Medicines Adverse Reactions Committee

Meeting date	7/12/2023	Agenda item	3.2.3
Title	Third generation aromatase inhibitors (AIs) and tendon disorders		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**[a]	**Sponsor**
Letrozole	Letrole Film coated tablet, 2.5 mg	Viatris Limited
	Letara Film coated tablet, 2.5 mg	Douglas Pharmaceuticals Limited
Anastrozole	Arimidex Film coated tablet, 1 mg	AstraZeneca Limited
	Anatrole Film coated tablet, 1 mg	Viatris Limited
	Rolin Film coated tablet, 1 mg	REX Medical Ltd
	Aremed Film coated tablet, 1 mg	AFT Pharmaceuticals Ltd
Exemestane	Exemestane Pfizer Coated tablet, 25 mg	Pfizer New Zealand Limited

[a] Products that are approved but not marketed in New Zealand are not shown.

PHARMAC funding	Letrole, Anatrole, Pfizer Exemestane (previously named Aromasin)
Previous MARC meetings	This topic has not previously been discussed by the MARC.
International action	Health Canada: Summary Safety Review (17 January 2023) [1] • Review concluded there was likely a link between third generation AIs and tendonitis and tenosynovitis, and a link with tendon rupture could not be ruled out. • Resulted in updates to product monographs (warnings and precautions, post-market adverse events) and patient medication information
Prescriber Update	N/A
Classification	Prescription medicine
Usage data	Dispensings in 2022: letrozole – 27,162; anastrozole – 7,863; exemestane – 5,556 (see section 2.2 for more information).
Advice sought	**The Committee is asked to advise:** • If there is sufficient evidence to support that there is a class effect for third generation AIs and tendon disorders. • If there is evidence to suggest the effect is not isolated to specific tendons/tendon sites. • If new adverse events/warnings should be added to the data sheet and CMI. If yes to the above, the Committee is asked to further advise: • Appropriate wording for new adverse events/warnings in the data sheet and CMI (e.g. adoption of the Canadian wording with or without modifications, or alternative wording). • If any further regulatory action is required (e.g. communications).

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1 PURPOSE

Medsafe was notified [redacted] about a safety review conducted by Health Canada on third generation aromatase inhibitors (AIs; anastrozole, exemestane, letrozole) and the potential risk of tendon disorders.

The purpose of this paper is to review the available information on this issue and consider whether further action is required in New Zealand.

2 BACKGROUND

2.1 Third generation aromatase inhibitors

Third generation AIs include letrozole, anastrozole, and exemestane; there are several products available in New Zealand [2-8]. They are indicated for the treatment of early and advanced breast cancer in post-menopausal women.

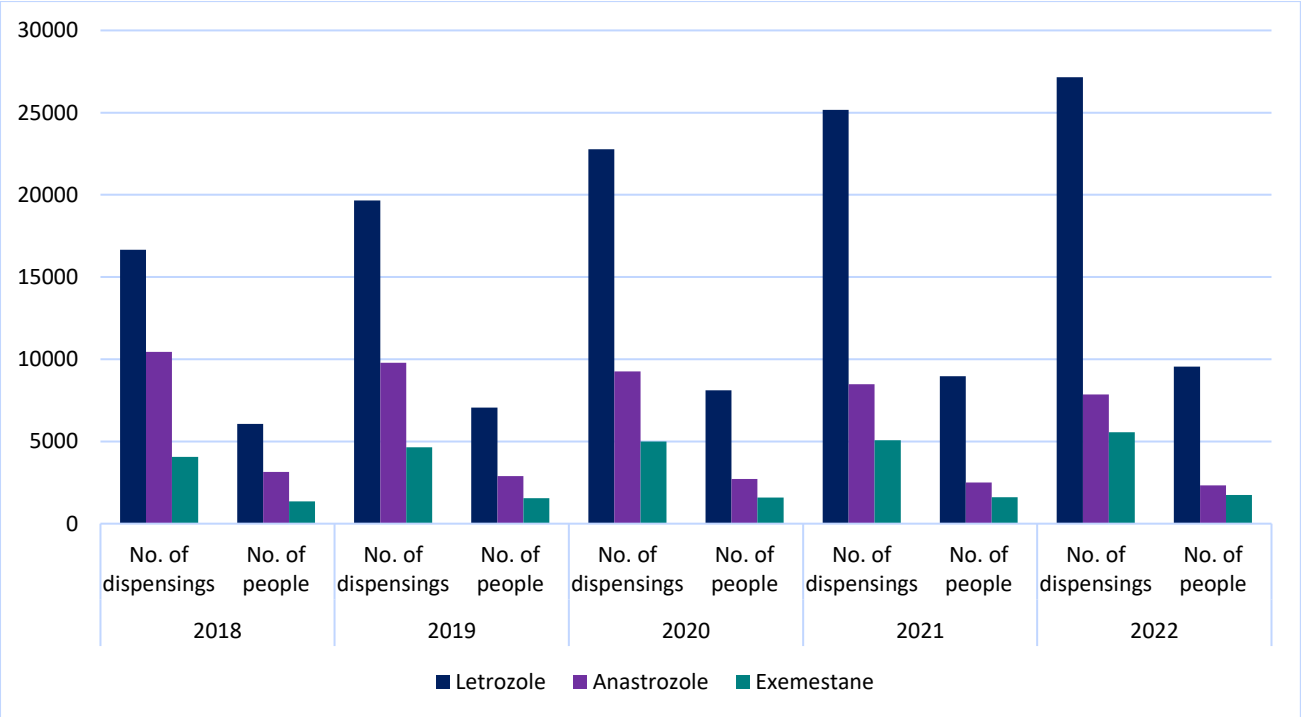
Anastrozole and letrozole are non-steroidal AIs, and exemestane is a steroidal AI [9]. AIs act predominantly by blocking the conversion of androgens to oestrogens in the peripheral tissues. They do not inhibit ovarian oestrogen synthesis. AIs are usually prescribed as initial adjuvant therapy in post-menopausal women with oestrogen-receptor-positive tumours.

Comments:
Note there are also off-label uses of aromatase inhibitors (e.g. letrozole for ovulation induction) [10].

2.2 Usage

Letrozole is the most frequently used third generation AI in New Zealand and its use is gradually increasing. In 2022 there were 27,162 dispensings to 9,546 people (Figure 1).

Figure 1 Third generation AI dispensing from 2018 to 2022



Source: Te Whatu Ora Pharmaceutical Data web tool (accessed 6 October 2023)

2.3 Tendon disorders

Tendon disorders include tendon inflammation (tendonitis), tendon tears (tendon rupture) and inflammation of the tendon sheath (tenosynovitis) [1]. Tendon disorders are often caused by overuse or sports injuries but are also associated with certain medical conditions (e.g., rheumatologic diseases and metabolic disorders) or medicines (e.g., fluoroquinolones and statins) [11]. Tendon disorders can cause serious physical limitations and, in some cases, require surgery [1].

