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Selective Estrogen Receptor Modulators (SERMS)

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ABSTRACT

Hormone receptors and, specifically, estrogen receptors were described about four decades ago. For estrogens, there are two receptors, estrogen receptor alpha (ERα) and estrogen receptor β (ERβ). The two receptors are coded by different genes and their tissue expression varies across organs. ERα is predominantly expressed in reproductive tissues (uterus, breast, ovaries) liver and central nervous system, whereas ERβ is expressed in other tissues such as bone, endothelium, lungs, urogenital tract, ovaries, central nervous system and prostate. More than seventy molecules that belong to the SERMS class have been described. There are 5 chemical groups: triphenylethylenes, benzotiophenes, tetrahydronaphtylenes, indoles and benzopyrans. All of these non-hormonal compounds are capable of activating the ER, reduce bone turnover rate and, as an antiresorptive, clearly improve bone density. Estrogens reduce bone turnover rate and, as an antiresorptive, clearly improve bone density. They are also beneficial for the relief of menopausal symptoms. An ongoing debate that extends over the decades, relates to to overall benefit/risk profile of estrogen or estrogen-progestin therapy since these therapies can increase the risk of serious health disorders, such as breast cancer. SERMs have increased our understanding of hormone-receptor regulatory mechanisms. Their development has permitted a targeted efficacy profile avoiding some of the side effects of the hormone therapy. Their clinical utility relies today mostly on the effects on breast cancer and bone. **(Arq Bras Endocrinol Metab 2006;50/4:720-734)**

Keywords: Raloxifene; Tamoxifene; Estrogen receptors; Bone turnover; Breast cancer

RESUMO

Moduladores Seletivos do Receptor Estrogênico (SERMs).
Os receptores hormonais e especificamente os receptores estrogênicos, foram descritos há cerca de 40 anos. Para os estrógenos, existem dois tipos: o alfa (ERα) e os beta (ERβ), os quais são codificados por diferentes genes e sua expressão tissular varia de tecido para tecido. O ERα se expressa predominantemente no aparelho reprodutivo (útero, mamas, ovários), fígado e sistema nervoso central (SNC). O ERβ se expressa em outros tecidos como osso, endotélio, pulmões, urogenital, além dos ovários, SNC e próstata. Mais de setenta moléculas pertencentes ao grupo dos SERMs têm sido descritas, em 5 grupos químicos: trifeniletilenos, benzotiofenos, tetrahidronaftilenos, indols e benzopiranos. Todos estes compostos não hormonais são capazes de ativar o ER, reduzindo a remodelação óssea e melhorando a densidade mineral óssea. Os estrógenos reduzem a remodelação óssea e aumentam a densidade mineral óssea, como também melhoram os sintomas da menopausa. Um debate permanente existe a respeito da relação risco/benefício da terapia estrógeno-progestínica, em virtude do aumento do risco de problemas de saúde mais sérios como câncer de mama. Os SERMs aprimoraram o conhecimento sobre os mecanismos de regulação hormônio-receptor, e o seu desenvolvimento permitiu

uma eficiente modalidade de ação terapêutica hormonal, evitando-se alguns dos efeitois adversos da terapia hormonal *per si*. **(Arq Bras Endocrinol Metab 2006;50/4:720-734)**

Descritores: Raloxifeno; Tamoxifeno; Receptores estrogênicos; Remodelação óssea; Câncer mamário

