Lunate	Triquetrum	Pisiform
Bone erosion (0-10)				
Bone oedema (0-3)				

	Distal radius	Distal ulna
Bone erosion (0-10)		
Bone oedema (0-3)		

13.7. LABORATORY GUIDELINES (SOP) FOR ARIAD STUDY (XXX070)

Version 2 30th September 2008

URINE

2nd void of morning and date and time of sample to be recorded
Aliquot into **2x YELLOW** top (1.8ml) cryovials: 1-1.8ml in each vial.

Cryo-tubes to be labelled with:
XXX070/ARIAD
Patient Study number
Date of birth
Date of sample
Visit – BL, M1, M2, M3, M6, M12
URINE

Freeze at -80 degrees celsius, separating the samples so have a back-up sample (Sheffield only)
Time / date of freezing to be documented

PLASMA

FILL 2x 4ml EDTA purple top (contains an anticoagulant) – time / date of venepuncture to be documented
Invert 5-6 times to prevent coagulation
Needs to be centrifuged at **2000G (NOT RPM) for 10 minutes** at room temperature **WITHIN 30 minutes** of collection

Pipette off plasma into **2x PURPLE** top cryovials aiming for a volume of 1-1.8ml in each vial

Label each vial with
XXX070/ARIAD
Patient Study number,
Date of birth
Date of sample
Visit – BL, M1, M2, M3, M6, M12
PLASMA

Freeze at -80 degrees celsius, separating the samples (as above – Sheffield only)

Time / date of freezing to be documented

SERUM

FILL 2x 6ml (Sheffield) OR 3x 4ml (Leeds) GOLD top (serum separator) tubes – time / date of venepuncture to be documented

Allow to clot at room temperature for a **minimum of 30 minutes, maximum of 60 minutes**
Centrifuge at **2000G (NOT RPM) for 10 minutes** at room temperature following the above

Label each vial with:

XXX070/ARIAD,
Patient Study number,
Date of birth
Date of sample
Visit – BL, M1, M2, M3, M6, M12
SERUM

Pipette off serum into **4x RED** top cryovials aiming for a volume of 1-1.8ml in each vial

Freeze at -80 degrees celsius, separating the samples storing two vials in one freezer and the other 2 in a separate freezer so have a back-up sample (Sheffield only)
Time / date of freezing to be documented

13.8. EXTERNAL PEER REVIEW LETTER FROM DR DAVID MILES

East and North Hertfordshire NHS

NHS Trust
Mount Vernon Hospital

Ref: DM/wl

8 December 2008

Mount Vernon Cancer Centre
Rickmansworth Road
Northwood
Middlesex
HA6 2RN

Tel: 01923 826111
Fax: 01923 844138
Direct Dial: 01923 844703

Professor David Dodwell
Consultant Clinical Oncologist
St James Institute of Oncology
Level4 Bexley Wing
St James Hospital
Becker Street
Leeds LS9 7TF

Dear Professor Dodwell

Re: An investigation of aromatase inhibitor induced arthralgia in the adjuvant treatment of breast cancer; the ARIAD study

Thank you very much for asking me to review this protocol, which aims to characterise the frequency and severity of joint symptoms with biochemical and radiological changes during aromatase inhibitor treatment of early stage breast cancer. As you highlight, the evaluation of this troublesome side effect of treatment has been inconsistent in the randomised data so far since most quality of life instruments used did not incorporate specific questions on arthralgia or problems with tenosinovitis. While there are some series in the literature as quoted in your introduction, these are frankly extremely small and identifying patients most likely at risk is limited and similarly the pathophysiology of this side effect is poorly identified.

While problems with aromatase inhibitors are now clearly recognised, your study also has the strength of including a cohort of patients treated with tamoxifen, which while widely regarded as not having problems with joint pain, clinical experience forces us to recognise that once again the incidence of such problems on tamoxifen was probably underestimated in the past.

While the aromatase inhibitors are clearly a significant development and associated with further reduction in risk of relapse and possibly death from early stage breast cancer, the frequency of these rheumatological symptoms certainly compromises compliance and strategies to improve our understanding of the aetiology and management of it are therefore extremely important.

It is encouraging to see that the primary endpoint of your study is an objective assessment of grip strength, which seems to correlate well with the limited data at least with radiological changes, particularly MRI.

Such observational studies in relatively unselected population are extremely important for the relatively unselected non-trial population and I am sure your study will yield useful information for the future management of patients on these medications.