It is well recognised that AIs are associated with various musculoskeletal adverse effects, which have become known as the AI-associated musculoskeletal syndrome (AIMSS) [12]. Musculoskeletal symptoms that have been described include arthralgias, myalgias, joint stiffness, and tendinopathy. Bone loss and associated fractures have also been reported. Arthralgias and bone loss are the most common reasons for early treatment discontinuation.

2.4 International regulatory action

2.4.1 Health Canada review [1]

On 17 January 2023 Health Canada published a Summary Safety Review which outlined the findings of their investigation into the risk of tendon disorders (tendonitis, tenosynovitis, tendon rupture) with the use of third generation aromatase inhibitors (anastrozole, exemestane, letrozole).

This review was triggered by an update to the letrozole product safety information to include the risks of tendonitis and tendon rupture, made by the European Medicines Agency (EMA). At the time of the review, the Canadian product monographs (CPMs) already included the risk of tenosynovitis of the hands.

Health Canada reviewed information from published and unpublished population-based studies and case reports of individual patient cases. The report briefly discusses findings from five randomised controlled trials (RCTs) and 25 case reports:

- *RCTs (total 28,873 patients):* Tendonitis and tenosynovitis were uncommon (<1%) and tendon rupture was rare (<0.1%).
- *Case reports (10 cases of tendon rupture and 15 cases of tendonitis):* Cases were reported for all three types of third generation AI and involved both the upper and lower limbs. Other medications and/or conditions were present that could have contributed to the adverse event. Case reports of tenosynovitis were not included in the review due to insufficient information in these reports.

The review concluded there was likely a link between third generation aromatase inhibitors and tendonitis and tenosynovitis, and a link with tendon rupture could not be ruled out. The Warnings and Precautions, Adverse Reactions (Post-Market Adverse Reactions), and Patient Medication Information sections of the CPM for Arimidex, Aromasin and Femara have been updated with the risks of tendonitis, tenosynovitis and tendon rupture [13]. The following statement is now included:

> *"The use of third generation aromatase inhibitors, including [AI type], was found to be associated with tendonitis and tenosynovitis as reported in randomized controlled trials. Tendon rupture was found to be a potential risk. Tendonitis and tenosynovitis were estimated to be of uncommon occurrence, and tendon rupture of rare occurrence. Treating physicians should monitor patients for these adverse drug reactions."*

2.4.2 Other regulators

2.4.2.1 EMA [14]

In 2019, the EMA reviewed the issue of tendonitis and tendon rupture in association with letrozole. PRAC reviewed the available evidence and concluded that the product information (section 4.4 and 4.8) should be updated to include the adverse drug reactions tendonitis (frequency uncommon) and tendon rupture (frequency rare).

They reviewed case reports as well as clinical trial data and other published literature. Seventy-seven post-marketing reports describing tendinopathies other than tenosynovitis of the hand were described as follows (cases could have more than one preferred term reported):

- tendonitis (47)
- tenosynovitis (22)
- tendon rupture (14)
- tendon disorders (14)
- tendon pain (8)
- epicondylitis/tennis elbow (5)
- tendon injury (3)
- tendon calcification (2)
- tendinous contracture (1)

The site of the tendonitis (and associated terms) varied: shoulder (24), Achilles (12), elbow (7), other (<3), and unspecified (18).

The clinical trial data and other published literature suggested that tendonitis occurred more commonly with letrozole versus placebo and other hormone therapies. A possible class effect with aromatase inhibitors and a potential pathophysiological mechanism (presence oestrogen receptors in tendons) was noted.

2.4.2.2 FDA [15]

The FDA is currently evaluating a safety signal for tendon disorders in relation to third generation aromatase inhibitors. As of 13 September 2023, they are evaluating the need for regulatory action.

2.4.2.3 Other

Pakistan – The Pharmacovigilance Risk Assessment Expert Committee (PREAC) have recommended updates to prescribing information, as per the Health Canada recommendations [16].

Hong Kong – The Drug Office has published a letter to healthcare professionals, and the issue will be reviewed by the Registration Committee of the Pharmacy and Poisons Board [17].

Malaysia – The National Pharmaceutical Regulatory Agency (NPRA) has published advice for healthcare professionals [18].

2.5 Prescribing information

2.5.1 New Zealand

New Zealand data sheets for third generation AIs already include some information relating to tendon disorders. The letrozole data sheets list tendonitis and tendon rupture (section 4.4 and 4.8), and trigger finger (a type of tenosynovitis of the hand; section 4.8). Trigger finger is listed in the anastrozole and exemestane data sheets (section 4.8), and tenosynovitis stenosans (also a type of tenosynovitis of the hand) in the exemestane data sheet (section 4.8).

Relevant sections of the data sheets and Consumer Medicine Information (CMI) of innovator products (or funded product where there is no approved innovator) are shown in Table 1.

Table 1 Presence of tendon disorders in New Zealand data sheets and CMI

Product (Sponsor)	Data sheet	CMI
Anastrozole		
Arimidex [3, 19] (AstraZeneca Limited)	**4.8:** Musculoskeletal and connective tissue disorders Uncommon – Trigger finger	**Side effects:** Trigger finger (where your fingers or your thumb catches in a bent position)
Letrozole		
Letrole [8, 20] (Viatris Limited)[a]	**4.4:** Tendonitis and tendon rupture Tendonitis and tendon ruptures (rare) may occur. Close monitoring of the patients and appropriate measures (e.g. immobilisation) must be initiated for the affected tendon (see section 4.8). **4.8:** Musculoskeletal and connective tissue disorders Uncommon – Tendonitis Rare – Tendon rupture Not known – Trigger finger	**Side effects:** Locking of the finger and pain (trigger finger)
Exemestane		
Exemestane Pfizer [5, 21] (Pfizer New Zealand Limited)	**4.8:** Post-marketing experience: Musculoskeletal and connective tissue disorders Trigger finger, tenosynovitis stenosans	Not listed

[a] Letrole is a funded generic. Approval for the innovator product has lapsed.
Source: Data Sheets and Consumer Medicine Information (medsafe.govt.nz)

Comments:

Only relevant adverse effects from the datasheet/CMI are listed above. Although the letrozole data sheets were include tendonitis and tendon rupture, the CMIs have not been updated to include these risks.

In addition to the above tendon disorders, the data sheets/CMI also list other musculoskeletal adverse events such as arthralgia, myalgia, bone pain, osteoporosis, bone fractures, arthritis, and carpal tunnel syndrome. There are also warnings regarding osteoporosis/fractures in section 4.4 of the data sheets.

2.5.2 International

Tendon disorders as listed in international prescribing/patient information of innovator products for anastrozole, letrozole, and exemestane are shown below.

