J Cancer Immunol. 2024;6(1):40-43.

Journal of Cancer Immunology Commentary

Aromatase Inhibitors and their Connection to Autoimmunity

Savannah Bowman[1,2*], Carlos H Barcenas[3], Huifang Lu[1]

[1]Department of General Internal Medicine, Section of Rheumatology and Clinical Immunology, The University of Texas MD Anderson Cancer Center, 1400 Pressler St., Unit 1465 Houston, TX 77030, USA

[2]Department of Medicine, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

[3]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Unit 1345, Houston TX, 77030, USA

[*]Correspondence should be addressed to Savannah Bowman, savannah.bowman@bcm.edu

Received date: April 04, 2024, **Accepted date:** May 07, 2024

Citation: Bowman S, Barcenas CH, Lu H. Aromatase Inhibitors and their Connection to Autoimmunity. J Cancer Immunol. 2024;6(1):40-43.

Keywords: Aromatase inhibitors, Autoimmune disease, Inflammatory myopathy, Rheumatoid arthritis

Commentary

The aromatase inhibitors (AIs) anastrozole, letrozole, and exemestane are often prescribed as endocrine therapy for patients with estrogen receptor–positive breast cancer [1]. AIs are associated with musculoskeletal side effects such as bone loss, arthralgias, myalgias, and tenosynovitis [2]. Notably, exemestane is a steroidal AI and both anastrozole and letrozole are non-steroidal AIs. There is limited evidence comparing the difference in joint and muscle symptoms between exemestane and the non-steroidal AIs [3,4]. However, there is evidence that exemestane results in less bone mineral density loss compared to the non-steroidal AIs [5]. Up to 50% of women treated with AIs will experience polyarthralgias [6]. In recent years however, there has been emerging evidence that AIs are associated with the development of autoimmune diseases. Our recent case series sheds light on a novel and concerning finding- the development of inflammatory myopathies in patients on AI therapy [7]. We described three women who each developed a form of inflammatory myopathy (polymyositis, amyopathic dermatomyositis, and fasciitis) while undergoing AI therapy. All three women had no history of autoimmune disease, and all had undergone recent cancer surveillance with no evidence of breast cancer reoccurrence. The time to onset after initiation of AI ranged from 7 months to 2.5 years. In all three cases, only completion or discontinuation of the AI resulted in resolution of the inflammatory myopathy suggesting a link between the AI and the inflammatory myopathy.

Rheumatoid arthritis

The autoimmune disease with the most substantial evidence for being associated with AIs is rheumatoid arthritis (RA). Using a large U.S. national database that included 238,880 women with breast cancer, Chen and Ballou found there was a cumulative dose dependent increased odds ratio (OR) of developing new onset RA in patients taking AIs: [1.32 for 2–11 months (95% CI 1.21–1.44; p = 4.14 × 10−11) and 1.85 for 12+ months (95% CI 1.57–2.17; p = 4.23 × 10−15)] [8]. Similarly, a large population-based study conducted in Italy found 113 new cases of RA among 7,533 women undergoing AI therapy for breast cancer [9]. With tamoxifen treatment used as a reference, AI therapy was associated with an increased risk of developing new-onset RA (adjusted HR 1.62, 95% CI 1.03–2.56). In particular, patients receiving anastrozole had the highest risk of new-onset RA even when the analysis was adjusted for age and stage of neoplasia (adjusted HR 1.75, 95% CI 1.07–2.86). However, evidence is conflicting as a nationwide Swedish registry found that neither tamoxifen or AIs seemed to increase the risk of developing RA [10]. The conflicting results between the Swedish study compared to the Italian and U.S. studies could be seen due to differing patient populations as well as differences in study design. The Italian study did not evaluate the rate of RA in the general population. The U.S. study did not take into account follow up time or age. The Swedish study did not include hormonal receptor status and some confounding factors could not be accounted for including body mass index and smoking [8-10]. Therefore, larger and more diverse patient populations should be evaluated to assess the risk between AIs and RA.

