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A double-blind placebo-controlled study to evaluate endometrial safety and gynaecological symptoms in women treated for up to 5 years with tamoxifen or placebo – A substudy for IBIS I Breast Cancer Prevention Trial ☆

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Abstract ***Aims of the study:*** This prospective study was performed to investigate the effects of 5-year's use of tamoxifen in preventive setting on endometrium and gynaecological symptoms.
Material and methods: Altogether 96 women were treated either with tamoxifen (TAM, $n = 45$) or placebo (PLA, $n = 51$) for up to 5 years in a randomised, double-blind IBIS I breast cancer prevention trial, clinically followed-up for an additional year and for the occurrence of malignancies at least 9 years between 2/1995 and 7/2009 in Finland. The gynaecological follow-up with trans-vaginal ultrasound and endometrial biopsies were performed at baseline, at 2.5 and 5 years and at the 6 years follow-up visit.
Results: Women in the TAM group discontinued the treatment significantly more often (44% versus 22%; $p = 0.017$) and earlier (at 15 versus 30 months; $p = 0.044$), than those in the PLA group. In postmenopausal women the median endometrial thickness was significantly increased at five years in the TAM group (median 4.3 versus 2.0 mm, $p = 0.011$), but there was no difference between the groups at one year after the treatment. There were also statistically significantly

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more referrals to hospitals due to gynaecological findings in the TAM group (risk rates (RR) 3.15; 95% confidence intervals (CI) 1.12–10.10), but no differences in hysterectomy rates or other serious adverse event rates were observed.

Conclusions: The discontinuation rate in the TAM group was high, and the discontinuations also occurred early. Even though there were significantly more non-serious gynaecological events during the TAM treatment, routine gynaecological follow-up cannot be recommended.

1. Introduction

The finding of a decrease in the contralateral breast cancer incidence following tamoxifen administration for adjuvant therapy has led to its use in breast cancer prevention. Four large prevention trials with tamoxifen have been published. Initially, in the National Surgical Adjuvant Breast and Bowel Project's (NSABP) Breast Cancer Prevention Trial, tamoxifen reduced the risk of invasive breast cancer by 49%.[1] Three other randomised prevention trials comparing tamoxifen with placebo have shown reduction of 38% in the overall breast cancer incidence and reduction of 48% in the oestrogen receptor-positive breast cancer.[2]

One important determinant of tamoxifen safety is the endometrium. The first report connecting tamoxifen and endometrial cancer was published in 1989[3] and since then several reports have described the endometrial changes in postmenopausal breast cancer patients treated with tamoxifen.[4–6] The most common endometrial changes include endometrial polyps (with the incidence between 8–36% versus 0–10% in untreated women and endometrial hyperplasia (1.3–20% versus 0–10%). The risk for the endometrial carcinoma was 1.3–7.5-fold risk compared to untreated women. Also cystic atrophy/adenomyosis and growth of leiomyomas have been reported.[7] At present, detailed guidelines give recommendations for the follow-up of patients taking tamoxifen for the treatment of breast cancer.[8] Currently no active screening for asymptomatic patients treated with tamoxifen, other than routine annual gynaecological surveillance, is recommended.[7]

In the prevention studies with tamoxifen, the risk for endometrial cancer has been estimated to increase by 2.5-fold relative to placebo.[2] Further, the findings from the NSABP Breast Cancer Prevention Trial showed that the risk was increased only in postmenopausal women, but no increase in premenopausal women was observed. It has also been postulated, that even though the frequency of adverse events is in general reduced after stopping the tamoxifen treatment, the adverse effects on endometrium may persist.[8] There are also recommendations for the follow-up of endometrial safety when tamoxifen is used in the preventive setting.[9] Since uterine safety becomes more important when only a small benefit of the treatment is to be expected, as in the use of tamoxifen for breast cancer prevention, more active surveillance is needed, including annual vaginal ultrasonography.[7] The more recent United States (US) guidelines for subjects taking tamoxifen for preventive setting include a baseline gynaecological examination before starting tamoxifen, and the annual follow-up thereafter, and also emphasise continuing surveillance post-treatment. Since tamoxifen-induced endometrial changes only appear after 2–3 years from the start of the treatment, annual transvaginal sonography may be started after that[7] However, routine endometrial biopsy is not needed in the absence of abnormal vaginal bleeding.[7,10]

In the first International Breast Cancer Intervention Study (IBIS I), a total of 7145 women at risk of breast cancer were randomised to receive either tamoxifen 20 mg or placebo for 5 years.[11] After a median follow-up of 96 months after randomisation, the risk ratio for breast cancer was 0.73 (95% confidence intervals (CI) = 0.58–0.91; $p = 0.004$) for those treated with tamoxifen compared to those treated with placebo.[12] The results also indicated that even though the risk-reducing effect of tamoxifen appeared to persist for at least 10 years, the majority of the adverse effects did not continue after the 5-year treatment period. A total of 28 endometrial cancers were reported, 17 in the tamoxifen group and 11 in the placebo group (risk rates (RR) 1.55; 95% CI = 0.68–3.65). Twelve of the cancers in the tamoxifen group but only three in the placebo group were detected during the active treatment period. Detailed data on other endometrial safety findings were not reported.

Even though the adverse effects of tamoxifen, including uterine cancer and endometrial hyperplasia, are well documented, there are only few data available from clinical studies on endometrial findings with tamoxifen use in preventive setting. This led us to perform this prospective, randomised, double-blind gynaecological sub-study to obtain detailed data on gynaecological symptoms and signs and to evaluate long-term endometrial effects.

2. Materials and methods

2.1. Subjects

This study was a sub-study for the IBIS I-study, in which in total 7145 women aged 35–70 years at the risk