Congratulations on an excellent study design, which I am sure will yield valuable information in a timely fashion.

With very best wishes
Yours sincerely

Professor David Miles MB BS BSc MD FRCP
Consultant Medical Oncologist

15 DEC 2008

13.9. ARIAD STUDY CASE REPORT FORM

Cancer Research Centre
Weston Park Hospital STH
The University of Sheffield

ARIAD

Trial eligibility and randomisation form

Patient's Initials |_|_|_|

Date of birth |_|_|_|_|_|_|

Date of informed consent |_|_|_|_|_|_|

Hospital/Centre _____

Hospital Number _____

Clinician _____

Inclusion criteria

Has the patient signed the informed consent form? ☐ Yes ☐ No

Does the patient have WHO performance status of 0, 1 or 2? ☐ Yes ☐ No

Is the patient a post-menopausal woman? ☐ Yes ☐ No

Post-menopausal status is defined as
- Age >55 and more than 5 years since cessation of menses
- Age ≤55 with cessation of menses for more than 12 months and serum FSH (follicle stimulating hormone) ≥ 15mU/ml and oestradiol levels of < 30 pg/ml
- Bilateral oophorectomy

Does the patient have

Completely resected oestrogen receptor positive breast cancer? ☐ Yes ☐ No

OR

Completely resected oestrogen receptor negative breast cancer and has not had adjuvant chemotherapy? ☐ Yes ☐ No

OR

Carcinoma in Situ or resected benign breast disease? ☐ Yes ☐ No

Exclusion criteria

Has the patient's menopause resulted from the administration of cytotoxic drugs or an LHRH analogue within 2 yrs? ☐ Yes ☐ No

Does the patient have a history of metabolic bone disease (Paget's disease, hyperparathyroidism)? ☐ Yes ☐ No

Does the patient use NSAIDs or corticosteroids daily? ☐ Yes ☐ No

If the patient uses NSAIDs has there been a two week washout period? ☐ Yes ☐ No

Is there evidence of recurrent or metastatic breast cancer or other active malignancy ☐ Yes ☐ No

Is there any medical, social or psychiatric condition making participation undesirable? ☐ Yes ☐ No

Registration

Due to start AI as upfront endocrine therapy for 5 years. ☐ Cohort A

Due to start AI as switch endocrine therapy after 2-3 years of prior tamoxifen treatment. ☐ Cohort B

Due to start tamoxifen for 5 years. ☐ Cohort C

Not receiving any endocrine therapy or chemotherapy ☐ Cohort D

Signature of investigator _____ Date of entry into trial |_|_|_|_|_|_|

Telephone 0114 226 5217 to register the patient and you will be given the trial number.

Date of registration |_|_|_|_|_|_|

Trial Number |_|_|_|_|_|

Trial ID Cohort code

Eligibility & Registration Page 1 of 1

STH15006

ARIAD XXX070
Draft Version 2 Date 09/09/2008

Patient's Initials |_|_|_| Trial Number |_|_|_|_| ARIAD

Previous medical history

		If yes specify diagnosis	Date of onset	Ongoing ✔
1. Neurological	☐ Yes ☐ No		|_|_|_|_|_|_|	☐
2. Psychiatric	☐ Yes ☐ No		|_|_|_|_|_|_|	☐
3. Cardiovascular	☐ Yes ☐ No		|_|_|_|_|_|_|	☐
4. Respiratory	☐ Yes ☐ No		|_|_|_|_|_|_|	☐
5. Gastrointestinal	☐ Yes ☐ No		|_|_|_|_|_|_|	☐
6. Hepatic	☐ Yes ☐ No		|_|_|_|_|_|_|	☐
7. Renal	☐ Yes ☐ No		|_|_|_|_|_|_|	☐
8. Genitourinary	☐ Yes ☐ No		|_|_|_|_|_|_|	☐
9. Musculoskeletal	☐ Yes ☐ No		|_|_|_|_|_|_|	☐
		NB Joint disease is recorded on next page		
10. Endocrine	☐ Yes ☐ No		|_|_|_|_|_|_|	☐
11. Haematological	☐ Yes ☐ No		|_|_|_|_|_|_|	☐
12. Other (specify) _____	☐ Yes ☐ No		|_|_|_|_|_|_|	☐

Menopause & HRT use

Date of menopause |_|_|_|_|_|_|

Has the patient previously taken HRT? ☐ Yes ☐ No If yes specify what _____

Length of time HRT taken |_|_| yrs Date stopped HRT |_|_|_|_|_|_|

Signature of investigator _____ Date |_|_|_|_|_|_|

Patient's Initials |_|_|_| Trial Number |_|_|_|_| ARIAD

Previous history of joint disease (inc family)

