



Review

Art of prevention: The importance of dermatologic care when using aromatase inhibitors ☆☆☆★



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ABSTRACT

As of January 2021, there are more than 3.8 million women in the United States with a history of breast cancer. The current standard of care for breast cancer involves surgical resection, radiation therapy, adjuvant endocrine therapy, and/or adjuvant chemotherapy. Aromatase inhibitors (AIs) are the gold standard for endocrine therapy in postmenopausal women. Dermatologic adverse events (dAEs) associated with AIs are rare but have been reported in the literature. Commonly reported dAEs include unspecified rash, pruritus, alopecia, vulvovaginal atrophy, vasculitis, and autoimmune/connective tissue disorders. Appropriate preventative strategies and careful management considerations have the potential to optimize the comprehensive care of patients with cancer and improve quality of life. Furthermore, prevention of dAEs can lead to a reduction in cancer treatment interruptions and discontinuations. Herein, we characterize dAEs of AIs and discuss preventative management to reduce the incidence of AI therapy interruption.

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What is known about this subject with regard to women and their families?

Aromatase inhibitors (AIs) are the preferred endocrine therapy for postmenopausal women with breast cancer. Dermatologic adverse events associated with AIs are highly clinically variable and may negatively affect patient quality of life, often leading to oncologic treatment interruption or discontinuation. Preventative management to potentially reduce dermatologic adverse events associated with AI therapy may help limit treatment interruption and improve patient outcomes.

What is new from this article as messages for women and their families?

Common dermatologic adverse events include pruritus, immune-mediated reactions, vulvovaginal atrophy, and alopecia. Prevention and management strategies include adequate moisturizers, nonhormonal vulvovaginal lubricants, and pretherapy counseling regarding hair loss. Dermatologists can improve quality of life in patients on AI therapy by aiding in the prevention, recognition, and management of these dermatologic adverse events.

Aromatase inhibitors

More than 3.8 million women in the United States have a history of breast cancer (BC; [Biglia et al., 2015](#); [Ferreira et al., 2019](#); [Kharb et al., 2020](#); [Sussman et al., 2019](#)). The majority of BCs in premenopausal (~60%) and postmenopausal (~75%) women are estrogen receptor positive ([Augusto et al., 2018](#)), and treatment may include a combination of surgical resection, radiation therapy, endocrine therapy, and traditional chemotherapy ([Ferreira et al., 2019](#); [Sussman et al., 2019](#)). Endocrine therapies include aromatase inhibitors (AIs)—the most common of which are anastrozole, letrozole, and exemestane—and tamoxifen, a selective estrogen receptor modulator ([Pistelli et al., 2018](#)), although AIs are preferred in postmenopausal women due to their favorable side-effect profile. AIs may be either steroidal or nonsteroidal ([Table 1](#)) and have been successfully used in the treatment of estrogen receptor-positive BC in multiple settings, including the treatment of metastatic disease, as an adjuvant treatment, and as chemoprevention for patients at high risk ([Chumsri, 2015](#)). AIs are also indicated in a wide variety of other conditions other than BC, including in the treatment of male gynecomastia, infertility, fibrocystic breast disease, and endometriosis ([Ferreira et al., 2019](#); [Kharb et al., 2020](#); [Peters and Tadi, 2020](#)). Of note, third-generation nonsteroidal AIs (i.e., anastrozole, letrozole) may interact with tamoxifen, and thus it is preferable to avoid co-administration of these therapies ([Lønning et al., 2003](#)).

Aromatase plays an important role in estrogen metabolism and is the rate-limiting step that catalyzes the conversion of peripheral androgens to estrogens. The aromatase gene is complex and highly regulated and exhibits tissue-specific expression in the ovaries/testes, breast tissue, adipose/skin, brain, placenta, and bone

([Santen et al., 2009](#)). As a result, AIs may have significant effects on these tissues, particularly on the bone and joints where the rates of bone loss are increased. Similarly, in the skin, AIs decrease the conversion of androgens to estrogens, which in turn increases the amount of androgen that can be converted into dihydrotestosterone and results in side effects such as androgenetic alopecia ([Rossi et al., 2020](#)). Additionally, estrogens have been shown to promote cell-proliferation in human tissue, thereby having the potential to lead to tumor formation. Estrogens also significantly affect humoral immunity and increase immunoglobulin levels ([Aguilar-Pimentel et al., 2020](#); [Cutolo et al., 2012](#)).