2.5.2.1 Canada

<table>
<tr><th>Product (Sponsor)</th><th>Product monograph</th><th>Patient medication information</th></tr>
<tr><td colspan="3">Anastrozole</td></tr>
<tr><td>Arimidex [22]
(AstraZeneca Canada Inc)</td><td>7 Warnings and Precautions:
<u>Tendon Disorders</u>
The use of third generation aromatase inhibitors, including anastrozole, was found to be associated with tendonitis and tenosynovitis as reported in randomized controlled trials. Tendon rupture was found to be a potential risk. Tendonitis and tenosynovitis were estimated to be of uncommon occurrence, and tendon rupture of rare occurrence. Treating physicians should monitor patients for these adverse drug reactions.
8.5 Post-Market Adverse Reactions:
<u>Musculoskeletal and connective tissue disorders</u>
Tendonitis and tendon rupture</td><td>What are possible side effects from using ARIMIDEX?
• Trigger finger
<table>
<tr><th colspan="4">Serious side effects and what to do about them</th></tr>
<tr><th rowspan="2">Symptom / effect</th><th colspan="2">Talk to your healthcare professional</th><th rowspan="2">Stop taking drug and get immediate medical help</th></tr>
<tr><th>Only if severe</th><th>In all cases</th></tr>
<tr><td colspan="4">UNCOMMON</td></tr>
<tr><td>Tendon disorders including tendonitis (inflammation of the tendon) and tenosynovitis (inflammation of the tissue around the tendon): pain, swelling and tenderness near a joint.</td><td></td><td>✓</td><td></td></tr>
<tr><td colspan="4">RARE</td></tr>
<tr><td>Tendon tears: feel a snap or pop when the tear happens, severe pain, swelling.</td><td></td><td>✓</td><td></td></tr>
</table>
</td></tr>
<tr><td colspan="3">Letrozole</td></tr>
<tr><td>Femara [23]
(Novartis Pharmaceuticals Canada Inc)</td><td>7 Warnings and Precautions:
<u>Tendon Disorders</u>
The use of third generation aromatase inhibitors, including letrozole, was found to be associated with tendonitis and tenosynovitis as reported in</td><td>What are possible side effects from using FEMARA?
• Trigger finger, a condition in which your finger or thumb catches in a bent position.</td></tr>
</table>

<table>
<tr>
<td></td>
<td>randomized controlled trials. Tendon rupture was found to be a potential risk. Tendonitis and tenosynovitis were estimated to be of uncommon occurrence, and tendon rupture of rare occurrence. Treating physicians should monitor patients for these adverse drug reactions.
8.5 Post-Market Adverse Reactions:
<u>Musculoskeletal and connective tissue disorders</u>
Trigger finger, tendonitis, and tendon rupture</td>
<td>
<table>
<tr><th colspan="4">Serious side effects and what to do about them</th></tr>
<tr><th rowspan="2">Symptom / effect</th><th colspan="2">Talk to your healthcare professional</th><th rowspan="2">Stop taking drug and get immediate medical help</th></tr>
<tr><th>Only if severe</th><th>In all cases</th></tr>
<tr><td colspan="4">UNCOMMON</td></tr>
<tr><td>Tendon disorders including tendonitis (inflammation of the tendon) and tenosynovitis (inflammation of the tissue around the tendon): pain, swelling and tenderness near a joint.</td><td></td><td>✓</td><td></td></tr>
<tr><td colspan="4">RARE</td></tr>
<tr><td>Tendon tears: feel a snap or pop when the tear happens, severe pain, swelling.</td><td></td><td>✓</td><td></td></tr>
</table>
</td>
</tr>
<tr><td colspan="3">Exemestane</td></tr>
<tr>
<td>Aromasin [24]
(Pfizer Canada ULC)</td>
<td>7 Warnings and Precautions:
<u>Tendon Disorders</u>
The use of third generation aromatase inhibitors, including exemestane, was found to be associated with tendonitis and tenosynovitis as reported in randomized controlled trials. Tendon rupture was found to be a potential risk. Tendonitis and tenosynovitis were estimated to be of uncommon occurrence, and tendon rupture of rare occurrence. Treating physicians should monitor patients for these adverse drug reactions.</td>
<td>What are possible side effects from using AROMASIN?
<table>
<tr><th colspan="4">Serious side effects and what to do about them</th></tr>
<tr><th rowspan="2">Symptom / effect</th><th colspan="2">Talk to your healthcare professional</th><th rowspan="2">Stop taking drug and get immediate medical help</th></tr>
<tr><th>Only if severe</th><th>In all cases</th></tr>
<tr><td colspan="4">UNCOMMON</td></tr>
<tr><td>Tendon disorders including tendonitis</td><td></td><td>✓</td><td></td></tr>
</table>
</td>
</tr>
</table>

	8.5 Post-Market Adverse Reactions: Musculoskeletal and connective tissue disorders Trigger finger and de Quervain's tendonitis (tenosynovitis stenosans) have been reported in post-marketing reports as well as in clinical trials in association with AROMASIN. Tendonitis and tendon rupture have also been reported.	(inflammation of the tendon) **and tenosynovitis** (inflammation of the tissue around the tendon): pain, swelling and tenderness near a joint.			
		RARE			
		Tendon tears: feel a snap or pop when the tear happens, severe pain, swelling.		✓	

Source: Drug Product Database online query (canada.ca)

2.5.2.2 Australia

Product (Sponsor)	Product information	CMI
Anastrozole		
Arimidex [25, 26] (AstraZeneca Pty Ltd)	**4.8:** Musculoskeletal and connective tissue disorders Uncommon – Trigger finger	**Side effects** Uncommon side effects can include, trigger finger which is a condition in which one of your fingers or your thumb catches in a bent position.
Letrozole		
Femara [27, 28] (Novartis Pharmaceuticals Australia Pty Ltd)	**4.8:** Musculoskeletal and connective tissue disorders Uncommon – Trigger finger	**Are there any side effects?** **Less serious side effects** / **What to do** **Muscle or joint problems:** • Trigger finger (finger bent and stuck) **Speak to your doctor if you have any of these less serious side effects and they worry you.**
Exemestane		
Aromasin [29, 30] (Pfizer Australia Pty Ltd)	**4.8:** Post-marketing experience: Musculoskeletal and connective tissue disorders Trigger finger, tenosynovitis stenosans	Not listed

Source: Information about therapeutic goods in Australia (tga.gov.au)

2.5.2.3 United States

Product (Sponsor)	Prescribing information	Patient information
Anastrozole		
Arimidex [31] (ANI Pharmaceuticals Inc)	**6.2 Post-Marketing Experience:** Trigger finger	Not listed
Letrozole		
Femara [32] (Novartis Pharmaceuticals Corporation)	**6.2 Post-Marketing Experience:** Trigger finger	Could not locate
Exemestane		
Aromasin [33] (Pharmacia & Upjohn Company LLC)	**6.1 Clinical Trial Experience** In the IES study, as compared to tamoxifen, AROMASIN was associated with a higher incidence of events in musculoskeletal disorders and in nervous system disorders, including the following events occurring with frequency lower than 5%: … trigger finger (0.3% vs. 0%) … **6.2 Post-Marketing Experience:** Musculoskeletal and connective tissue disorder Tenosynovitis stenosans	Not listed