Morning stiffness ☐ Yes ☐ No

Limitation of movement ☐ Yes ☐ No

Joint pain ☐ Yes ☐ No

Numbness of hands ☐ Yes ☐ No

	Y/N	Year of onset	Family History
Gout	☐ Yes ☐ No	|_|_|_|_|	☐ Yes ☐ No
Osteoarthritis	☐ Yes ☐ No	|_|_|_|_|	☐ Yes ☐ No
Rheumatoid arthritis	☐ Yes ☐ No	|_|_|_|_|	☐ Yes ☐ No
Other (specify)			
_____	☐ Yes ☐ No	|_|_|_|_|	☐ Yes ☐ No
Psoriasis			☐ Yes ☐ No
IBD			☐ Yes ☐ No

Smoking History

Smoking ☐ Current ☐ Ex ☐ Never Cigarettes per day |_|_|_| Number of years |_|_|_|

Other therapies

Record herbal treatments, supplements etc under Concomitent medications

Other therapies eg Physiotherapy

Type of therapy	Start date	Ongiong	Provided benefit
_____	|_|_|_|_|_|_|	☐ Yes ☐ No	☐ Yes ☐ No
_____	|_|_|_|_|_|_|	☐ Yes ☐ No	☐ Yes ☐ No
_____	|_|_|_|_|_|_|	☐ Yes ☐ No	☐ Yes ☐ No

Signature of investigator _____ Date |_|_|_|_|_|_|

Patient's Initials ___ Trial Number ___ ARIAD

Baseline Visit

Samples

	Date		Not done	Date
Calcium	___.___ mmol/L	☐ N/K	FSH	___ IU/L	☐ N/K
Alkaline phospatase	___ IU/L	☐ N/K	LH	___ IU/L	☐ N/K
Phosphate	___.___ mmol/L	☐ N/K	Oestradiol	___ IU/L	☐ N/K

Has serum been stored? ☐ Yes ☐ No Has plasma been stored? ☐ Yes ☐ No

DXA scan

Date of Baseline DXA scan - must be within 4 weeks of commencing study ___

Height ___.___ m Weight ___.___ kg BMI ___.___ kg/m^2

L hand BMD (g/cm^2) **R hand** BMD (g/cm^2) **Average** BMD (g/cm^2)

Total ___.___ Total ___.___ ___.___

Radiology/MRI

Xray hand ☐ Yes ☐ No **Date** ___ **Results** ☐ Normal ☐ Abnormal

Comments _____

_____

_____

_____

USS hand ☐ Yes ☐ No **Date** ___ If yes complete USS scoring sheet

MRI hand Selected to have Hand MRI? ☐ Yes ☐ No If yes please complete scoring sheet

