

Anastrozole and depressed mood disorders

Introduction

Anastrozole (Arimedex®) is a non-steroid aromatase inhibitor indicated for *treatment of hormone receptor-positive breast cancer in postmenopausal women*. In postmenopausal women, the main route of oestrogen biosynthesis is through conversion of adrenal androgens (primarily androstenedione and testosterone) by the aromatase enzyme to oestrone and oestradiol in peripheral tissue. Anastrozole inhibits this conversion leading to lower serum oestradiol concentrations. As the growth of many breast cancers is stimulated or maintained by oestrogens, this mechanism of action results in a reduction of growth of these types of breast cancers [1, 2]. Anastrozole has been registered in the Netherlands since 1996 as Arimedex® and is nowadays also available as various generic brands [1, 3].

Reports

In the period from 30 August 2004 until 13 January 2020, the Netherlands Pharmacovigilance Centre Lareb received 14 reports of depressed mood associated with the use of anastrozole. All MedDRA preferred terms (PT) under the high level group term (HLGT) 'Depressed mood disorders and disturbances' were included, resulting in the following PTs: depressed mood (8 reports), depression (5) and depressive symptom (1).

Table 1. Reports of depressed mood disorders and disturbances associated with anastrozole in the Lareb database [4]

Patient, WWUCID, Date first received, Sex, age, Primary source	Suspect drug, Dosage, Indication	Concomitant medication	Reported ADRs (LLT)	Latency after start, Action taken, Outcome
A, NL-LRB-46033, 30-08-2004, F, 40-50 Years Pharmacist	Anastrozole, -, Malignant breast neoplasm	Clodronic acid	Restlessness	2 Weeks Dose not changed Recovered
			Depression Aggression	3 Weeks Dose not changed Recovered
			Self injurious ideation Emotional disorder	4 Weeks Dose not changed Recovered
B, NL-AstraZeneca-2006AC01117, 16-06-2006, F, 30-40 Years Physician	Anastrozole, 1 mg/day, Breast cancer	Alendronic acid, Calcium carbonate	Depression	1 year Drug withdrawn Unknown
			Loss of libido	1 year Drug withdrawn Not recovered
C, NL-LRB-704590, 24-09-2007, F, 30-40 Years Consumer or other non health professional	Anastrozole, 1 mg/day, Breast cancer ----- Goserelin, -, Breast cancer ----- Alendronic acid 70mg/week, Prevention	Calcium carbonate/ Colecalciferol	Depressed mood Arthralgia Cough Insomnia Nausea	2 Months Drug withdrawn Recovered ----- 1 Months Drug withdrawn Recovered ----- 8 Months Drug withdrawn Recovered
D, NL-LRB-75528, 07-03-2008, F, 40-50 Years Consumer or other non health professional	Anastrozole, - Breast cancer		Oropharyngeal pain Depressed mood	3 Weeks Drug withdrawn Recovered
E, NL-LRB-103085, 29-01-2010, F, 40-50 Years Pharmacist	Anastrozole, 1 mg/day Breast carcinoma		Depressed mood	3 Days Drug withdrawn Recovering

