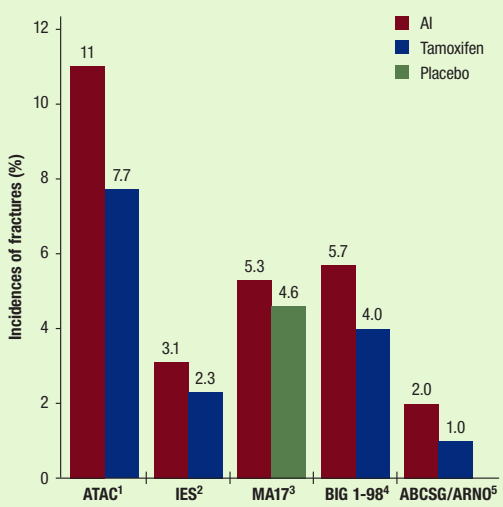
Short- and Long-Term Adverse Events of Endocrine Therapy with Tamoxifen and Aromatase Inhibitors

The long-term toxicities associated with adjuvant tamoxifen have been well delineated, with particular concerns about increased risk of thromboembolic events, endometrial cancer and gynecologic procedures. Several recent trials have demonstrated an efficacy advantage for the third-generation aromatase inhibitors compared to tamoxifen but have revealed a higher incidence of arthralgias and fractures. Preliminary data suggest that there may be distinct differences in the toxicities of anastrozole, letrozole and exemestane, particularly with regard to serum lipids and cardiovascular events. The LEAP trial reported at the 2005 San Antonio Breast Cancer Symposium revealed a differential impact of the three aromatase inhibitors on serum lipids in healthy postmenopausal women. Additional studies and longer-term follow-up will be necessary to further characterize the distinct toxicity profiles of the aromatase inhibitors.

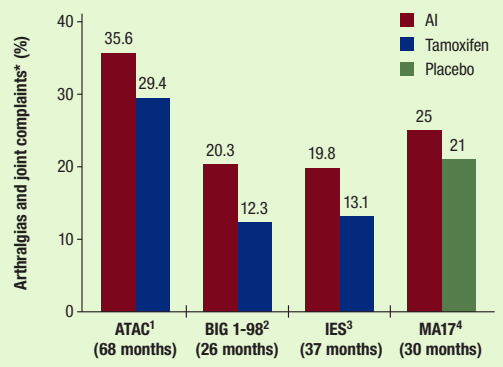
FRACTURES IN ADJUVANT AI TRIALS



AI = aromatase inhibitor; ATAC = Arimidex® (anastrozole), Tamoxifen, Alone or in Combination; IES = Intergroup exemestane study; MA17 = extended adjuvant treatment with letrozole trial; BIG 1-98 = IBCSG trial of letrozole versus tamoxifen; ABCSG/ARNO = combined Austrian-German trial

SOURCES: [1] Howell A et al. *Lancet* 2005;365(9453):60-2; [2] Coombes RC et al. *N Engl J Med* 2004;350(11):1081-92; [3] Goss PE et al. *J Natl Cancer Inst* 2005;97(17):1262-71; [4] Thürlimann B et al. Presentation. ASCO 2005; [5] Jakesz R et al. *Lancet* 2005;366(9484):455-62.

JOINT SYMPTOMS AND ARTHRALGIAS IN ADJUVANT AI TRIALS



SOURCES: [1] Howell A et al. *Lancet* 2005;365(9453):60-2; [2] Thürlimann B et al. Presentation. ASCO 2005; [3] Plourde P et al. Poster. Lynn Sage Breast Cancer Symposium 2005; [4] Goss PE et al. *J Natl Cancer Inst* 2005;97(17):1262-71.

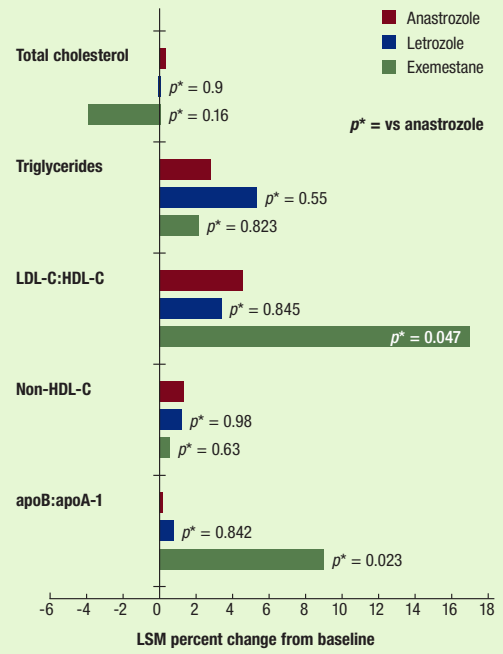
THE INCIDENCE OF GYNECOLOGIC ADVERSE EVENTS AND INTERVENTIONS IN THE ATAC TRIAL

Gynecologic event	Anastrozole (n = 3,092)	Tamoxifen (n = 3,094)	*p*-value
Vaginal bleeding	5.4%	10.2%	<0.0001
Vaginal discharge	3.5%	13.2%	<0.0001
Endometrial cancer*	0.2%	0.8%	0.02
Gynecologic intervention			
Ultrasound	8.1%	8.6%	NR
Polypectomy*	1.3%	3.1%	NR
Hysteroscopy*	1.8%	6.1%	NR
Dilatation and curettage*	1.3%	4.3%	NR
Endometrial biopsy*	1.3%	2.1%	NR
Oophorectomy	1.1%	1.9%	NR
Hysterectomy*	1.4%	5.3%	NR

NR = not reported
* Percentages calculated based on the number of patients with an intact uterus at baseline (anastrozole n = 2,228; tamoxifen n = 2,236)

SOURCE: Duffy SR, on behalf of the ATAC Trialists' Group. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 2056.