Spondyloarthropathy

The evidence for other autoimmune conditions being associated with AIs is largely case based. Scarpa et al. evaluated 18 consecutive patients on AIs who were referred to rheumatology for rheumatic complaints and found 10 of the 18 (55.5%) met criteria for undifferentiated spondyloarthropathy [11]. There is a recently published case report of a 7 year old child who developed an inflammatory arthritis and enthesitis after taking letrozole for 1 month for the off label use of premature thelarche [12]. This is the first published case of inflammatory arthritis and enthesitis being triggered by an AI in the pediatric population.

Vasculitis

There have been several case reports about AI associated cutaneous vasculitis [13-17]. To our knowledge, there have been no reports of AI induced organ threatening vasculitis.

Systemic lupus erythematosus

There have been reports of AI associated subacute cutaneous lupus erythematosus [18-20], however there are no published cases to our knowledge of AI induced systemic lupus erythematosus (SLE). The study by Chen and Ballou using a large U.S. national database actually found a non-statistically significant trend for reduced risk of SLE in patients on AIs [8].

Systemic sclerosis

There is one published case report of AI induced early systemic sclerosis with Raynaud's phenomenon that resolved after stopping AI therapy [21].

Sicca symptoms and Sjogren's syndrome

There have been several published cases of AI associated sicca symptoms and overt Sjogren's syndrome [22-24]. Laroche et al. examined 28 post-menopausal women on AIs referred for rheumatic complaints and found 10 patients had sicca syndrome of the eyes or mouth, 7 had probable Sjogren's, and 1 had definite Sjogren's syndrome [24].

Antiphospholipid antibody syndrome

There is one case report of suspected AI induced antiphospholipid antibody syndrome [25].

Autoimmune hepatitis

There are a few case reports of AI induced autoimmune hepatitis [26-28].

Inflammatory myositis

To our knowledge, apart from our case series, there is only one other published case of inflammatory myositis in the setting of AI therapy [29].

Estrogen deprivation may play a central role in the pathophysiology of how AIs cause rheumatic complaints. The literature indicates that elevated estrogen levels reduce the production of inflammatory cytokines [30]. Therefore, estrogen deprivation can lead to increased levels of inflammatory cytokines. RA is commonly diagnosed in post-menopausal women and menopause may increase the severity of RA [31]. AIs cause further estrogen deprivation that could potentially reveal or trigger RA. In a rat model of RA, anastrozole led to increased proinflammatory cytokines and increased the severity of arthritis [30]. In a mouse model of spondyloarthritis, mice that underwent ovariectomy treated with estrogen showed remarkable suppression of arthritis [32]. As mentioned above, in Chen and Ballou's study they found AIs to be statistically significantly associated with the development of new RA and on the other hand there was a non-statistically significant trend for reduced risk of SLE in patients on AIs [8]. The authors postulated this could be due to the greater role of estrogen in the pathogenesis of SLE compared to RA [8]. However, in a novel mouse model of AI-induced arthralgia, magnetic resonance imaging of the knee joints and legs showed enhanced signal detection in the joint space and surrounding tissue, which was corroborated by histopathological and pro-inflammatory cytokine analysis [33]. Interestingly, the responses observed with AI treatment were independent of oophorectomy, which may suggest a pathway other than estrogen deficiency. This further highlights the complex relationship between aromatase inhibitors and musculoskeletal complaints.

AIs have revolutionized breast cancer treatment. However, it is important for rheumatologists and oncologists alike to be aware of the potential role of AIs in causing or triggering autoimmune diseases. Our recent article highlights this phenomenon. If a patient develops an autoimmune disease while on AI therapy, there should be consideration given to the AI being the culprit and a discussion of risks versus benefits of continuing versus discontinuing the AI or switching to other endocrine therapy options such as tamoxifen in eligible patients. Apart from rheumatoid arthritis, only case reports and case series exist exploring the role between AIs and other autoimmune conditions. This may be because of the rarity of such events or because of under recognition of the link between AIs and autoimmunity. Future research should be aimed at larger population studies evaluating the link between AIs and other autoimmune diseases as well as elucidating the underlying mechanism for why aromatase inhibitors cause rheumatic complaints.