Patient, WWUCID, Date first received, Sex, age, Primary source	Suspect drug, Dosage, Indication	Concomitant medication	Reported ADRs (LLT)	Latency after start, Action taken, Outcome
F, NL-LRB-128005, 22-09-2011, F, 50-60 Years Consumer or other non health professional	Anastrozole, 1 mg/day Breast carcinoma		Arthralgia	2 Months Drug withdrawn Recovering
			Depressed mood	10 Months Drug withdrawn Recovering
			Migraine with aura	3 Months Drug withdrawn Recovering
G, NL-LRB-139886, 29-05-2012, F, 50-60 Years Physician	Anastrozole, -, - Breast carcinoma	Paroxetine	Depression aggravated	1 Months Drug withdrawn Recovered
H, NL-LRB-212571, 20-01-2016, F, 50-60 Years Physician	Anastrozole, -, - Breast carcinoma	Omeprazole, Salbutamol, Oxycodone, Ibuprofen, Clonidine, Salmeterol/Fluticasone, Premeno Duo	Depression	2 months Drug withdrawn Unknown
I, NL-LRB-214473, 28-02-2016, F, 50-60 Years Consumer or other non health professional	Anastrozole, 1 mg/day, Breast cancer		Depressive symptom Nausea Asthenia Dyspnoea Swollen tongue	1 day Drug withdrawn Recovering
J, NL-LRB-216963, 10-04-2016, F, 60-70 Years Consumer or other non health professional	Anastrozole (Focus), 1 mg/day, Breast cancer		Therapeutic response unexpected with drug substitution Haemorrhage Dizziness Fatigue extreme Dyspnoea Depressed mood Osteoporosis	2 Weeks Drug withdrawn Not recovered
K, NL-LRB-240449, 29-05-2017, F, 40-50 Years Consumer or other non health professional	Anastrozole, 1 mg/day, Breast cancer	Ascorbic acid	Arthralgia Depressed mood Headache Haematoma Pruritus Hyperhidrosis Chills Dry eyes Joint stiffness Alopecia Visual acuity reduced Bone pain	3 Days Drug withdrawn Unknown
			Chest pain Chest tightness	6 Days Drug withdrawn Recovered
L, NL-LRB-00366050, 2811-2019, F, 60-70 years Consumer or other non health professional	Anastrozole, 1 mg/day, Prophylaxis	Calcium carbonate/Colecalciferol, Osta k2&d3 algae (Vitakruid), Magnesium bisglycinaat (Now), Multi 50+ meer-in-1 (Vitortho)	Neuralgia	7 Days Dose not changed Recovering
			Fatigue Abdominal disorder Vision blurred Disorder equilibrium Feeling down Flushing Musculoskeletal pain Concentration impaired	14 Days Dose not changed Not recovered
			Hypercholesteraemia	7 Months Dose not changed Unknown

Patient, WWUCID, Date first received, Sex, age, Primary source	Suspect drug, Dosage, Indication	Concomitant medication	Reported ADRs (LLT)	Latency after start, Action taken, Outcome
M, NL-LRB-00370928, 24-12-20019 F, 50-60 years Consumer or other non health professional	Anastrozole, 1 mg/day, Breast cancer		Depressed mood Fatigue Disturbance in attention Memory disturbance	3 Weeks Dose not changed Recovered
N, NL-LRB-00373287, 13-01-2020 F, 40-50 years Physician	Anastrozole, 1 mg/day, Breast cancer		Depression	1 Year Dose not changed Recovered

Patient A: Premenopausal patient who used anastrozole for four months in total. It is unknown if the patient recovered during anastrozole use or after withdrawal.

Patient C: Anastrozole and goserelin were withdrawn. A few days after withdrawal the reactions improved and after five weeks the patient made a complete recovery. A positive rechallenge was performed. The reactions are less severe since the patient switched from the 3-months depot tot the 1-month depot of goserelin.

Patient D: Complete recovery within two weeks after withdrawal

Patient G: Had a medical history of depression which had been under control for years with paroxetine.

Patient M: The patient recovered after one week, but it is unknown if anastrozole was withdrawn or not.

Patient N: At first the depression was considered the result of personal circumstances, but these improved after one year and the depression continued. Therefore, the depression is associated with the use of anastrozole. The patient was treated with citalopram and recovered. One of the reasons to report this case was that depression in not mentioned in the patient information leaflet while it is generally known that emotional instability can occur during use of aromatase inhibitors.

Other sources of information

Dutch summary of product characteristics (SmPC) and patient information leaflet (PIL)

The Dutch SmPC of Arimedex® mentions mood disturbances as an adverse reaction reported in de ATAC study [1]. However, the Dutch PIL of Arimedex® doesn't mention mood disturbances or similar reactions as an adverse reaction of anastrozole [5].