ESTROGEN RECEPTOR ACTIVATION BY ESTROGENS AND SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

HORMONE RECEPTORS AND, SPECIFICALLY, estrogen receptors were described about four decades ago (1-3). For estrogens, there are two receptors, estrogen receptor alpha (ERα) and estrogen receptor β (ERβ). The two receptors are coded by different genes and their tissue expression varies across organs. ERα is predominantly expressed in reproductive tissues (uterus, breast, ovaries) liver and central nervous system, whereas ERβ is expressed in other tissues such as bone, endothelium, lungs, urogenital tract, ovaries, central nervous system and prostate (4-10). Both ERs are formed by a single polypeptide chain with 565 aminoacids for the ERα and 530 for the ERβ (11). There are 6 homologous regions, A to F, with the ERβ lacking the carboxiterminal F domain (12). The domains of the estrogen receptors include sites for nuclear location, hormone binding, dimerization, DNA binding and transcription activation (12-16). Estrogens and SERMS activate estrogen genes by a series of events that occur after their binding to the ER. The interaction of the hormone with the naïve receptor induces conformational changes of the ligand-receptor binding to nuclear proteins or adaptor proteins or corregulators (17,18) that induces the dissociation of heat-shock proteins associated with the inactive receptor. This results in receptor activation and and an interaction with DNA (19). This ligand-receptor complex binds to DNA response elements, called Estrogen-Response-Elements (ERE), located in the promoter region of the estrogen target genes, initiating the transcription process and mRNA synthesis. The final result of the process, either inducing or inhibiting gene transcription by the ligand-ER dimer, depends on the type of cell and the presence of corregulator proteins and gene promoters. Rapid acting, non-genomic pathways are also activated by estrogens and SERMS such as those dependent upon NO (vasodilatation, ischemic myocardial damage, response to endothelial damage, coronary artery relaxation or vasodilation in hypertensive rats) (20-24). Figure 1 summarizes the general activation pathways of the estrogen receptor.

Several characteristics differentiate ER activation induced by estrogens from those induced by SERMS. Estrogen and raloxifene, a prototypical SERM, occupy the same ER ligand binding site (25) but induce conformational changes in the receptor that are distinct (26). This is a relevant point, namely that the different structure of the ligand-receptor complex depends on the molecular characteristics of the ligand. The ER contains a ligand-binding domain, which includes a series of amino acids called Activating Function-2 (AF-2) essential for the activation of genes that mediate the estrogen effect in reproductive tissues as the breast or uterus. Therefore, the different ligands can induce different gene transcription processes. For example, the union of the ligand binding domain with tamoxifene, another SERM, results in a partial agonistic effect in the uterus whereas this same interaction is fully antagonistic in the breast. In contrast, when binding to estradiol, the conformation of the ligand-receptor complex permits an interaction with a coactivator that results in a fully agonistic effect in breast tissue (27). Similar to tamoxifene, the Raloxifene-ER complex displays a conformational shape in which the interaction with the corregulatory protein is not feasible and the transcription process cannot be produced, thus resulting in an antagonistic effect (28). In general, because of these differences in the 3-dimenstinal conformation of the ligand-receptor complex, there is a wide range of subsequent actions from full activation in the case of estradiol to complete antagonism in the case of the pure antiestrogens. The different SERMS exhibit intermediate properties because they induce transitional conformations closer to one or the other boundary (29). The tissue itself, of course, plays a role in terms of subsequent gene steps. In bone tissue, for example, candidate genes either activated or repressed at the ERα and ERβ level by estrogen or SERMS are different (30). Moreover, estrogen and SERMS exert different effects on estrogen response element (ERE) transcriptional activity (31). Although the mechanism of activation of estrogen receptor is not fully clarified, the discovery of SERMS greatly contributed to our understanding of their intrinsic functions, opening the way for the discovery of selective "a la carte" ligands for different hormone receptors. The 'a la carte' concept refers to the potential to produce clinically desirable effects while avoiding those that constitute a problem.