Conflict of Interest

All authors declare no conflict of interest.

References

1. Joshi H, Press MF. Molecular oncology of breast cancer. In: Bland KI, Copeland III EM, Klimberg VS, Gradishar WJ, eds. The Breast. 5th Edn. United States: Elsevier; 2018. pp. 282-307.

2. BIG 1-98 Collaborative Group. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. New England Journal of Medicine. 2009 Aug 20;361(8):766-76.

3. Iwata H, Masuda N, Ohno S, Rai Y, Sato Y, Ohsumi S, et al. A randomized, double-blind, controlled study of exemestane versus anastrozole for the first-line treatment of postmenopausal Japanese women with hormone-receptor-positive advanced breast cancer. Breast Cancer Research and Treatment. 2013 Jun;139(2):441-451.

4. Goss PE, Ingle JN, Pritchard KI, Ellis MJ, Sledge GW, Budd GT, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA. 27—a randomized controlled phase III trial. Journal of Clinical Oncology. 2013 Apr 4;31(11):1398.

5. Goss PE, Hershman DL, Cheung AM, Ingle JN, Khosla S, Stearns V, et al. Effects of adjuvant exemestane versus anastrozole on bone mineral density for women with early breast cancer (MA. 27B): a companion analysis of a randomised controlled trial. The Lancet Oncology. 2014 Apr 1;15(4):474-482.

6. Singer O, Cigler T, Moore AB, Levine AB, Hentel K, Belfi L, et al. Defining the aromatase inhibitor musculoskeletal syndrome: a prospective study. Arthritis Care & Research. 2012 Dec;64(12):1910-1918.

7. Bowman S, Lu H. Aromatase inhibitor-induced inflammatory myopathies: a case series. Joint Bone Spine. 2022 Mar 1;89(2):105308.

8. Chen JY, Ballou SP. The effect of antiestrogen agents on risk of autoimmune disorders in patients with breast cancer. The Journal of Rheumatology. 2015 Jan 1;42(1):55-59.

9. Caprioli M, Carrara G, Sakellariou G, Silvagni E, Scirè CA. Influence of aromatase inhibitors therapy on the occurrence of rheumatoid arthritis in women with breast cancer: results from a large population-based study of the Italian Society for Rheumatology. RMD open. 2017 Sep 1;3(2):e000523.

10. Wadström H, Pettersson A, Smedby KE, Askling J. Risk of breast cancer before and after rheumatoid arthritis, and the impact of hormonal factors. Annals of the Rheumatic Diseases. 2020 May 1;79(5):581-586.

11. Scarpa R, Atteno M, Peluso R, Costa L, Padula S, Di Minno D, et al. Rheumatic complaints in women taking aromatase inhibitors for treatment of hormone-dependent breast cancer. JCR: Journal of Clinical Rheumatology. 2011 Jun 1;17(4):169-172.

12. Baba O, Kisaoglu H, Kalyoncu M. Letrozole-induced inflammatory arthritis and tendinopathy in pediatric rheumatology setting. International Journal of Rheumatic Diseases. 2023 Nov;26(11):2314-2316.

13. Santoro S, Santini M, Pepe CA, Tognetti E, Cortelazzi C, Ficarelli E, et al. Aromatase inhibitor-induced skin adverse reactions: exemestane-related cutaneous vasculitis. Journal of the European Academy of Dermatology and Venereology. 2011 May;25(5):596-598.

14. Woodford RG, Becker GJ, Jain A. Leukocytoclastic vasculitis associated with use of aromatase inhibitors. Internal Medicine Journal. 2019 Sep;49(9):1162-1167.

15. Bock VL, Friedlander M, Waring D, Kossard S, Wood GK. Cutaneous adverse effects of hormonal adjuvant therapy for breast cancer: a case of localised urticarial vasculitis following anastrozole therapy and a review of the literature. Australasian Journal of Dermatology. 2014 Nov;55(4):282-285.

16. Mohaghegh F, Bahrami B. Necrotizing leukocytoclastic small vessel vasculitis associated with letrozole: A case report. International Journal of Clinical Pharmacology and Therapeutics. 2020 Dec 1;58(12):732.