Letrozole (Femara®) is another non-steroid aromatase inhibitor available in the Netherlands. Both the Dutch SmPC and PIL of letrozole mention depression as an adverse reaction with an incidence of 1-10% [6, 7].

FDA label

The FDA label of Arimedex® mentions depression as a common adverse reaction in the introduction of the adverse drug reactions section. It is also mentioned as an adverse reaction seen in the ATAC study [2].

Literature

Depressive disorders have been associated with the use of aromatase inhibitors e.g. anastrozole, letrozole or exemestane. Chang et al. state that adjuvant treatments of breast cancer, including aromatase inhibitors, increase the risk of developing depressive disorders [8]. Smith et al. describe depression as an adverse event for both anastrozole and letrozole in patients a randomized trial comparing letrozole to anastrozole [9]. In a database study using the case/non case method a significant reporting odds ratio (ROR) was found in the French pharmacovigilance database for anastrozole and depression [10].

Mechanism

Depression is described as an adverse reaction of letrozole and exemestane, suggesting a class effect among aromatase inhibitors [6, 11]. Aromatase inhibitors lower the concentration of oestrogen in

serum. Goodwin suggest that this mechanism of effect could also result in mood disturbances as with postpartum mood disturbances [12].

Other databases

Table 2. Quantitative information regarding reports of depressed mood disorders and disturbances associated with anastrozole in the Lareb database, Eudravigilance and WHO Vigibase [4, 13, 14]

Database	Drug	Preferred terms	Number of reports	ROR (95% CI)
Lareb	Anastrozole	Depressed mood	8	2.96 (1.46-5.97)
		Depression	5	2.21 (0.91-5.36)
		Depressive symptom	1	-
Eudravigilance	Anastrozole	Depression	169	2.28 (1.96-2.66)
		Depressed mood	43	2.32 (1.72-3.13)
		Tearfulness	7	3.49 (1.66-7.34)
		Anhedonia	3	2.43 (0,78-7.53)
		Decreased interest	3	1.41 (0,46-4.39)
		Depression suicidal	3	2.69 (0.87-8.35)
		Depressive symptom	2	-
		Feeling guilty	2	-
		Feeling of despair	2	-
		Major depression	2	-
		Feelings of worthlessness	1	-
		Negative thoughts	1	-
WHO Vigibase	Anastrozole	Depression	455	3.35 (3.06-3.68)
		Depressed mood	80	3.14 (2.52-3.91)
		Tearfulness	14	6.11 (3.62-10.34)
		Anhedonia	8	0.82 (0.41-1.64)
		Decreased interest	8	2.44 (1.22-4.88)
		Depression suicidal	5	3.70 (1.54-8.90)
		Feeling of despair	5	3.31 (1.38-7.96)
		Feeling guilty	4	5.91 (2.21-15.77)
		Major depression	4	1.04 (0.39-2.77)
		Feelings of worthlessness	2	-
		Depressive symptom	2	-
		Negative thoughts	2	-

*Eudravigilance and WHO Vigibase data include the number of reports of Pharmacovigilance Centre Lareb

The last data lock point for reports of depressed mood disorders in association with anastrozole for an assessment performed by a marketing authorization holder based on Eudravigilance data was 10 August 2017. Therefore, reports that have been received in Eudravigilance after that date are highlighted below.

In the period from 10 August 2017 till 3 March 2020 42 reports were sent to Eudravigilance by the marketing authorization holders and other EU authorities regarding anastrozole and PTs in the HLGT depressed mood disorders and disturbances. This number excludes Lareb reports and one duplicate

[13]. To determine if these reports support the association between the reported depressed mood disorders and anastrozole use, they were assigned a strength by assessing the availability of information on time to onset, action taken with the suspect drug, outcome of the reaction and possible confounding factors. Of these 42 case-reports, three present an average to strong case with outcome and impact on the patient, eight present an average to strong case with outcome and five cases are average without outcome. The other 22 cases have limited information on many factors and are considered weak cases and in in four cases it is mentioned that the reported depressive mood disorder occurred during use of a suspect drug other than anastrozole (see Appendix 1). Table 3 gives an overview of other characteristics of the 42 reports in Eudravigilance.