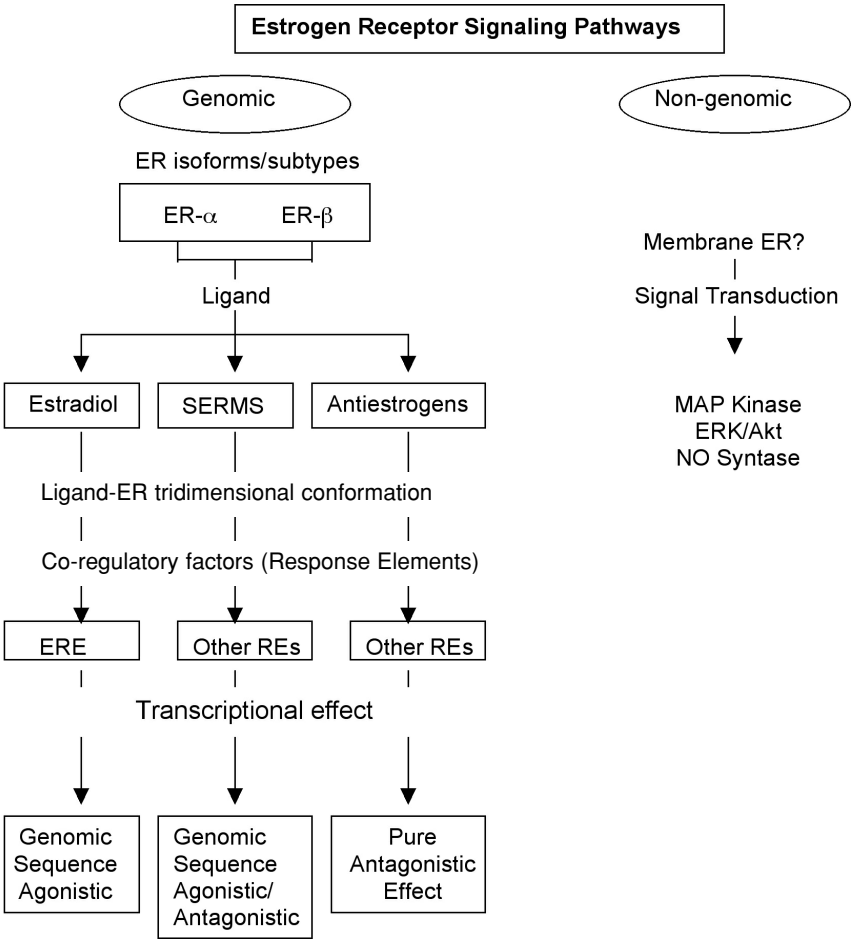

Figure 1. Summary of the estrogen receptor signaling pathways. The interaction of the ER subtypes/isoforms with the different ligands induces characteristic tridimensional conformations of the ligand-receptor complex. The interaction with the diverse response elements acting as co-regulatory factors produces different transcriptional effects inducing a pure agonistic, pure antagonistic or a mixture of agonistic/antagonistic effects (33). The fast non-genomic signaling pathway acts through a potential membrane ER regulating MAP kinase, ERK/Akl and NO synthase responses (22-24).

CHEMICAL CLASSIFICATION OF SERMS

More than seventy molecules that belong to the SERMS class have been described (32). There are 5 chemical groups: triphenylethylenes, benzotiophenes, tetrahydronaphtylenes, indoles and benzopyrans (33) (table 1). All of these non-hormonal compounds are capable of activating the ER.

Triphenylethylenes were developed for the treatment of the estrogen-dependent breast cancer. Tamoxifene is widely used for this indication and is a reference compound for prevention and treatment (34-36). Toremifene has been also marketed for breast cancer treatment (37). Tamoxifene induces positive effects on bone density whereas toremifene use is accompanied by slight reductions in bone density (38). Both toremifene and tamoxifene have an estrogen-agonistic effect on the endometrium (39,40). Other compounds of the group of the triphenylethylenes also induce uterine stimulation and, for this reason, their development has been limited and their use restricted to cases of advanced breast cancer (41-48) whereas others are in early phases of development (49-52).

Benzotiophenes constitute a second chemical group. Raloxifene is the main molecule of this class and is currently the most widely used for osteoporosis treatment and prevention. This class of SERMS is antiresorptive on bone. There is no stimulatory effect on the endometrium (53) and an estrogen-like effect on lipids (53,54). Raloxifene has an inhibitory effect on ER-pos-

Table 1. SERMS: Chemical groups (33).