Source: FDA Label Search (fda.gov)

2.5.2.4 Ireland

Product (Sponsor)	SmPC	Package leaflet
Anastrozole		
Arimidex [34, 35] (Laboratoires Juvise Pharmaceuticals)	**4.8:** Musculoskeletal and connective tissue disorders Uncommon – Trigger finger	**Possible side effects** Uncommon side effects (affect 1 to 10 people in 1,000) • Trigger finger (a condition in which your finger or thumb catches in a bent position)

Letrozole		
Femara [36, 37] (Novartis Ireland Limited)	**4.4:** Tendonitis and tendon rupture Tendonitis and tendon rupture (rare) may occur. Close monitoring of the patient and appropriate measures (e.g immobilisation) must be initiated for the affected tendon (see section 4.8). **4.8:** Musculoskeletal and connective tissue disorders Uncommon – Tendonitis Rare – Tendon rupture Not known – Trigger finger	**What you need to know before you take Femara** Warnings and precautions Letrozole may cause inflammation in tendons or tendon injury (see section 4). At any sign of tendon pain or swelling – rest the painful area and contact your doctor. **Possible side effects** Some side effects could be serious: Uncommon (may affect up to 1 in 100 people): • Inflammation of a tendon or tendonitis (connective tissues that connect muscles to bones) Rare (may affect up to 1 in 1,000 people): • Rupture of a tendon (connective tissues that connect muscles to bones) Side effects with frequency not known (frequency cannot be estimated from the available data) • Trigger finger, a condition in which your finger or thumb catches • in bent position.
Exemestane		
Aromasin [38, 39] (Pfizer Healthcare Ireland)	Not listed	Not listed

Source: Find a medicine (hpra.ie)

Comments:

With the exception of Canada and the Irish information on letrozole, international prescribing/patient information is much the same as in New Zealand. The Canadian product monograph and patient medication information have been updated to include tendonitis, tenosynovitis, and tendon rupture following their review.

3 SCIENTIFIC INFORMATION

3.1 Published literature

A literature search was conducted to identify studies looking at aromatase and the potential risk of tendon disorders. Manual citation searching was also performed.

There is extensive literature on musculoskeletal side effects of AIs, however the literature on tendon disorders is more limited and consists mainly of prospective observational studies (mostly non-comparative) and case reports. No relevant data from randomised trials was identified.

Tendonitis and tenosynovitis following the use of AIs is often reported to be in the hand or wrist, but there are also reports of other areas of the body being affected. The method of diagnosis differs between studies. In some cases it is based on diagnostic imaging (e.g. MRI or ultrasound) while other studies based the diagnosis on clinical history and examination alone. Three cases of tendon rupture of the rotator cuff tendons have also been reported.

There is insufficient information to compare the different AI types. Most reports relate to anastrozole and letrozole which are more widely used than exemestane.

Relevant studies from the literature search are described below in alphabetical order (by author name).

Comments:

Health Canada refers to randomised trial data in their Summary Safety Review, however these studies were not identified in our literature search. Some randomised trials were identified through citation searching and a separate Google search, however review of these publications did not identify any reporting of tendon disorders.

Health Canada has been approached for more information about the evidence they reviewed. Their response is awaited.

3.1.1 Studies examining various body sites

3.1.1.1 Briot 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 [40]

Aims: To evaluate the effect of a switch of AI (from anastrozole to letrozole) on musculoskeletal symptoms in postmenopausal women with hormone-receptor-positive (HR+) breast cancer, and to identify the factors associated with subsequent discontinuations from AI therapy (letrozole). The trial also evaluated the prevalence and severity of the musculoskeletal symptoms.

Methods: This was a prospective, non-randomised, open-label, multicentre trial (37 centres in France) conducted between 2005 and 2007.

Eligible patients were postmenopausal women with HR+ breast cancer treated with adjuvant anastrozole who were experiencing lasting and severe musculoskeletal symptoms to the point of stopping their treatment. Patients who wanted to stop anastrozole were switched to letrozole after a 1-month washout and were followed up for 6-months. Musculoskeletal symptoms were systematically assessed for severity, location of the

symptoms, presence of swelling and of morning stiffness by the oncologist at study entry, 1 month after the discontinuation of anastrozole, and 1, 3, and 6 months after initiating the letrozole therapy.

Results: 179 patients were enrolled over 2 years. The average age of participants was 61.3 years (SD 8.4). At study entry, participants had been taking anastrozole for a mean of 14.3 months (SD 10.5). At the baseline visit, 156 patients (87.2%) reported symptoms of arthralgia, 71 (39.7%) myalgia, 49 (27.4%) polyalgic syndrome, 36 (20.1%) tendinitis, and 31 (17.3%) arthritis. The hands, knees, spine, shoulder, and wrist were most commonly affected, and most patients experienced symptoms in 4 or more joints (72.6%).

At the end of the 6-month study, 128 (71.5%) patients were still taking letrozole and 51 (28.5%) had discontinued treatment due to musculoskeletal symptoms. At the end of the 6-month treatment with letrozole, 116 (73.9%) patients had arthralgia, 33 (21.0%) myalgia, 25 (15.9%) arthritis, 22 (14.0%) tendinitis, and 20 (12.7%) polyalgic syndrome. The number of joints affected also reduced on switching with only 37.6% of patients experiencing symptoms in 4 or more joints. See Figure 2.

Figure 2 Proportion of patients with musculoskeletal symptoms after first AI treatment (anastrozole) and after 6-months treatment with second AI (letrozole) (a) and number of joints involved (c)

Study author's conclusions: Aromatase inhibitors use results in increased musculoskeletal symptoms which can be managed by non-pharmacological and pharmacological interventions. This study suggests that switching from one non-steroidal AI to another one can result in prolong treatment with the adjuvant hormonal therapy in postmenopausal women with HR+ breast cancer troubled by musculoskeletal symptoms.

Comments:
This study indicates in patients with severe AI-related musculoskeletal symptoms, tendinitis was a common presentation. The study also suggests that musculoskeletal symptoms may improve on switching to a different AI (at least enough to prolong treatment), however there was no comparison group. The study reported the joints most commonly affected and the number of joints involved, however this was for pain in general rather than for tendonitis specifically.

3.1.1.2 Dizdar et al, 2009 – Sonographic and electrodiagnostic evaluations in patients with aromatase inhibitor-related arthralgia [41]

Aims: To investigate the prevalence of arthralgia in breast cancer patients taking AIs and perform a detailed rheumatologic assessment including autoimmune serology, musculoskeletal sonography, and electromyography (EMG) in these patients.

Methods: Consecutive postmenopausal patients with stage I to III breast cancer taking anastrozole, letrozole, or exemestane as adjuvant endocrine therapy were enrolled from one centre in Turkey. Patients currently not receiving hormone treatment were included as a control group. At study entry patients were asked "Have you had any joint pain recently, which started or worsened after initiation of AI treatment?" A detailed

rheumatologic assessment including autoimmune serology, musculoskeletal sonography, and EMG was assessed.