LEAP STUDY: CHANGE IN LIPIDS FOLLOWING 24 WEEKS OF AROMATASE INHIBITORS IN HEALTHY POSTMENOPAUSAL WOMEN



SOURCE: McCloskey E et al. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 2052.

SELECT PUBLICATIONS

Coleman R. **Association between prior chemotherapy and the adverse event profile of adjuvant anastrozole and tamoxifen: A retrospective analysis of data from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial on behalf of the ATAC Trialists' Group.** Poster. European Society for Medical Oncology Congress 2004.

Coombes RC et al; Intergroup Exemestane Study. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92.

Duffy SR, on behalf of the ATAC Trialists' Group. **Gynecologic interventions during adjuvant therapy with anastrozole or tamoxifen: Results from the ATAC trial.** Poster. San Antonio Breast Cancer Symposium 2005;Abstract 2056.

Gnant M. **Zoledronic acid effectively counteracts cancer treatment induced bone loss (CTIBL) in premenopausal women receiving adjuvant goserelin and tamoxifen or goserelin and anastrozole for hormone-responsive breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2004.

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA17.** *J Natl Cancer Inst* 2005;97(17):1262-71.

Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2.

Jakesz R et al. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005;366(9484):455-62.

Lonning PE et al. **Lipid profile and homocysteine levels in postmenopausal women with early breast cancer at low risk treated for two years with exemestane: Follow-up results of a randomized, placebo-controlled study.** Poster. San Antonio Breast Cancer Symposium 2005;Abstract 4108.

McCloskey E et al. **Initial results from the LEAP study: The first direct comparison of safety parameters between aromatase inhibitors in healthy postmenopausal women.** Poster. San Antonio Breast Cancer Symposium 2005;Abstract 2052.

Plourde P et al. **Arthralgia in postmenopausal breast cancer patients on adjuvant endocrine therapy: A risk-benefit analysis.** Poster. Lynn Sage Breast Cancer Symposium 2005.

Thürlimann BJ et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** *Proc ASCO* 2005;Abstract 511.

AROMATASE INHIBITORS AND FRACTURES

The five-year overall toxicity data are very favorable for anastrozole compared to tamoxifen because the three life-threatening toxicities — endometrial cancer, arterial and venous vascular events — are all significantly less with anastrozole. Many oncologists have concern regarding bones, but I believe it's going to be not only a preventable, treatable situation but also something that is likely to go away completely in the near future. There is no difference in hip fractures after 68 months with anastrozole and tamoxifen. This is for a group of patients who had no prescreening when they entered the study and no ongoing protocol-defined follow-up for bone. If you're going to actually do any screening or treating, you're going to have lower numbers than that.

— Rowan T Chlebowski, MD, PhD.
Breast Cancer Update *2005 (7)*

AROMATASE INHIBITORS AND MUSCULOSKELETAL DISORDERS

Arthralgia is a condition with effective available treatment options. Whereas the incidence of arthralgias reported in clinical trials is higher with anastrozole, the absolute difference compared with tamoxifen treatment is relatively small; this finding is similar for the other aromatase inhibitors, letrozole and exemestane… . The variability in which this type of adverse event data is collected confounds the ability to make cross-trial comparisons and identify any potential differences in the occurrence of arthralgia among aromatase inhibitors.

— Paul Plourde, MD et al. Poster. Lynn Sage Breast Cancer Symposium 2005

GYNECOLOGIC INTERVENTIONS DURING ADJUVANT ENDOCRINE THERAPY

The incidence of gynecologic adverse events in the main ATAC trial was significantly lower for anastrozole compared with tamoxifen. An almost four-fold reduction in the incidence of both hysteroscopy and hysterectomy was observed in patients receiving anastrozole… .

The significant difference in the incidence of gynecologic AEs previously reported for anastrozole compared with tamoxifen in the ATAC trial appears to translate to a requirement for fewer gynecologic interventions in patients receiving the AI. Therefore, treatment with anastrozole rather than tamoxifen may avoid the psychologic distress and the associated costs of the investigation/treatment of gynecologic events in many women. These findings offer further support to the use of anastrozole as the preferred primary adjuvant treatment for postmenopausal women with early breast cancer.

— Sean R Duffy, MD et al. Poster 2056. San Antonio Breast Cancer Symposium 2005

DIFFERENTIAL EFFECTS OF THE AVAILABLE AROMATASE INHIBITORS ON SERUM LIPIDS

I wrote a paper several years ago speculating before any of these data were published that these drugs will have a different safety signal because they are structurally different. And now these data are emerging. With exemestane there is small but definite increased risk of cardiac dysfunction. If you look at the letrozole data, at 25 months there is small but definite increased risk of cerebrovascular accident (CVA) and increased risk of myocardial infarct. At 68 months' follow-up in ATAC, none of those things are true. For cardiac deaths, it is 46 versus 49 at 68 months and CVAs are substantially reduced with anastrozole compared to tamoxifen.

Also, the LEAP study took close to 102 healthy postmenopausal volunteers and gave them up to 24 weeks of anastrozole, letrozole or exemestane in a blinded fashion. The study looked at their effects on lipids and demonstrated that these effects are totally different between these drugs, specifically with the steroidal compound. So I think we have to be cognizant of this. I do not think we can say, "An AI is an AI and just pull one out of a hat and use it."

— Aman U Buzdar, MD. Meet The Professors Session San Antonio Breast Cancer Symposium 2005