Triphenylethylenes	**Tetrahydronafthylenes**
Tamoxifen	Lasofoxifene
Droloxifene	Nafoxidine
Idoxifene	**Indoles**
Clomiphene	Bazedoxifene
Toremifene	**Benzopyrans**
Benzotiophenes	EM-800
Raloxifene	Levormeloxifene
Arzoxifene	

itive breast cancer cells (55) and in clinical cases (56). Arzoxifene is another SERM of this group currently in a phase III trial. In breast cancer cells lines, arzoxifene has a more potent effect than raloxifene but is similar or more potent in skeletal systems (57-59).

Tetrahydronafthylenes. Lasofoxifene is the main representative of this group. In vivo animal experiments have shown a great affinity for ER-α (60). The effect of these molecules in ovariectomized (OVX) rat models is prevention of bone loss and positive changes in lipid profile. In male orchidectomized old rats, these SERMS are also efficacious in preventing bone loss and preserving biomechanical properties (61,62). Lasofoxifene is currently in advanced states of development (phase 3 clinical trials). Trioxifene, another member of the group, was abandoned because of side effects (63).

Indoles. Bazedoxifene and pipendoxifene are the 2 main molecules of this group. In a phase 3 clinical trial, bazedoxifene demonstrated bone protective, cholesterol lowering and no uterine effects in OVX and intact rat models (64). This class of SERMS antagonizes C3 gene and counteracts naloxone-induced vasomotor responses in rats (65). In addition, mechanical strength of bone is improved in treated animals (66).

Benzopyrans. A number of compounds belong to this group. Ormeloxifene is used as contraceptive (67). The development of Levormeloxifene was stopped because of uterine safety issues (68). Other molecules in active development are SP500263 (69), EM-800 and EM-652 (70,71) among others.

SERMS AND BONE

Estrogens play an important role in female bone homeostasis; in the estrogen deficient state, bone resorption is increased. As a result of these predictable postmenopausal findings, estrogens have been extensively used as the main therapy to prevent bone loss in postmenopausal women. Estrogens reduce bone turnover rate and, as an antiresorptive, clearly improve bone density. They are also beneficial for the relief of menopausal symptoms. An ongoing debate, that extends over the decades, relates to to overall benefit/risk profile of estrogen or estrogen-progestin therapy since these therapies can increase the risk of serious health disorders, such as breast cancer (72,73).

It is in this area that SERMS became attractive. Breast cancer patients treated with tamoxifen showed protection against postmenopausal bone loss (74). This observation led to a new appreciation that estrogen-like molecules (SERMS) can act in some organs or tissues as estrogen agonists and in some others as antagonists. The fundamental premise of SERMS is based upon this concept, namely that they can be both estrogen agonist and antagonists...

Preclinical models

Tamoxifen

The most extensively used animal model to evaluate the action of SERMs on bone has been the ovariectomized (OVX) rat. In rats, tamoxifen reduces bone resorption, uterine growth (74,75) and reduces the number and size of osteoclasts. Similar effects on bone have been observed in dogs and immobilised male rats (76,77). However, the antiresorptive potency of tamoxifen is inferior to 17β-estradiol (78) and has no effect when the endogenous production of estrogens is normal (79).

Raloxifene

OVX rats treated with raloxifene show significantly lower rates of bone remodeling (80) and preservation of bone mineral density (BMD) as measured by single photon absorptiometry (53) in distal femur metaphysis and in proximal tibia, and by dual-energy X-ray absorptiometry (54) in lumbar vertebrae and femur. This prevention of bone loss is similar to that achieved with ethinyl-estradiol (EE) (54,81). Histomorphometry in OVX rat models have demonstrated a reduction of bone resorption area in trabecular surfaces similar for raloxifene and EE treated animals (81,82).

Biomechanical testing shows an increased strength in rats treated with raloxifene and EE vs. control rats (81) in both the femoral neck and vertebrae. In another study in which raloxifene, EE, tamoxifen and alendronate were all assessed (53), all drugs except tamoxifen showed increased strength in comparison to control animals. Moreover, treatment with raloxifene was associated with a smaller number of microcracks (83). A raloxifene analogue, LY 117018, inhibited osteocyte apoptosis induced by oophorectomy in a rat model (84).

