Aromatase Inhibitors and their Connection to Autoimmunity

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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 recurrence. 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.
Spondyloarthritis

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 spondyloarthritis [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