17. Pathmarajah P, Shah K, Taghipour K, Ramachandra S, Thorat MA, Chaudhry Z, et al. Letrozole-induced necrotising leukocytoclastic small vessel vasculitis: first report of a case in the UK. International Journal of Surgery Case Reports. 2015 Jan 1;16:77-80.

18. Fisher J, Patel M, Miller M, Burris K. Anastrozole-induced subacute cutaneous lupus erythematosus. Cutis. 2016 Aug 1;98(2):E22-26.

19. Russell-Goldman E, Nazarian RM. Subacute cutaneous lupus erythematosus with positive anti-Ro antibodies following palbociclib and letrozole treatment: A case report and literature review. Journal of Cutaneous Pathology. 2020 Jul;47(7):654-658.

20. Trancart M, Cavailhes A, Balme B, Skowron F. Anastrozole-induced subacute cutaneous lupus erythematosus. British Journal of Dermatology. 2008 Mar 1;158(3):628-629.

21. Pokhai G, Buzzola R, Abrudescu A. Letrozole-induced very early systemic sclerosis in a patient with breast cancer: a case report. Archives of Rheumatology. 2014;29(2):126-9.

22. Bilge NS, Korkmaz C. Does aromatase inhibitors cause sjogren's syndrome and polyneuropathy?. World Journal of Oncology. 2014 Aug;5(4):181.

23. Guidelli GM, Martellucci I, Galeazzi M, Francini G, Fioravanti A. Sjögren's syndrome and aromatase inhibitors treatment: Is there a link. Clin Exp Rheumatol. 2013 Apr 3;31(4):653-4.

24. Laroche M, Borg S, Lassoued S, De Lafontan B, Roché H. Joint pain with aromatase inhibitors: abnormal frequency of Sjögren's syndrome. The Journal of Rheumatology. 2007 Nov 1;34(11):2259-2263.

25. Tenti S, Giordano N, Cutolo M, Giannini F, Fioravanti A. Primary antiphospholipid syndrome during aromatase inhibitors therapy: A case report and review of the literature. Medicine. 2019 Mar 1;98(13):e15052.

26. Islam MS, Wright G, Tanner P, Lucas R. A case of anastrazole-related drug-induced autoimmune hepatitis. Clinical Journal of Gastroenterology. 2014 Oct;7:414-417.

27. Klapko O, Ghoulam E, Jakate S, Eswaran S, Usha L. Anastrozole-induced autoimmune hepatitis: a rare complication of breast cancer therapy. Anticancer Research. 2017 Aug 1;37(8):4173-4176.

28. Inno A, Basso M, Vecchio FM, Marsico VA, Cerchiaro E, D'Argento E, et al. Anastrozole-related acute hepatitis with autoimmune features: a case report. BMC Gastroenterology. 2011 Dec;11:1-4.

29. Mascella F, Gianni L, Affatato A, Fantini M. Aromatase inhibitors and anti-synthetase syndrome. International Journal of Immunopathology and Pharmacology. 2016 Sep;29(3):494-97.

30. Tenti S, Correale P, Cheleschi S, Fioravanti A, Pirtoli L. Aromatase Inhibitors—induced musculoskeletal disorders: current knowledge on clinical and molecular aspects. International Journal of Molecular Sciences. 2020 Aug 6;21(16):5625.

31. Talsania M, Scofield RH. Menopause and rheumatic disease. Rheumatic Disease Clinics. 2017 May 1;43(2):287-302.

32. Jeong H, Bae EK, Kim H, Eun YH, Kim IY, Kim H, et al. Estrogen attenuates the spondyloarthritis manifestations of the SKG arthritis model. Arthritis Research & Therapy. 2017 Dec;19:1-11.

33. Young NA, Hampton J, Sharma J, Jablonski K, DeVries C, Bratasz A, et al. Aromatase-inhibitor-induced musculoskeletal inflammation is observed independent of oophorectomy in a novel mouse model. Pharmaceuticals. 2022 Dec 17;15(12):1578.