In transient cotransfection experiments using a transforming growth factor-β promoter-chloramphenicol acetyltransferase reporter construct (TGFβ promoter-CAT reporter) and an ER expression plasmid in human MG63 osteosarcoma cells (85) it has been shown that TGFβCAT expression was significantly up-regulated by raloxifene (7-fold), and by 17β-estradiol or tamoxifen (2-fold). This suggests that raloxifene regulates TGFβ3 gene expression with two possible sequellae: promotion of osteoblast numbers and inhibition of osteoclast differentiation (85).

Different SERMs, as well as the natural ligand, estradiol, can activate more predominantly one or the other estrogen receptors (alpha or beta) creating conformational changes of the ER-ligand complex that vary for different ligands (86). Furthermore, the various ligands can activate different intracellular pathways along with different response elements (26). Altogether, genomic responses for the various SERMS differ within this class and in relationship to estradiol effects on these 2 receptor subtypes (31).

Other SERMs

In rats, levormeloxifene increases lumbar spine and tibial bone mass in a rat model, with a decrease in osteocalcin and cholesterol levels. The uterus is not affected (30,87). In monkeys, it has been also demonstrated that bone remodelling is controlled and bone loss is prevented (88). The actions of Idoxifene, another SERM that activates the ER through the classical estradiol pathway, on bone are similar, serving as a full antagonist on mammary and uterine tissue (89,90). Droloxifene is efficacious in the prevention of bone loss in OVX rats as well as in the reduction of serum cholesterol levels again without deleterious effects on the uterus (44,91-94). Ormeloxifene can also prevent bone loss in animal models (95,96).

Lasofoxifene protects against bone loss, reduces cholesterol levels and exerts a positive effect on bone strength in male rats (97). This compound is in the latest stages of clinical development. Two other SERMs, also in advanced phase III trials are bazedoxifene and arzoxifene, both showing protective effects against ovariectomy-induced bone loss. Arzoxifene has shown to reduce the rate of bone remodelling with positive effects on bone quality as well as reduction of cholesterol levels in OVX rats (98).

A raloxifene analogue, LY117018 HCl, is also effective in reducing bone loss in OVX rats (99). In addition, the administration of this analogue permits a significant reduction of the minimal effective dose of human parathyroid hormone (PTH) required in the treatment of osteopenic rats (59,100). Other compounds are FC1271a (101) and HMR-3339 (47) both with promising results in preclinical studies.

CLINICAL EFFECTS OF SERMs ON BONE

Tamoxifen

The effects of tamoxifen on bone have been evaluated mainly in breast cancer patients who received the product as adjuvant therapy. A number of observations (102-106) have shown a decrease in bone formation (102,104,106) and bone resorption by biochemical markers (105-107).

Initial retrospective (107) and prospective studies (108,109) that compared tamoxifen-treated women against the placebo group, found no significant differences in BMD at the lumbar spine or femoral neck. Subsequent prospective and randomized studies also carried out with breast cancer patients (102,103), revealed, over a 3-year period, significant prevention of bone loss in women. Grey et al. (105) studied the effect of tamoxifen on BMD in healthy, late postmenopausal women who were on average 11 years postmenopausal. There was no significant difference in hip BMD but an incease in lumbar spine BMD. Different from these observations in a breast cancer prevention study in premenopausal healthy women, progressive reductions in BMD in a tamoxifen-treated group was observed (50).

Similarly, Wright et al. (105) found no differences in tamoxifen-treated subjects when histomorphometric changes in cancellous bone was assessed. In the tamoxifen group, bone formation rate was significantly decreased, the total bone-remodelling span was longer and the trabecular connectivity indexes were increased.

