vascular risk [10] and may be less stimulatory to the uterus [6,11]. Accrual to the Study of Tamoxifen and Raloxifene (STAR) NSABP P-2 began in July 1999 at almost 500 centres in North America. Eligible women must be postmenopausal women, 35 years or older and have an increased risk reflected in a $\geqslant 1.66\%$ projected 5-year probability of developing invasive breast cancer according to the breast cancer Risk Assessment Profile (RAP) generated by the NSABP Biostatistical Center. The RAP incorporates Gail model criteria, as well as a history of benign breast biopsies, LCIS and AH, as well as general health status, personal and family medical history and lifestyle. The plan is to randomise 22 000 eligible women to tamoxifen 20 mg or raloxifene 60 mg per day for 5 years. Study endpoints include invasive and noninvasive breast cancer, cardiovascular disease, endometrial cancer, bone fractures and vascular events.

Appendix

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Update on raloxifene to prevent endometrial-breast cancer

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Abstract

In the mid 1980s when tamoxifen was shown to be associated with endometrial neoplasia there was a renewed interest in another SERM compound, raloxifene. Experimental animal data suggested that raloxifene did not stimulate the endometrium as tamoxifen does while having similar anti-oestrogenic effects in breast tissue as tamoxifen. Clinical data has now shown that raloxifene does not stimulate the endometrium in postmenopausal women. It results in no hyperplasia, no increase in endometrium thickness or polyp formation and virtually no proliferation. Further studies are necessary to see if long-term raloxifene use will reduce the risk of endometrial cancer. In studies of raloxifene as treatment for osteoporosis, when viewed as a secondary endpoint there was a significant reduction in risk of new onset breast cancer. Further studies with breast cancer as a primary endpoint are ongoing (the STAR Trial). © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: SERMs; Raloxifene; Tamoxifen; Endometrial Cancer; Breast Cancer; Transvaginal ultrasound; Sonohysterography

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1. Introduction

In the mid to late 1980s a series of case reports and letters to the editors suggested an association between tamoxifen and endometrium neoplasia [1]. The first prospective study was published by P. Neven [2] in 1990. Of 16 postmenopausal women treated with tamoxifen for 3 years and followed by hysteroscopy, 50% maintained inactive atrophic endometrium, while 44% developed proliferation including 25% polyps and 6% adenocarcinoma. At the same time transvaginal ultrasound was gaining popularity as a method of excluding endometrial pathology in women with postmenopausal bleeding [3]. An unusual ultrasound appearance of the uterus seen in tamoxifen patients was first described in 1994 [4]. This was felt to represent glandular cystic atrophy sometimes located in the basalis of the endometrium, the proximal myometrium or even in endometrial polyps.

Raloxifene is a benzothiophene derivative. It too had been tested in the early 1980s as a breast cancer agent in a phase II trial. Patients who had failed tamoxifen therapy did not show any response to raloxifene and the drug was placed on the shelf. When news of tamoxifen's association with endometrial neoplasia surfaced a review of raloxifene revealed that in experimental animals it was a pure oestrogen antagonist in the uterus unlike the triphenylethylene derivatives (tamoxifen, droloxifene and idoxifene) which all display partial agonistic and antagonistic activity [5]. Raloxifene also had positive tamoxifen-like effects in skeletal remodelling and lipid metabolism. Thus, phase III trials for osteoporosis prevention and treatment were initiated. Clearly a lack of tamoxifen-like activity in the female postmenopausal endometrium would be essential for raloxifene to be a viable agent.

A Canadian study blindly comparing a relatively high dosage of raloxifene (150 mg) with continuous combined hormone replacement therapy (0.625 mg conjugated equine oestrogen and 2.5 mg medroxyprogesterone acetate) [6] underwent a 1 year interim analysis. 100% of endometrial biopsies read blindly in raloxifene-treated patients were inactive or atrophic. Only 66% of patients on continuous combined hormone replacement therapy maintained inactive/atrophic endometrium. 31% had proliferative endometrium and 3% had polyps. No patients in the raloxifene group had any polyps. No patients in either group had any hyperplasia. A subsequent study [7] with uterine safety as the primary endpoint was then performed. 415 women who demonstrated a lack of uterine pathology by transvaginal ultrasound, saline infusion sonohysterography and negative endometrial biopsy, were randomised to receive either a placebo, conjugated equine oestrogen 0.625 mg, raloxifene 60 mg or raloxifene 120 mg for 1 year. Transvaginal ultrasound was performed at 3-month intervals and saline infusion sonohysterography and endometrial biopsy was done at 6 and 12 months. As one might expect, the oestrogen only group by 3 months had thickened their endometrial echo by nearly 5 mm and this drifted up to nearly 6 mm at 1 year. Neither raloxifene group was statistically different from placebo at 1 year. Similar findings were seen with saline infusion sonohysterography. Finally on biopsy at endpoint, 35 and 23% of the unopposed oestrogen group had proliferative and hyperplastic endometria, respectively. In the placebo group, 2% had proliferation and 2% had hyperplasia. No raloxifene patient developed hyperplasia and in the raloxifene 120 mg group there was no proliferation while 3% of the raloxifene 60 mg group developed proliferation — a number not statistically significant from placebo. Thus, it seems clear that raloxifene is not stimulatory to the endometrium in the postmenopausal woman and clearly it is not tamoxifen-like resulting in no cancers, no hyperplasia and no polyps.

In terms of a possible reduction in endometrial cancers by this oestrogen antagonist the data are not yet sufficient. The More Trial [8] was an osteoporosis treatment study of 7705 women. These women had no baseline screening for endometrial disease. At 3 years, the rate of endometrial cancer was 0.7 per thousand women in the placebo group versus 0.5 per thousand women years in raloxifene group. This yields a relative risk = 0.8 (95% CI: 0.21–2.67). Further studies will be necessary to see if long-term raloxifene use may indeed reduce the risk of endometrial carcinoma. In terms of breast cancer raloxifene has been shown to have anti-oestrogen effects in oestrogen-dependent mammary cancer cell lines [9] as well as experimental animals [10]. The More Trial had breast cancer as a secondary endpoint. Mammography at 1 year was optional and was performed in 46% of patients. At 2 and 3 years it was required and was performed in 87% in the placebo patients and 89% of raloxifene patients. Total number of cases of new onset breast cancer was 40. The rate in the placebo group was 3.6 per 1000 women years, and in the raloxifene it was 0.9 per 1000 women years. This yielded a relative risk of 0.24 (95% CI: 0.13–0.24). A new study known as STAR (Study of Tamoxifen and Raloxifene) began in July 1999. It will be a head-to-head comparison of tamoxifen and raloxifene with breast cancer as its primary endpoint.

In summary, raloxifene does not stimulate the endometrium in postmenopausal women. It results in no hyperplasia, no increase in endometrial thickness or polyps, and virtually no proliferation. Further studies are necessary to see if long-term use will reduce the risk of endometrial cancer. In studies of osteoporosis treatment, there was a significant reduction in risk of new onset breast cancer when viewed as a secondary endpoint. Further studies with breast cancer as a primary endpoint are ongoing.

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