Table 3. Characteristics of the 42 case-reports in Eudravigilance regarding PTs in the HLGT depressed mood disorders and disturbances associated with anastrozole

Patient characteristics		Case-report characteristic	
Sex		Seriousness	Country of Origin
Female	39	Serious	28
Male	1	Non-serious	14
Unknown	2	Primary source	France
Age		Health care professional	16
Range	38-85 years	Consumer	26
Median age	63 years	Suspect drug(s)	Poland
		Anastrozole	26
		Anastrozole + one other	5
		Anastrozole + two others	4
		Anastrozole + three others	4
		Anastrozole + four others	2
		Anastrozole + 19 others	1
		Dechallenge information	Sweden
		Positive dechallenge	10
		Rechallenge information	
		Any information	0

Prescription data

Table 4. Number of patients using anastrozole in the Netherlands between 2014 and 2018 [15]

Drug	2014	2015	2016	2017	2018
Anastrozole	17,270	17,279	17,479	17,309	16,605

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received fourteen reports that mentioned depressed mood disorders associated with the use of anastrozole. In Eudravigilance and Vigibase reports of similar associations can be found. It is known that patients with cancer diagnoses can develop emotional distress like anxiety and depression [16]. A possible reason for reporters to associate their depressed mood disorder to use of anastrozole instead of their breast cancer diagnoses could be the reported dechallenges in six reports to Lareb. Also, one reporter mentioned

that at first the depression was linked to personal circumstances, but while these improved the depression continued. Therefore the depression was linked to anastrozole use in that patient.

One of the reporting physicians stated that he was surprised that depression wasn't mentioned in the PIL as an adverse reaction of anastrozole. He stated that it is generally known that aromatase inhibitors can cause emotional instability.

As mood disturbances are mentioned in the SmPC, but not in the PIL and since depressive mood disorders can have a great impact on the patient's daily life, attention for this potential adverse reaction is warranted.

References

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This signal has been raised on July 29, 2020. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl

Appendix 1

Table 1. Case strength of the 42 reports in Eudravigilance regarding PTs in the HLGT depressed mood disorders and disturbances associated with anastrozole

	EU local number
Average to strong case with outcome and impact on the patient	EU-EC-10000298826 EU-EC-10003722094
Average to strong case with outcome	EU-EC-10000864601 EU-EC-10000970559 EU-EC-10002301362 EU-EC-10002439046 EU-EC-10002673147 EU-EC-10003336708 EU-EC-10003344420 EU-EC-10003544137
Average case without outcome	EU-EC-10000650499 EU-EC-10001220651 EU-EC-10003562854 = EU-EC-10003588192 EU-EC-10004960381 EU-EC-10004999619
Weak case	EU-EC-10002435212 EU-EC-10002664228 EU-EC-10003705822 EU-EC-10003754686 EU-EC-10003955366 EU-EC-10004061432 EU-EC-10004640958 EU-EC-10005068389 EU-EC-10005171572 EU-EC-10005417316 EU-EC-10005527107 EU-EC-10001372166 EU-EC-12772881 EU-EC-12839650 EU-EC-10002778312 EU-EC-10002168657 EU-EC-12743258 EU-EC-10000093865 EU-EC-10003745936 EU-EC-10003855611 EU-EC-10004020307 EU-EC-10005547127
Cases where depressive mood disorder did not start during anastrozole use	EU-EC-10000789372 EU-EC-10002505025 EU-EC-10003565540 EU-EC-10003722552