Aromatase Inhibitors and Arthralgia: A Growing Pain?

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In the current issue of ONCOLOGY, Henry et al comprehensively review the current state of knowledge regarding the incidence and pathogenesis of aromatase inhibitor (AI)-associated arthralgia, and its potential implications in terms of delivering adequate, effective adjuvant therapy. It has clearly been demonstrated in several large adjuvant trials that the addition or substitution of AIs provides an improved outcome over tamoxifen alone.[1-6] It is also apparent that arthralgia has been much more of a problem in the general population than it at first appeared to be in the clinical trial setting.

In two retrospective reviews of patients receiving aromatase inhibitors either as upfront adjuvant endocrine therapy, or following tamoxifen, a high dropout rate of 20% was noted.[7,8] The majority of patients discontinuing AIs cited arthralgia as a major reason. Clearly, such a degree of treatment intolerance, if truly greater than that seen in clinical trials, could potentially attenuate the beneficial effects of aromatase inhibitors. Effective management strategies to limit the impact of the arthralgia syndrome on patients’ quality of life and improve compliance are therefore of paramount importance.

Confounding Factors
One of the problems confounding our understanding of this topic is the high prevalence of arthralgia and joint problems in patients receiving therapy for breast cancer and, indeed, in the population as a whole. While a retrospective review of patients on the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial demonstrated a high incidence of arthralgia (36.5%) in patients receiving anastrozole (Arimidex), a considerable number of patients (30.9%) taking tamoxifen also reported this problem.[9] This is likely to reflect the background prevalence of arthralgia in the population rather than a tamoxifen effect, as no difference in the incidence of “joint ache” between tamoxifen and placebo was documented in a prevention trial.[10] A US population-based cohort study identified aches, joint pain, and stiffness in more than 40% of premenopausal women and in 72% of postmenopausal women.[11] One in six women participating in the Study of Women’s Health Across the Nation (SWAN) cohort study reported daily aches and pain symptoms over the previous 2 weeks.[12] Again, menopausal status was associated with the prevalence of aches and pain, with significantly higher levels in postmenopausal as compared to premenopausal women on multivariate analysis. A further challenge is that no unifying terminology to describe joint symptoms was employed in the large adjuvant trials, which leads to difficulty in interpreting data across the trials.

Pathogenesis of Arthralgia
Despite multiple hypotheses regarding the etiology of arthralgia with AIs, there is a lack of firm evidence supporting any particular explanation. It appears to be a class effect, having been demonstrated in association with various nonsteroidal and steroidal agents.[1-3,5,6] The relationship between estrogen deprivation and arthralgia seems intuitive, with multiple potential sites of interplay, as described by Henry and colleagues. As yet, however, no studies have established a clear link between absolute estrogen level and the development of arthralgia. An ongoing multicenter trial sponsored by the Pharmacogenetics Research Network (PGRN) of the National Institutes of Health will evaluate estradiol levels over time, while incorporating patient symptom questionnaires, and may help to clarify this issue.[13] This trial will also investigate whether inherited variation in pathways for anastrozole pharmacokinetics and/or pharmacodynamics might contribute to individual variations in anastrozole side effects.

The potential role of vitamin D deficiency in the pathogenesis of this syndrome is also tantalizing. Evidence shows that vitamin D deficiency is surprisingly common at breast cancer diagnosis and may be associated with poorer outcomes.[14] With the emergence of early data suggesting a
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potential role for high-dose vitamin D in the management of AI-induced arthralgia,[15] the opportunity may exist to improve outcomes on several fronts. A presumptive link between vitamin D deficiency and arthralgia is by no means definitive, however. Two trials are currently accruing patients to try to explore this issue further.[16,17] The role of bisphosphonates as possible preventive or therapeutic agents for this syndrome also remains to be proven; any usefulness may be tempered by their own tendency to cause musculoskeletal complaints.

Symptom Relief
With the etiology remaining unclear, management necessarily focuses on symptom relief, and a virtual panoply of agents has been used. As detailed in this thorough review, the use of different therapeutic options—including multiple pharmacologic, physical, and alternative approaches—tends to be based mainly on anecdotal rather than clinical trial evidence. Henry and coauthors discuss the practice of switching patients to another aromatase inhibitor or to tamoxifen as a potential strategy. Although some retrospective data support this strategy,[7] it has not as yet been prospectively proven to improve symptoms or compliance. In the absence of a clear understanding of the underlying mechanism of arthralgia, we support a policy of heightened awareness of this toxicity and appropriate early intervention with symptom control measures, in order to prevent noncompliance and the attendant threat to patient outcomes.

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The main article can be found here:
Aromatase Inhibitor–Associated Musculoskeletal Symptoms: Etiology and Strategies for Management

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