Results: 92 AI patients and 28 controls were included, median age 57 years (range 42-78). AIs were anastrozole (46 patients), letrozole (40 patients), and exemestane (3 patients). Thirty (30) AI patients reported new or worsening arthralgia of the knee (70%), wrist (70%), hand (63%), and back (17%).

Sonography was performed in 66 AI patients (26 with arthralgia and 40 without) and 19 controls. Overall, tendons of AI patients were thicker than those of controls ($p < 0.001$) and this difference persisted after correction for BMI. In subgroup analysis, total tendon thicknesses of patients with and without AI-related arthralgia were similar and both were higher than those of controls ($p < 0.001$) (Table 2).

Table 2 Sonographic Findings of the Patients and Controls

In nerve conduction studies more AI patients with arthralgia had EMG findings consistent with carpal tunnel syndrome compared to AI patients without arthralgia (46.2% vs 30%, $p = 0.024$). The difference was not significant compared to controls. The authors state that thickened tendons and effusion in tendon sheaths may increase the intracompartmental pressure and could lead to carpal tunnel syndrome.

No significant differences were observed in the autoimmune/inflammatory laboratory tests.

Study author's conclusions: Patients with AI-related arthralgia often show tenosynovial changes suggesting tenosynovitis, exerting local problems but lacking a systemic inflammatory component. However, some patients have no tenosynovial or electrophysiologic changes despite having symptoms of arthralgia which indicates that other mechanisms also play a role in the pathogenesis of these symptoms.

Comments:

Although no statistical comparison of Group B (AI without arthralgia) vs controls is presented, the clinical parameters for tendon thickness for Group B appear similar to the AI with arthralgia group.

Arthralgia is one of the most commonly reported adverse reactions reported in clinical trials for all three third generation AIs (listed as 'very common' in the data sheets). This study may suggest that tendon abnormalities could be an underlying cause in some cases.

Note the authors also suggest that tendon thickening/effusion may be a cause of carpal tunnel syndrome (carpal tunnel syndrome was seen in clinical trials and is already included in the data sheets).

3.1.1.3 Henry et al, 2008 – Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors [42]

Aims: To describe the musculoskeletal symptoms that developed in the first 100 subjects enrolled in the study who had at least 6 months follow-up.

Methods: This is a sub-study of a multicentre (3 centres in the US) randomised clinical trial where women with early stage hormone receptor-positive breast cancer were randomised to letrozole or exemestane. In this sub-study patients completed the Health Assessment Questionnaire (HAQ) and Visual Analog Scale (VAS) at baseline, 1, 3, 6, and 12 months to assess changes in function and pain, respectively. Patients were referred for evaluation by a rheumatologist if their HAQ and/or VAS scores exceeded a predefined threshold.

Results: 100 patients were enrolled in the sub-study with a median follow-up time of 12 months (range 6.5-20.1), median age 59 years (range 38-83). 44 patients (45%) were referred for rheumatological assessment and 38 were assessed. There were no significant differences in baseline characteristics of patients who met criteria for referral versus those who did not. At time of rheumatology evaluation, the primary symptoms were joint pain and achy and stiff joints. Other symptoms included muscle pain, morning stiffness, tingling, numbness, and joint swelling. The joints primarily involved were hands and wrists (14 patients), shoulders (12), knees (11), feet and ankles (9), spine (7), and hips (5). None of the laboratory findings suggested a rheumatologic aetiology for the musculoskeletal symptoms. Diagnoses are shown below in Table 3 (some patients had more than one diagnosis). Tendonitis was diagnosed in 36.8% of patients (most commonly at the shoulder). 13 patients discontinued therapy because of intolerable musculoskeletal toxicity.

Table 3 Clinical diagnoses for patients referred to rheumatology (n = 38)

[redacted]

Study author's conclusions: Musculoskeletal side effects were common in AI-treated patients, resulting in therapy discontinuation in more than 10% of patients. There are no identifiable pre-therapy indicators of risk, and the aetiology remains unclear.

Comments:
Tendonitis appears to be a common diagnosis in patients taking AIs who present with musculoskeletal pain. It appears that diagnosis was based on clinical history and examination (rather than imaging) however this is not completely clear. Results were not reported separately for patients taking letrozole versus exemestane. Note there is no comparison group in this study.

3.1.1.4 Laroche et al, 2014 – Classification of and Risk Factors for Estrogen Deprivation Pain Syndromes Related to Aromatase Inhibitor Treatments in Women With Breast Cancer: A Prospective Multicenter Cohort Study [43]

Aims: 1) To describe and classify the AI-related pain symptoms developing within 1 year of oestrogen deprivation related to the initiation of AI treatment in previously pain-free women and 2) To investigate extensive predictors of pain development in an oestrogen deprivation clinical model of pain.

Methods: This was a 1-year observational multicentre prospective cohort study with recruitment at 4 medical oncology departments and extensive pain assessment at 1 pain clinic in university hospitals in Paris, France. Consecutive women treated for early breast cancer at four medical oncology departments were eligible to

participate if they were free of pain and starting AI treatment. Pain was classified through questionnaires and clinical examination. Psychological and quality of life questionnaires were also conducted.

Results: 135 postmenopausal women were recruited and included in the analysis. Mean age was 61.5 years (SD 7.1)and 67% received letrozole, 32% anastrozole, and 0.74% exemestane. During the study period, 77 (57%) of the 135 patients developed pain. 12 people stopped their AI treatment because of pain.

5 primary types of pain syndromes were identified: joint pain (36%), diffuse pain (22%), tendinitis (22%), neuropathic pain (9%), and mixed pain (a combination of joint and tendinitis pain, 11%) (Table 4). In multivariate logistic regression higher levels of fatigue (MFI–20) and more severe arm symptoms (QLQ-BR23) were independent predictors for tendinitis.

Table 4 Characteristics of 4 Isolated Pain Types

[redacted]

Study author's conclusions: AI-related pain is frequent and may develop in patients initially free of pain. Oestrogen deprivation-related pain syndromes are not limited to arthralgia. Even in this biologically induced pain condition, the risk factors for pain development are mostly psychological, with genetic and biological factors not appearing to play a major role.

Comments:
Cause of pain was not reported separately based on AI type. Tendinitis pain was reported to typically affect the upper limbs. Diagnosis was based on symptoms and clinical examination (no imaging performed). Note there is no comparison group in this study.

3.1.1.5 Martens et al, 2007 – Severe disabling tendinopathy caused by anastrozole [44]

This is a case report describing a patient with severe, disabling tendinopathy during treatment with the aromatase inhibitor anastrozole (Arimidex®). Diagnosis was made via MRI.