Assessments

Date ___

If no please give reason

Assessment sheet completed ☐ Yes ☐ No _____

HAQ completed ☐ Yes ☐ No _____

SF-36 completed ☐ Yes ☐ No _____

BPI completed ☐ Yes ☐ No _____

Complete Concomitant medications pages

Signature of investigator _____ Date ___

Patient's Initials | | | | Trial Number | | | | | ARIAD

1 month visit

Date of visit | | | | | | |

Has serum been stored? ☐ Yes ☐ No Has plasma been stored? ☐ Yes ☐ No

If no please give reason

Assessment sheet completed ☐ Yes ☐ No _____

HAQ completed ☐ Yes ☐ No _____

SF-36 completed ☐ Yes ☐ No _____

BPI completed ☐ Yes ☐ No _____

Complete Concomitant medications and Adverse events pages

Investigations

USS hand

Only performed if symptoms severe

☐ Yes ☐ No **Date** | | | | | | |

If yes complete USS scoring sheet

☐ Not done	**Date**		
FSH		IU/L	☐ N/K
LH		IU/L	☐ N/K
Oestradiol		IU/L	☐ N/K

2 month visit

Date of visit | | | | | | |

Has serum been stored? ☐ Yes ☐ No Has plasma been stored? ☐ Yes ☐ No

If no please give reason

Assessment sheet completed ☐ Yes ☐ No _____

HAQ completed ☐ Yes ☐ No _____

SF-36 completed ☐ Yes ☐ No _____

BPI completed ☐ Yes ☐ No _____

Complete Concomitant medications and Adverse events pages

Investigations

USS hand

Only performed if symptoms severe

☐ Yes ☐ No **Date** | | | | | | |

If yes complete USS scoring sheet

☐ Not done	**Date**		
FSH		IU/L	☐ N/K
LH		IU/L	☐ N/K
Oestradiol		IU/L	☐ N/K

Signature of investigator _____ Date | | | | | | |

Patient's Initials ___ Trial Number ___ ARIAD

3 month visit

Date of visit ___

Has serum been stored? ☐ Yes ☐ No Has plasma been stored? ☐ Yes ☐ No

Selected to have Hand MRI? ☐ Yes ☐ No If yes please complete supplementary sheet

If no please give reason

Assessment sheet completed ☐ Yes ☐ No _____

HAQ completed ☐ Yes ☐ No _____

SF-36 completed ☐ Yes ☐ No _____

BPI completed ☐ Yes ☐ No _____

Complete Concomitant medications and Adverse events pages

Investigations

USS hand

☐ Yes ☐ No **Date** ___

If yes complete USS scoring sheet

☐ Not done	**Date** ___
FSH	___ IU/L ☐ N/K
LH	___ IU/L ☐ N/K
Oestradiol	___ IU/L ☐ N/K

6 month visit

Date of visit ___

Has serum been stored? ☐ Yes ☐ No Has plasma been stored? ☐ Yes ☐ No

If no please give reason

Assessment sheet completed ☐ Yes ☐ No _____

HAQ completed ☐ Yes ☐ No _____

SF-36 completed ☐ Yes ☐ No _____

BPI completed ☐ Yes ☐ No _____

Complete Concomitant medications and Adverse events pages

Investigations

☐ Not done	**Date** ___
FSH	___ IU/L ☐ N/K
LH	___ IU/L ☐ N/K
Oestradiol	___ IU/L ☐ N/K

Signature of investigator _____ Date ___

Patient's Initials ___ Trial Number ___ ARIAD

12 month visit

Blood tests

	Date ___
Calcium	___.___ mmol/L ☐ N/K
Alkaline phospatase	___ IU/L ☐ N/K
Phosphate	___.___ mmol/L ☐ N/K

☐ Not done	Date ___
FSH	___ IU/L ☐ N/K
LH	___ IU/L ☐ N/K
Oestradiol	___ IU/L ☐ N/K

Has serum been stored? ☐ Yes ☐ No Has plasma been stored? ☐ Yes ☐ No

DXA scan

Date of 12 month DXA scan ___

Height ___.___ m Weight ___.___ kg BMI ___.___ kg/m^2

	BMD (g/cm^2)	T score +/-
L hand Total	___.___	___.___

	BMD (g/cm^2)	T score +/-
R hand Total	___.___	___.___

Assessments

Date of visit ___

If no please give reason

Assessment sheet completed ☐ Yes ☐ No _____

HAQ completed ☐ Yes ☐ No _____

SF-36 completed ☐ Yes ☐ No _____

BPI completed ☐ Yes ☐ No _____

Complete Concomitant medications and Adverse events pages

Hand Ultrasound

Only performed if changes seen at 3 month scan

☐ Yes ☐ No **Date** ___ If yes complete USS scoring sheet

Signature of investigator _____ Date ___

Patient's Initials |_|_|_| Trial Number |_|_|_|_| ARIAD

Off study form

Reason for coming off study

Date off study |_|_|_|_|_|_|

Tick one

Completed 12 months ☐

Patient wishes ☐

Death ☐

Date of death |_|_|_|_|_|_|

Cause of death _____

_____

Recurrence of breast cancer ☐

Investigator recommendation ☐

Signature of investigator _____ Date |_|_|_|_|_|_|

13.10. AROMATASE INHIBITOR-INDUCED ARTHRALGIA QUESTIONNAIRE

Please tick your response

1) Who are you?

- o Breast Surgeon
- o Clinical Oncologist
- o Medical Oncologist
- o Breast Care Nurse
- o Other……..(please specify)

2) Do you treat or see patients with early breast cancer?

- o No – Thanks for your time. **Please return questionnaire**
- o Yes - How many new (postmenopausal) ER+ patients do you treat PER YEAR?
  - o 0 - 20
  - o 20 - 50
  - o 50 – 100
  - o 100-150
  - o >150

3) To what proportion of your postmenopausal ER+ early breast cancer patients would you prescribe aromatase inhibitors (upfront or switch) over tamoxifen CURRENTLY?