Dermatologic adverse events (dAEs) associated with AIs are highly clinically variable ([Biglia et al., 2015](#); [2017](#)); they may negatively affect patient quality of life (QoL), ultimately leading to oncologic treatment interruption or even discontinuation ([Biglia et al., 2015](#); [2017](#); [Ferreira et al., 2019](#); [Sussman et al., 2019](#); [Woodford et al., 2019](#)). Herein, we characterize dAEs of AIs and discuss preventative management to potentially reduce AI therapy interruption and improve patient outcomes.

Dermatologic adverse events

Our literature review included data on AI usage in 5296 patients ([Table 2](#)). The median age of patients on AI therapy was 64 years. The most commonly used AI was anastrozole (39%), followed by letrozole (36%) and exemestane (17%). Onset of dermatology-related adverse events ranged from 2 days to 9 months. Commonly reported side effects included unspecified rash, pruritus, various immune-mediated reactions, vulvovaginal atrophy, and alopecia ([Balagula et al., 2011](#); [Budell et al., 1986](#); [Crockett and Burkemper, 2011](#); [De Placido et al., 2018](#); [Jhaveri et al., 2007](#); [Moscetti et al., 2015](#); [Ooi and Jaffar, 2019](#); [Paridaens et al., 2003](#); [Pellegrini et al., 2009](#); [Pokhai et al., 2014](#); [Potter and Moore, 2013](#); [Rossi et al., 2013](#); [Schadler et al., 2018](#); [Sestak et al., 2014](#); [Shoda et al., 2005](#); [Sonke et al., 2018](#); [Stein et al., 1990](#); [Stratakis and Chrousos, 1994](#); [Tominaga et al., 2003](#); [Trancart et al., 2008](#); [Tryfonidis et al., 2016](#); [Williams and Leslie, 1987](#); [Wong et al., 2008](#); [Yang et al., 2020](#); [Zarkavelis et al., 2016](#)).

Immune-mediated dAEs include erythema nodosum, subacute cutaneous lupus erythematosus, cutaneous vasculitis, and other autoimmune/connective tissue disorders ([Meade et al., 2015](#); [Pathmarajah et al., 2015](#); [Santoro et al., 2011](#); [Williams and Leslie, 1987](#)). Eruptive keloids, which have been associated with connective tissue disorders, have also been reported with AI use ([Meade et al., 2015](#)). The development of immune-mediated dAEs associated with AI therapy suggests an immunomodulatory mechanism secondary to an altered hormonal environment, namely low estrogen levels ([Chao et al., 2009](#); [Meade et al., 2015](#); [Zarkavelis et al., 2016](#)). Many of these dAEs, including systemic sclerosis and vasculitis, have been reported to resolve after AI discontinuation, further suggesting endocrinologic influence ([Pokhai et al., 2014](#)).

Diverse mechanisms of action have been proposed for the immunologic effects of estrogen, including altered wound healing and disruption of neutrophil function. Specifically, low estrogen levels result in disinhibition of neutrophils, which may then adhere to the endothelium of blood vessels, provoking autoimmune vasculitis or related reactions ([Conti-Beltraminelli et al., 2007](#); [Jhaveri et al., 2007](#); [Pathmarajah et al., 2015](#); [Pellegrini et al., 2009](#); [Shoda et al., 2005](#); [Woodford et al., 2019](#); [Zarkavelis et al., 2016](#)). Keloidal fibroblasts may also function via a hormonally mediated mechanism; thus, dysregulated estrogen levels may result in adverse effects on cutaneous wound healing ([Meade et al., 2015](#)). Of note, patients who develop immune-mediated dAEs while on an AI may be able to tolerate other AIs. There have been cases of patients subsequently treated with a different AI or tamoxifen without re-

Table 1
Aromatase inhibitor classes

Generation	Type I steroidal inhibitor	Type II nonsteroidal inhibitor
First	Not applicable	Aminoglutethimide
Second	Formestane	Fadrozole Rogletimide
Third	Exemestane	Anastrozole Letrozole Vorzole