A 55 year old female was referred to a Department of Rheumatology for severe, disabling pain and swelling at the wrists. A year before she had started treatment with anastrozole for oestrogen receptor-positive breast cancer. Since commencing anastrozole she experienced non-severe myalgias and morning stiffness. Worsening pain and swelling at the radial side of the right wrist developed 5 months into treatment (she later developed left wrist pain too). She also had pain in the Achilles tendons, but no pain or swelling of joints. There were no signs of underlying systemic disease, there was no abnormal physical activity preceding the complaints, and the patient was on no other medicines.

Physical examination: Tender swelling on the radial side of both wrists. Resisted extension and abduction of the thumbs produced pain, but Finkelstein's test was negative. Both Achilles tendons were tender. There were no signs of arthritis, and no further abnormalities at physical examination.

Investigations: Inflammatory and rheumatoid markers were normal, as were other routine blood tests. Radiographs of hands and wrists and a bone scan was normal. Ultrasound showed a thickening and irregular

aspect of the tendon of the abductor pollicis longus muscle on the right wrist, but there were no signs of tenosynovitis. Power Doppler revealed an increased vascularity of the tendon, confirming active inflammation.

Diagnosis and management: The diagnosis of tendinopathy of the tendon of the abductor pollicis longus muscle was made. De Quervain's tenosynovitis was considered unlikely based on the ultrasound findings. The involvement of both wrists and the Achilles tendons suggest the presence of a (diffuse) tendinopathy. Non-steroidal anti-inflammatories and splinting of the wrist had no effect. Symptoms improved after discontinuation of anastrozole.

Study author's conclusions: To our knowledge, this is the first case describing a tendinopathy caused by an aromatase inhibitor. As complaints caused by tendinopathy can be severe and aromatase inhibitors are increasingly used in the treatment of breast cancer, one has to be aware of this possible side effect.

Comments:
This paper suggests that tendinopathy secondary to AI use can involve multiple tendons and that hand symptoms may not always be due to tenosynovitis.

3.1.1.6 Mitsimponas et al, 2018 – Aromatase Inhibitor-Associated Tendinopathy and Muscle Tendon Rupture: Report of Three Cases of This Exceedingly Rare Adverse Event [45]

This is case series of three postmenopausal women who were treated with letrozole in the adjuvant setting and developed severe tendinopathy or muscle tendon rupture. Diagnosis was made via MRI.

Case 1: 74 year old female, stage IIB hormone-receptor positive breast cancer treated with mastectomy followed by adjuvant chemotherapy and radiotherapy, and subsequently letrozole. Persistent left shoulder pain one year after the initiation of letrozole. MRI revealed partial rupture of supraspinatus tendon.

Case 2: 62 year old female, stage I hormone-receptor positive breast cancer treated with lumpectomy followed by adjuvant chemotherapy and radiotherapy, and subsequently letrozole. Persistent left shoulder pain 11 months after the initiation of letrozole. MRI revealed severe tendinopathy of the supraspinatus tendon.

Case 3: 71 year old female, stage IIA hormone-receptor positive breast cancer treated with lumpectomy followed by radiotherapy, and subsequently letrozole. Persistent right shoulder arthralgia 18 months after the initiation of letrozole. MRI revealed complete rupture of the supraspinatus and subscapularis tendons and partial rupture of the infraspinatus tendon.

There were no signs of underlying systemic disease, no abnormal physical activity preceding the complaints, and no use of other drugs beside letrozole in any of the patients. The treatment of tendinopathy or tendon rupture consisted of AI discontinuation, initiation of corticosteroids, or surgical treatment.

Study author's conclusions: AIs are one of the most commonly used drugs in antihormonal therapy for hormone receptor-positive breast cancer. In every case of a female patient with hormone receptor-positive breast cancer under treatment with AIs and arthralgia, an MRI should be performed in order to exclude the presence of tendinopathy or muscle tendon rupture.

Comments:
There is limited literature on tendon rupture in association with AI treatment. One reason could be that diagnostic imaging is not routinely performed in people presenting with joint pain.

3.1.1.7 Singer et al, 2012 – Defining the Aromatase Inhibitor Musculoskeletal Syndrome: A Prospective Study [46]

Aims: The objective of this study was to define the musculoskeletal syndrome associated with use of Aromatase Inhibitors (AIs). The specific aims are to describe its incidence, time to onset, risk factors and clinical presentation.

Methods: This was a prospective single centre study. Post-menopausal women with stage I-III hormone receptor positive breast cancer, starting adjuvant AI therapy were enrolled. Patients with prior history of AI use, recent corticosteroid use, or prior rheumatologic diagnosis were excluded. Participants were evaluated by a rheumatologist at baseline, 3- and 6-months. Patients were considered symptomatic if they reported new or worsening muscle and/or joint symptoms since starting AIs. Participants had bilateral hand and wrist MRI at baseline and 6-months. MRIs were interpreted using a modified OMERACT Rheumatoid Arthritis MRI Scoring system with Tenosynovitis Subscale (RAMRIS-TS). Quality of life (QOL) questionnaires were performed.

Results: 55 patients were enrolled (52 analysed), mean age 60.3 years (range 44-76). Ninety-two percent of the patients were prescribed anastrozole and 8% letrozole, 54% had switched from tamoxifen and 61% had stage I disease.

28 patients (54%) developed new or worsening musculoskeletal symptoms, most commonly of the hands and/or wrists (68%) or feet and/or ankles (32%). Two (3.8%) stopped AIs as a result of musculoskeletal symptoms. Mean time to symptom onset was 6 weeks (range 2-18). Later stage cancer and poorer QOL were predictive of symptom development.

On physical examination, 13 patients showed signs of tendon sheath inflammation and/or enthesitis. This related to the hand in 8 patients (3 patients had a positive Finkelstein test for de Quervain's tendinitis, 4 had tenderness over the digital flexor tendons, and 1 had locking of the digit), and the feet in 5 patients (4 had tenderness over the plantar fascia and 1 the Achilles tendon).

38 patients had both baseline and follow-up MRIs of the hand/wrist. There was no difference in either the mean or the proportion of abnormal baseline RAMRIS-TS scores between symptomatic and asymptomatic groups (data not shown), and there was no difference in the change in RAMRIS-TS scores between groups.

Study author's conclusions: The incidence of AI associated musculoskeletal syndrome is over 50% with most women developing symptoms by 8 weeks of treatment. The key finding in symptomatic women was focal tenosynovitis of the hands and feet, without evidence of autoimmune disease or systemic inflammation.

Comments:
Clinical signs of tenosynovitis were not consistently demonstrated on MRI in this group of patients based on the scoring system used (only hands/wrists were imaged). Authors commented that the scoring system may not have been ideal. Hands were most commonly affected, but signs of tendon sheath inflammation and/or enthesitis were also reported in the foot/ankle.

3.1.2 Studies examining hand/wrist only

3.1.2.1 Henry et al, 2010 – A prospective study of aromatase inhibitor-associated musculoskeletal symptoms and abnormalities on serial high-resolution wrist ultrasonography [47]

Aims: Tendon sheath fluid and tenosynovial changes have been demonstrated by imaging symptomatic patients who were treated with AIs. The authors hypothesized that these abnormalities are correlated with aromatase inhibitor-associated musculoskeletal symptoms and abnormalities (AIMSS).