- o 0%
- o 1 - 5%
- o 5 - 10%
- o 10 - 25%
- o 25 – 50%
- o 50 –75%
- o >75%

4) Do you think Arthralgia related to endocrine treatment is an important clinical problem?

- o Very important
- o Important
- o Neither important nor unimportant
- o Unimportant
- o Not a issue

5) How large an effect do you think it can have on patients' quality of life?

- o Very large
- o Large
- o Neither large nor small
- o Small
- o Very small

- No effect

6) In your opinion which of the AIs is associated most frequently with arthralgia?

- Anastrazole
- Letrozole
- Exemestane
- They are all the same
- Tamoxifen is just as bad

7) What do you think is the main cause of AI Arthralgia?

- Oestrogen deprivation
- Inflammatory joint process
- Inflammatory periarticular process
- Change in pain sensitivity
- Exacerbation of prior asymptomatic joint disease
- Don't know

8) In your experience which of the following characteristics do you associate with AI Arthralgia? (tick all that apply)

- Typically develops within a few weeks of starting an AI
- Persists until AI treatment discontinued
- Usually settles after a few months
- Predominantly affects large joints – e.g. hips and knees
- Predominantly affects small joints – e.g. hands and wrist
- Usually affects all joints

9) How often does AI arthralgia cause you to change endocrine treatment in your patients?

- Never
- Less than 5%
- 5-10%
- 10-20%
- 20-50%
- >50%

10) Are you aware of any guidelines for the management of AI Arthralgia?

- Yes…… … (please specify)
- No

11) What is your first step in the management of AI Arthralgia? (tick all that apply)

- Reassurance
- Non-opioid analgesic (e.g. Paracetamol)
- Mild opioid analgesic (e.g. Codeine)
- Strong opioid analgesic (e.g. Morphine)
- Anti-inflammatory (e.g. Diclofenac)
- Corticosteroid (e.g. Prednisolone)

- Physiotherapy
- Herbal remedy…….....
  (please specify)
- Change to tamoxifen
- Change to alternative AI……...……...
  (please specify)
- Refer to rheumatologist
- Other……...
  (please specify)

12) What is your second step in the management of persisting AI Arthralgia?

(tick all that apply)

- Reassurance
- Non-opioid analgesic (e.g. Paracetamol)
- Mild opioid analgesic (e.g. Codeine)
- Strong opioid analgesic (e.g. Morphine)
- Anti-inflammatory (e.g. Diclofenac)
- Corticosteroid (e.g. Prednisolone)
- Physiotherapy
- Herbal remedy……..…….
  (please specify)
- Change to tamoxifen
- Change to alternative AI…….…...……...
  (please specify)
- Refer to rheumatologist
- Other…….....
  (please specify)

13) What is your next step in the management of SEVERE persisting AI Arthralgia?

(tick all that apply)

- Reassurance
- Non-opioid analgesic (e.g. Paracetamol)
- Mild opioid analgesic (e.g. Codeine)
- Strong opioid analgesic (e.g. Morphine)
- Anti-inflammatory (e.g. Diclofenac)
- Corticosteroid (e.g. Prednisolone)
- Physiotherapy
- Herbal remedy……...
  (please specify)
- Change to tamoxifen
- Change to alternative AI…….……..
  (please specify)
- Refer to rheumatologist
- Other……..
  (please specify)

14) Do you check any blood parameters in patients reporting arthralgia?

(tick all that apply)

- Don't check bloods
- Check routine haematology, biochemistry, liver function
- Check simple inflammatory markers (ESR, CRP)
- Check autoantibody screen
- Other…… … (please specify)

15) Do you perform any radiological investigations in patients reporting arthralgia?

(tick all that apply)

- Never
- X-ray of affected joint(s)
- Ultrasound of affected joint(s)
- MRI of affected joint(s)
- Other……... (please specify)

16) Do you ever refer to a rheumatologist to exclude other causes of arthralgia?

- Yes, occasionally
- Yes, routinely
- No

17) On a scale of 1-5 how confident are you at managing AI Arthralgia?
(1=not at all confident, 5 = very confident)

1 2 3 4 5

18) Who do you think should be responsible for managing AI Arthralgia?

- GP
- Oncologist
- Breast Surgeon
- Rheumatologist
- Don't know

19) Do you feel your practice would benefit from national guidelines for the management of AI Arthralgia in early breast cancer patients?

- Yes
- No
- Don't know

Thank you for completing this questionnaire