Table 2
Dermatologic adverse events associated with aromatase inhibitors

AI (%) ^a	Dermatologic AE	Treatment of dermatologic AE	AI discontinued due to dermatologic AE?
Exemestane (16.7)	Pruritus	Unknown	No
	Erythema with scaling	Unknown	No
	Rash, NOS	Unknown	No
	Vasculitis [†]	Methylprednisolone	Yes
	Mucosal	Unknown	No
Anastrozole (39)	Alopecia	Unknown	Yes
	Pruritus	Unknown	Yes
	Xerosis	Unknown	No
	Rash, NOS	None	Yes
	Autoimmune/connective tissue	Hydroxychloroquine, topical steroids	Yes
	SCLE	Clobetasol propionate	Yes
	Erythema nodosum	None	Yes
	Vasculitis [†]	Unknown	No
	Mucosal	Unknown	No
	Lichenoid	Estradiol vaginal tablets	No
Letrozole (36)	Alopecia	Minoxidil	Yes
	Pruritus	Unknown	No
	Rash, NOS	None	Yes
	Autoimmune/connective Tissue	Topical steroids	Yes
	Systemic sclerosis	Unknown	Yes
	Eruptive keloids	Cryotherapy, intralesional steroids	Yes
	Vasculitis [†]	None	No
	Mucosal	Unknown	No
	Lichenoid	Topical steroids	Yes
	Alopecia	Minoxidil/unknown	No
Fadrozole (2.1)	Miliary osteoma cutis	None	No
	Rash, NOS	Unknown	No
	Pruritus	Unknown	No
	Vasculitis [†]	Unknown	Yes
Aminoglutethimide (0.3)	Cutaneous drug eruption	None, medroxyprogesterone acetate	No, yes
	Lichenoid	None	No

AE, adverse event; AI, aromatase inhibitor; NOS, not otherwise specified; SCLE, subacute cutaneous lupus erythematosus

^a Review of 5296 patients reported in clinical trials, case series, and case reports. Of the 5296 patients, 246 received an unknown AI (5%); 58 (2%) received voriozole (1%) and liarozole (1%) with no published dermatologic AEs and were thus not included in the table.

[†] Vasculitis from AI use tends to present early but may occur as late as 90 days after AI induction (Woodford et al., 2019).

currence of vasculitis or autoimmune/connective tissue disorders (Woodford et al., 2019).

Given the high expression of estrogen receptors in the vulva, antiestrogen therapy with AIs may result in mucosal and lichenoid vulvovaginal effects. Mucosal dAEs, such as vulvovaginal atrophy (also known as genitourinary syndrome of menopause [GSM]), may occur in up to 74% of patients receiving AI therapy (Balagula et al., 2011; Biglia et al., 2015; 2017; Ferreira et al., 2019; Moegele et al., 2012; Witherby et al., 2011). In the setting of low estrogen levels, there may be reduced blood flow to the vulvovaginal area, thinning of the epithelium with loss of vaginal rugae, and reduced collagen and elastin, all of which may contribute to GSM symptoms (e.g., dryness, itching, burning, dysuria, dyspareunia, and postcoital bleeding; Biglia et al., 2015; 2017; Cook et al., 2017; Ferreira et al., 2019; Sussman et al., 2019). Treatment includes improving vaginal elasticity and lubrication. In women for whom estrogen therapy is contraindicated, therapeutic options include vaginal dilators, pelvic floor physical therapy, moisturizers, lubricants, thermoablative fractional CO₂ laser, U.S. Food and Drug Administration–approved intravaginal dehydroepiandrosterone, and the novel selective estrogen receptor modulator ospemifene (Biglia et al., 2015; 2017; Cook et al., 2017; Ferreira et al., 2019; Moegele et al., 2012; Witherby et al., 2011) Lichen sclerosus is another vulvovaginal dAE that may present similarly to GSM and has been described in association with AI use in a case report (Potter and Moore, 2013). Treatment options include potent topical corticosteroids and topical immunomodulators, such as calcineurin inhibitors (Potter and Moore, 2013).

Women taking AIs may also experience alopecia, which often has the pattern of androgenetic alopecia and may be due to androgenization of hair follicles secondary to AI-mediated hormonal imbalances (Carlini et al., 2003; Freites-Martinez et al., 2018; 2019;

Pathmarajah et al., 2015) Based on a meta-analysis of endocrine therapy-induced alopecia (EIA), it is estimated that approximately 2.5% of patients receiving AIs are affected by hair loss, with a mean time to onset of 16.8 months (range, 1.0–91.0 months; Ferreira et al., 2019; Karatas et al., 2016; Trüeb, 2018). QoL may be severely affected, with 8% of patients discontinuing treatment due to alopecia and 17% reporting EIA to be the most traumatic dAE during treatment (Ferreira et al., 2019; Freites-Martinez et al., 2018; 2019; Trüeb, 2018). Minoxidil, which facilitates hair growth by increasing the duration of the anagen phase of hair follicles, has led to improvement of EIA in up to 80% of patients (Ferreira et al., 2019; Freites-Martinez et al., 2018; 2019; Lacouture and Sibaud, 2018; Trüeb, 2018). For severe EIA refractory to topical minoxidil, spironolactone, wigs, tattooing, tinted powders, and transplantation may be considered (Ferreira et al., 2019). Other causes of hair loss should also be ruled out by evaluating hormone levels, serum iron, serum ferritin, total iron binding capacity, thyroid levels, venereal disease research laboratory testing, and a complete blood count (Ferreira et al., 2019). Additional hair changes reported with AI therapy include pigmentary and textural hair changes and hirsutism (Freites-Martinez et al., 2019).