Methods: This is a sub-study of a multicentre randomised clinical trial (see Henry et al, 2008) including 30 consecutive patients intending to initiate AI therapy. The patients had no history of significant wrist injury, surgery, or carpal tunnel syndrome. Patients underwent high-resolution ultrasonography of the wrists bilaterally and completed the Health Assessment Questionnaire (HAQ) and pain Visual Analog Scale (VAS). AIMSS were defined as an increase in the HAQ or VAS score during AI therapy that exceeded a predefined cutoff.

Results: 25 patients completed the baseline and 3-month assessment. 72% reported joint pain at the 3-month assessment. Wrist ultrasound abnormalities at baseline were common (48.3% tendon sheath abnormalities, 6.9% tendon abnormalities, and 82.8% joint recess abnormalities). Most new changes at the 3-month assessment related to the joint recess (48%), but only a small number of patients developed tendon-related

abnormalities (20% tendon sheath abnormalities, no tendon abnormalities). 15 patients developed AIMSS during the 12 month follow-up. There was no statistically significant association between the presence of tendon sheath abnormalities on wrist ultrasound at baseline and the development of AIMSS.

Study author's conclusions: Clinically relevant musculoskeletal symptoms develop in women treated with AIs, leading to treatment discontinuation in a substantial percentage of these patients. However, in the current study, patient-reported symptoms were not found to be associated with changes visible on wrist ultrasonography.

Comments:

Only a small number developed new tendon sheath abnormalities of the wrist during the study, but it is not clear what proportion of these patients were symptomatic. Joint abnormalities were more common. Results were not reported separately for patients taking letrozole versus exemestane. Note there is no comparison group in this study.

3.1.2.2 Morales et al, 2008 – Prospective Study to Assess Short-Term Intra-Articular and Tenosynovial Changes in the Aromatase Inhibitor–Associated Arthralgia Syndrome [48]

Aims: To investigate the changes in clinical rheumatologic features and magnetic resonance imaging (MRI) of hands and wrists in AI and tamoxifen users.

Methods: This is a prospective single-centre study including consecutive postmenopausal patients with early breast cancer receiving either tamoxifen. At baseline and 6 months, patients completed a rheumatologic questionnaire, had a rheumatologic examination including a grip strength test, and an MRI of the hands and wrists.

Results: 17 patients were included (12 AI and 5 tamoxifen), mean age 65 years (range 54-74). Patients in the tamoxifen group were younger. AIs used were letrozole, (5), exemestane (4), and anastrozole (3). Most (12) patients had baseline degenerative joint disease. On baseline MRI there was fluid accumulation seen in the joints of 3 AI patients and 1 tamoxifen patient. Tenosynovial abnormalities were seen in 3 AI patients and 1 tamoxifen patient.

At 6 months, 92% of AI patients and 60% of tamoxifen patients had changes from baseline in clinical examination parameters or patient complaints. AI patients had statistically significantly reduced grip strength (p=0.0049), and this was significantly correlated with tenosynovial changes on MRI (Spearman correlation = −0.64; P = .0074). On MRI follow-up, 11 AI patients had worsening of pre-existing changes or new onset of any pathology of joints or tendons; tenosynovial changes were statistically significantly worse than baseline (0.001). Three of four tamoxifen patients with follow-up had no changes. See Table 5.

Table 5 Magnetic Resonance Imaging Tenosynovial Changes After 6 Months of Antihormone Therapy

[redacted]

Study author's conclusions: The functional impairment of hands in the AI-associated arthralgia syndrome is characterized by tenosynovial changes on MRI correlating with a significant decrease in hand grip strength.

Comments:

As seen in the 2010 paper by Henry et al, tenosynovial abnormalities were seen in baseline hand/wrist MRI in some patients. However, by 6 months almost all AI patients had developed changes in symptoms or

clinical examination, and tenosynovial changes on MRI were statistically significantly worse than baseline. Other joint abnormalities were also seen. Fewer tamoxifen patients experiences worsening of MRI findings, however patient numbers were small.

3.1.2.3 Shin et al, 2022 – Carpal tunnel syndrome and tenosynovitis in women with breast cancer associated with hormone therapy [49]

Aims: The study aims to evaluate the characteristics, treatments, and incidence rates of carpal tunnel syndrome (CTS) and tenosynovitis in women with breast cancer, according to the hormone therapy used.

Methods: Patients with breast cancer were identified from the clinical data warehouse of the six hospitals in Korea. The electronic medical record (EMR) of patients with CTS or tenosynovitis (ICD-10 codes for tenosynovitis, de Quervain's disease, or trigger finger; M65 and M75) were reviewed. Patients with tenosynovitis of the of the lower limbs and proximal upper limbs, or a prior history of CTS or tenosynovitis were excluded. Medicine use was determined by electronic prescribing records. The incidence of CTS or tenosynovitis was compared in patients who received aromatase inhibitors, tamoxifen, and no hormone therapy.

Results: A total of 101 patients among a population of 15,504 were included, mean age at diagnosis 54 years (IQR 47-59). Two patients were prescribed AIs, 32 tamoxifen and 27 were not prescribed hormone therapy. There were no significant demographic differences among the groups, except age (those who received tamoxifen or no hormone therapy were significantly more likely to be aged <60 years compared to those who received an AI). AI users presented with a higher incidence of CTS (1.3%) than patients without hormone therapy (0.4%), and tenosynovitis occurred at a higher rate in AI users (2.3%) compared to the tamoxifen (1.1%) and no hormone groups (0.5%) (Table 6).

Table 6 Overall incidence of carpal tunnel syndrome and tenosynovitis according to the treatment allocation

Study author's conclusions: In summary, the overall (CTS or tenosynovitis) disease incidence differed significantly according to the hormone treatment used. Patients with AI were more liked to develop CTS or tenosynovitis than patients without hormone therapy, and there were more cases of tenosynovitis in the AI group compared to the tamoxifen group.

Comments:

Carpal tunnel syndrome and tenosynovitis of the distal upper limb were more commonly reported in AI patients compared to those receiving tamoxifen or placebo. Results were not reported separately based on

AI type and it is not clear what proportion of patients received each type of AI. This study relies on electronic diagnosis coding and prescription records.

Note that there are other studies examining carpal tunnel syndrome and tenosynovitis/stenosing tenosynovitis of the hand, however given these are already listed in the data sheet they are not discussed further in this report.

3.1.3 Other papers of note

Kirchgesner et al, 2014 discuss tendon anatomy and the pathophysiology and radiological manifestations of tendinopathies as well as the main characteristics of each of the drugs classes associated with tendon toxicity [50]. The authors state that aromatase inhibitors have been incriminated in recent years in the occurrence of tendinopathy (specifically synovitis and tenosynovitis of the fingers) and that the presence of oestrogen receptors within the intermediate layer of the pulleys and retinacula has been proposed as a possible explanation.