In the Breast Cancer Prevention Trial (34), a randomized, placebo-controlled clinical study aiming at determining the potential of tamoxifen for breast cancer prevention in pre- or postmenopausal women at increased risk, 13,338 women were monitored over 5 years. Women in the treatment group (n= 6,681) were given a 20 mg daily dose of tamoxifen, while the remaining (n= 6,707) received a placebo. Although the overall rate of fractures was about the same in both groups, tamoxifen-treated women sustained fewer hip, spine and Colles' fractures. Since in this trial pre- and postmenopausal women were both included and no spinal radiographs were carried out, relevant data may have been overlooked.

In summary, available evidence on the effects of tamoxifen on the skeleton in human subjects seems to parallel data obtained in animalss. As a partial estrogen agonist, tamoxifen seems to have beneficial effects on the preservation of bone mass in postmenopausal women, while in estrogen-replete premenopausal women it might act as an estrogen antagonist.

Raloxifene

Early studies indicate that raloxifene has an effect on bone homeostasis similar to that of estrogens. In a survey by Draper et al. (110) in which postmenopausal women aged 45–60 were monitored over 8 weeks 251, subjects were randomized to 2 treatment groups (raloxifene or CEE) and placebo. Those in the treatment groups showed a significant reduction in bone turnover markers (osteocalcin, serum alkaline phosphatase, urinary pyridinoline crosslinks) and urinary calcium excretion in comparison to the placebo group. Similarly, the European survey (111), that monitored 601 postmenopausal women over 24 months, revealed a significant reduction in bone turnover markers in comparison to the placebo group. Lufkin et al. (112) recorded similar data in a 1 year clinical trial of 143 postmenopausal women with osteoporosis.

The effect of raloxifene to prevent bone mass has been assessed in several different studies including, European (111), American (113) and International cohorts. All 3 were concealed randomized placebo-controlled studies. In the European and American trials, 3 treatment doses were tested (30, 60 and 150 mg daily), while in the international trial, 2 raloxifene groups (with daily 60 and 150 mg doses) and conjugated equine estrogens (CEE) 0.625 mg daily were used. A total of 1,764 women were monitored, measuring the biochemical markers of bone remodelling and BMD at the lumbar spine and femoral neck. After 24 months of treatment, BMD increased significantly at all monitored skeletal sites in raloxifene-treated patients vs. the placebo group. This increase was detected after 12 months of treatment and maintained for the next 12 months. Other studies have evaluated the effect of raloxifene in Asian women with similar results (114,115). A recent meta-analysis has evaluated the overall efficacy of the drug across the different trials showing homogeneity in the drug effect and a consistent risk reduction for vertebral fracture (116).

The pivotal study on raloxifene is the Multiple Outcomes of Raloxifene Evaluation (MORE), a randomized, double-blind and placebo-controlled trial with the primary end point being the occurrence of vertebral fractures in a cohort of 7,705 women with osteoporosis (117-119). The effect of the drug on bone mass was also assessed in the study. After 4 years of treatment, BMD increased at the lumbar spine and femoral neck (119). In the extension of the MORE trial, this positive effect on BMD was extended up to 7 years of treatment (120). The most important outcome, however, was the significant risk reduction in the occurrence of new vertebral fractures. Women included in substudy 1 (cases with at least one prevalent vertebral fracture at baseline) had a significant reduction in the risk of sustaining new (incident) vertebral fractures after three (118) and four years (119) of treatment of 34% (RR 0.66 [95% CI= 0.55, 0.81]). Women enrolled in the substudy 2 (no baseline vertebral fracture) showed a risk reduction of 49% at the end of the four-year treatment (RR 0.51 [95% CI= 0.35, 0.73]) (119). The number needed to treat (NNT) to prevent an event after 4 years of treatment was 12 for patients with prevalent vertebral fracture and 34 for those without. Subgroup exploratory analyses showed a 93% reduction in the risk of suffering multiple vertebral fractures (121) with sustained efficacy during the fourth year. Other post hoc analyses also suggested an early efficacy on clinical vertebral fracture after 12 months of treatment (122), and fracture reduction in women with previous treatment with estrogens or estrogen-progestagens (123). Moreover, in cases with osteopenia (no fracture and BMD in this range) another exploratory analysis demonstrated not only BMD improvement but significant fracture risk reduction (124).