Prevention

Survival is prolonged with AIs; thus, there is a need for improved and widely available preventative strategies for dAEs, which would contribute to the optimal and comprehensive care of patients with cancer (Ferreira et al., 2019; Freites-Martinez et al., 2019). Patients receiving anticancer therapies are often at greater risk for dAEs and infection owing to dry, excoriated skin (Valentine et al., 2015), and patients who begin a gentle skin care regimen report improved QoL (Dalenc et al., 2018; Valentine et al., 2015).

Moisturization and skin barrier maintenance with urea-containing agents and salicylic acid are key components of this regimen (Valentine et al., 2015). Patients should also be counseled to minimize scrubbing and avoid potential allergens and irritants, such as products with fragrance.

Nonhormonal vaginal moisturizers and lubricants are first-line options to treat GSM (Biglia et al., 2015; 2017; Ferreira et al., 2019; Moegele et al., 2012; Sussman et al., 2019). Moisturizers can provide the function of physiologic vaginal secretions, and lubricants can decrease friction during sexual intercourse (Biglia et al., 2015; Moegele et al., 2012). However, the clinical benefit of these therapies is limited, and the prevention and management of GSM is largely unsolved (Biglia et al., 2015; Cook et al., 2017).

Systemic hormone therapy or vaginal estrogens might provide improved symptomatic relief, but they are often avoided in patients with BC in light of the theoretical potential of increasing cancer risk and interfering with efficacy (Biglia et al., 2015; 2017; Cook et al., 2017; Ferreira et al., 2019; Sussman et al., 2019). Of note, in one study, nonhormonal treatments were considered safe by 90% of oncologists and effective by 30% (Biglia et al., 2017). Hormonal treatments were considered safe and effective by 15% and 79% of oncologists, respectively (Biglia et al., 2017). However, for patients who have failed nonhormonal treatments and continue to experience distressing GSM symptoms, discussions with the oncologist regarding the use of local hormone therapies may be warranted; these therapies include low-dose intravaginal estrogen tablets, topical estrogen cream, or nonestrogen hormonal therapies with dehydroepiandrosterone (i.e., prasterone; Faubion et al., 2018; Sussman et al., 2019).

Providers may also encourage sexual intercourse because this facilitates active blood flow to the vagina and increases vaginal lubrication (Biglia et al., 2015; Moegele et al., 2012). Patients should also be counseled on avoiding products that may cause contact dermatitis (i.e., toilet tissue, soaps, clothing, and fabric softeners that contain fragrances; Moegele et al., 2012). Psychosocial interventions, pelvic floor physical therapy, and smoking cessation are also useful (Biglia et al., 2015; Ferreira et al., 2019).

Prevention strategies for EIA have not been well studied and remain a therapeutic issue for patients with BC (Freites-Martinez et al., 2018; Karatas et al., 2016). Preventative treatment with topical 5- α reductase inhibitors and nutritional supplements (i.e., vitamin C, omega-3 fatty acids) for EIA have shown promise and do not appear to adversely affect BC prognosis (Karatas et al., 2016). Additionally, pretherapy counseling should be done so that patients seek consultation immediately should they notice hair loss (Freites-Martinez et al., 2019). Although it is difficult to entirely prevent alopecia, being aware of management options, anticipating hair loss, and finding acceptance can promote coping (Trüeb, 2018).

Conclusion

Given the incidence of BC in postmenopausal women and the duration of use of AIs, it is important to effectively prevent, diagnose, and manage dAEs that may lead to severe reactions and consequently cancer therapy interruption or discontinuation (Woodford et al., 2019). These dAEs also affect patient QoL, altering a woman's self-image and confidence (Ferreira et al., 2019). Dermatologists can improve patient QoL by aiding in the prevention, recognition, and management of dAEs (Woodford et al., 2019).

Conflicts of Interest

None.

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