Hyder et al, 2021 discuss the AI Musculoskeletal Syndrome (AIMSS) and compare the different aromatase inhibitors [12]. AIMSS is described as a constellation of musculoskeletal symptoms such as arthralgias, myalgias, joint stiffness, and tendinopathy associated with AI use. The authors discuss the literature that evaluates differences between AIs. Letrozole is noted to be more potent than anastrozole and exemestane at prescribed doses. They describe two studies which demonstrated that letrozole suppressed oestrogen levels to a greater extent than anastrozole. However, the clinical significance is unclear and studies have not shown letrozole to be associated with more severe AIMSS. The data for exemestane was said to be limited.

Sara Christensen Holz, 2023 also discusses the literature on AIMSS [51]. Mechanisms for tendinopathy and tendon tears associated with AI use are discussed in the paper. Although the cause is not known, one proposed mechanism is apoptosis of tenocytes and tenoblasts leading to abnormal extracellular matrix maintenance and repair as well as disrupted intercellular signalling and structural disintegration. Increased expression of lytic enzymes, lessened cholesterol content in cell membranes, and neoangiogenesis within highly ordered tendon tissue are stated as possible factors. Intrinsic factors such as age and joint laxity and extrinsic factors such as occupation and activities are also considered likely risk factors.

Comments:

These papers are included as they provide some information on mechanism of action and possible differences between aromatase inhibitors which may be helpful in determining whether this is a class effect. The 2021 paper by Hyder et al may be of more limited relevance given the broad focus on AIMSS.

3.2 CARM data

As of 7 November 2023, there were 149 reports in the CARM database where letrozole, anastrozole, or exemestane were reported as a suspect medicine (accessed: 14 November 2023).

Of these, 41 (26 letrozole, 15 anastrozole, 1 exemestane)[1] relate to the musculoskeletal and connective tissue SOC, however none are specified as tendon disorders. Arthralgia and myalgia were most commonly reported.

3.3 International data

3.3.1.1 DAEN (Australia)

As of 1 November 2023, there were 993 reports in the Database of Adverse Event Notifications (DAEN) relating to the musculoskeletal and connective tissue SOC where letrozole (862), anastrozole (101), or exemestane (30) were reported as a suspect medicine (source: DAEN – medicines, accessed: 15 November 2023). However, only

[1] Total adds to 42 as one report had both letrozole and anastrozole listed as suspect medicines.

a small number of these reports are specified as tendon disorders – 3 trigger finger (1 letrozole, 2 anastrozole), 1 tendon pain (anastrozole), 1 tenosynovitis (anastrozole).

3.3.1.2 FAERS (United States)

As of 30 September 2023, there were 13,436 reports in the FDA Adverse Event Reporting System (FAERS) relating to the musculoskeletal and connective tissue SOC where letrozole (6,207), anastrozole (5,727), or exemestane (2,583) were reported as a suspect medicine. 709 cases relate to tendon disorders – these reactions are shown below in Table 7.

Table 7 FAERS database – case reports for tendon disorders and third generation AIs

Reaction (PT)	Number of Cases (All)	Number of cases (Letrozole)	Number of cases (Anastrozole)	Number of cases (Exemestane)
Total Cases	**709**	**280**	**377**	**118**
Trigger Finger	406	146	227	60
Tendonitis	194	91	97	29
Tendon Pain	44	21	29	8
Tenosynovitis Stenosans	43	21	16	7
Tenosynovitis	39	15	18	8
Tendon Disorder	38	11	19	9
Tendon Calcification	5	5	0	0
Tendon Discomfort	4	1	1	2
Tendinous Contracture	1	0	1	0

Source: FAERS Public Dashboard, accessed: 15 November 2023.

3.3.1.3 Vigibase (International)

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]

4 DISCUSSION AND CONCLUSIONS

Product information for third generation AIs in Canada have recently been updated to include a class warning for tendon disorders (tendonitis, tenosynovitis, and tendon rupture). This was in response to a safety review conducted by Health Canada which concluded there was likely a link between third generation aromatase inhibitors and tendonitis and tenosynovitis, and a link with tendon rupture could not be ruled out. The following warning is now included in the product monograph for all third generation AIs in Canada:

> *"Tendon Disorders*
> *The use of third generation aromatase inhibitors, including letrozole, was found to be associated with tendonitis and tenosynovitis as reported in randomized controlled trials. Tendon rupture was found to be a potential risk. Tendonitis and tenosynovitis were estimated to be of uncommon occurrence, and tendon rupture of rare occurrence. Treating physicians should monitor patients for these adverse drug reactions."*

In addition to the warning above, tendonitis and tendon rupture are listed as post-market adverse reactions in all of the Canadian product monographs, with trigger finger and de Quervain's tendonitis (tenosynovitis stenosans) also listed in some. Tendon disorders including tendonitis and tenosynovitis, tendon rupture, and in some cases trigger finger, are included in the Canadian patient medication information. There is limited information about tendon disorders in the New Zealand prescribing information currently.

There is extensive literature on musculoskeletal side effects of AIs, such as arthralgia, myalgia, osteoporosis, and fractures. Many of these risks were identified in clinical trials and are already reflected in the New Zealand prescribing information. However the literature on tendon disorders is more limited. Cases of tendonitis and tenosynovitis have been reported in prospective observational studies (often with no comparison group) and case reports in the literature. The hand and wrist were the most common sites affected (although many studies only looked at the hand and wrist), but cases of tendon disorders at other sites in the body were also seen. Studies involving a clinical evaluation (and in some cases diagnostic imaging) suggest that tendon disorders are common amongst patients taking AIs, and may be the underlying cause of some cases of AI-associated musculoskeletal pain. A link between tendon-related pathology and carpal tunnel syndrome (the latter of which is already included in the New Zealand prescribing information) is also suggested. Only three a cases of tendon rupture were identified (in a case series reporting three cases of rotator cuff tendon rupture). The oestrogen-lowering effects of third generation AIs and the presence of oestrogen receptors in tendons have been implicated as a potential mechanism behind the development of these disorders.

Data from international spontaneous adverse event reporting show a number of case reports for tendon disorders. Trigger finger is the most commonly reported tendon-related event, followed by tendonitis, tendon pain or discomfort, tendon rupture, tendon disorder, tenosynovitis, and tenosynovitis stenosans. No cases have been reported to CARM.

5 ADVICE SOUGHT

The Committee is asked to advise:

- If there is sufficient evidence to support that there is a class effect for third generation AIs and tendon disorders.
- If there is evidence to suggest the effect is not isolated to specific tendons/tendon sites.
- If new adverse events/warnings should be added to the data sheet and CMI.

If yes to the above, the Committee is asked to further advise:

- Appropriate wording for new adverse events/warnings in the data sheet and CMI (e.g. adoption of the Canadian wording with or without modifications, or alternative wording).
- If any further regulatory action is required (e.g. communications).

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