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New SERMs in development

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The ideal Selective Oestrogen Receptor Modulator (SERM) is an oestrogen receptor (ER)-antagonist in the breast and uterus and ER-agonist in bone and cholesterol, preventing bone loss, myocardial infarction and breast cancer without stimulating the uterus. Each different SERM has a specific affinity for the organ-specific ERα and/or ERβ that leads to a unique conformation of the ER–SERM complex. This tridimensional structure allows coregulatory proteins to induce or stop gene activation. This can be illustrated with a recently described pyrazole derivative that has a high affinity for the ERα in terms of binding and agonist potency. By incorporating a basic side-chain, the binding mode differs and converts this compound into an ER-antagonist with 20-fold higher affinity for ERα than ERβ [1]. This presentation is an update on new SERMs in development. Tamoxifen, the benzothiophenes raloxifene and arzoxifene and the pure anti-oestrogen, fulvestrant will be discussed elsewhere in this supplement.

It has been shown that triphenylethylene derivatives have a SERM profile. Toremifene's differences from tamoxifen in breast, uterus and bone are of no clinical signficance [2]. Droloxifene was less active than tamoxifen in a phase III advanced breast cancer trial and is not longer in development, even for the treatment of osteoporosis. The same is true for idoxifene which, although responses in tamoxifen-resistant breast cancer have been reported, leads to uterine polyps and prolapse [3]. Phase II results from Japan have been described for TAT-59, a structural analogue of tamoxifen also called miproxifene phosphate, in breast cancer but there, are no human data in bone, cholesterol nor the endometrium. GW7604 is the active metabolite of GW5638, a tamoxifen derivative. The novel carboxylic acid side-chain achieves more complete ant-oestrogenic activity in the breast and uterus whilst maintaining tamoxifen's beneficial effects in bone and cholesterol. They produce a more active ER/AP-1 conformation of the ER/AP-1 transcription factor complex when bound to ERβ than when bound to ERα [4,5]. This compound is now being used in clinical practice for metastatic breast cancer under the code DPC-9764, but no data are available at this stage.

The naphthalene structure CP-336156, lasofoxifene, prevents age-related bone loss and preserves bone strength in aged male and female rats. Preclinical data show a beneficial effect on breast cancer growth and serum cholesterol [6,7]. This compound is now in phase III trials, but the company has not yet disclosed any of the clinical data.

The centochrome levermoloxifene has been tested against a low-dose ccHRT (Activelle) for osteoporosis in a 1-year phase III trial in more than 300 healthy postmenopausal women. Patients had baseline and follow-up uterine measurements. Those on levormeloxifene experienced less vaginal bleeding and breast tenderness than those using the low-dose ccHRT. Levormeloxifene users developed severe endometrial thickening without endometrial proliferation, but with fluid accumulation in the endometrial stroma as has been observed with other SERMs like tamoxifen [8]. Although its bone and cholesterol effects were beneficial, the uterine effects of levormeloxifene led to the termination of any further development of this drug.

TSE-424, already known for its SERM profile in preclinical models, has been tested in a placebo-controlled clinical trial and shown to produce, like raloxifene, a dose-related decrease in markers of bone remodelling and this is observed after 3 months of treatment. Higher doses of TSE-424 are currently under study. ERA-923, a 2-phenyl indole, preserves bone mineral density and lowers serum total cholesterol in a rat model. It inhibits oestrogen-stimulated growth in breast and endometrial cancer models [9]. A phase II trial in women with metastatic breast cancer is in progress.

The antiproliferative effect of the oral active benzopyrene derivative, EM-800, seems spectacular. Relative to other SERMs, it has the highest affinity for the ER. The drug inhibits ER-positive breast cancer cells *in vitro* and in xenografts in ovariectomised nude mice supple-

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mented with oestrone [10]. The same authors showed the ability of EM-800 to prevent bone loss and lower serum cholesterol levels in the ovariectomised rat similar, but more potent, to that of raloxifene [11]. EM-800 did not stimulate the endometrium to grow. It may become the first non-steroidal pure anti-oestrogen in breast and endometrium with an oestrogenic profile in bone and cholesterol, but clinical data are not yet available. Phase II data in tamoxifen resistant breast cancer were promising but in a Phase III trial, EM-800 has a lower efficiacy compared with anastrazole, a new generation aromatase inhibitor.

The question of whether the clinical impact of all these different structures will translate into improved management of the osteoporotic patient with a high breast/endometrial cancer risk should be answered by the data from these studies outlined above.

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