In the raloxifene trials, the drug showed no reduction in nonvertebral fracture risk after three (118) or after 8 years of treatment (120). However, when exploratory, post-hoc analyses were carried out in the MORE trial results, high-risk patients were defined as those with a severe vertebral fracture at baseline. The cases in the placebo group with severe vertebral fractures at baseline had an increased risk of vertebral fracture during the observation period, as expected. Additionally, these subjects had an increased risk of non-vertebral fractures. In this high-risk population raloxifene showed a significant reduction in the risk of nonvertebral fractures (125). Similar results were observed after 8 years of treatment (120).Heaney and Draper (126) carried out a comparative histomorphometric study in which ten women received 60 mg/day of raloxifene and eight 0.625/day of CEE. Biopsies carried out before and after 6 months of treatment revealed a reduction in bone formation rate and activation frequency. The effects of raloxifene on bone histomorphometry were analyzed more in detail by

Ott et al. (127). In a group of 54 women enrolled in the MORE study, 2 transiliac bone biopsies were obtained at baseline and after two years of treatment. The results confirmed the safety of the drug on bone tissue since no woven bone, mineralization defect, cell toxicity or medullary fibrosis were observed. Moreover, the decreased number of empty osteocytic lacunae also suggested an anti-apoptotic effect on the osteocyte. More recent experimental data further confirm this anti-apoptotic effect of raloxifene on osteoblastic and osteocytic cells (128).

For years osteoporosis has been defined as a disease induced by a decrease in bone mass. Recently, a National Institute of Health Consensus Panel (129) has redefined the disease as a skeletal disorder characterized by an alteration in bone strength that predisposes a person to an increased risk of fracture. This concept of bone strength represents a new paradigm in our concepts about the disease (130-132). Added to the traditional element of bone mass are other aspects of bone strength such as geometry, microarchitecture, remodelling rate, mineralization degree and homogeneity and fatigue damage (54,130-137).

The relationship between the decrease in bone mineral density, assessed in any of the skeletal regions and measured by different techniques, with an increased fracture risk has been widely demonstrated (138-140). Marshall et al. (139) demonstrated in a meta analysis that one standard deviation decrease in bone mineral density (BMD) in lumbar spine, hip or proximal radius increased the risk of fracture in these locations by a 50 to 60%. While this relationship between a reduction in BMD and fracture risk is very powerful, the relationship between an increase in BMD and a reduction in fracture risk is much less certain (118,141-145). This relationship is of particular interest for raloxifene, a drug that has a limited effect to increase BMD. Sarkar et al. (146) analyzed the relationship between the observed increase in BMD in the placebo and in the raloxifene-treated patients from the MORE trial. Only a 4% of the fracture reduction could be explained by changes in BMD. These observations argue that other properties of bone, presumably affected by raloxifene in a positive manner, are more likely to account for most of the antifracture efficacy of the drug.

Bone turnover replaces old bone with fresh new bone. When in balance and not excessive, bone turnover is a beneficial feature of skeletal homestasis. However, in the adult, bone turnover is usually not balanced, with bone resorption exceeding bone formation, and sometimos excessive. In these settings, bone turnover can be deleterious for bone (130). The rapid reduction in the fracture risk observed after only a few months of starting antiresorptives can be explained by their effects to reduce bone turnover well before any improvement in BMD (130,147) .Bone remodeling rate is also a determinant of intrinsic material properties of the bone tissue such as the mean degree of mineralization or their homogeneity (148,149). Clinical data on raloxifene-treated patients demonstrate that the drug preserves a normal degree of mineralization and homogeneity (150), in accordance with the preclinical data. Collagen composition is also modulated by the remodeling rate since the crosslinking of the molecules influences the mechanical competence and can vary with aging (151).

There is considerable debate on what is the normal remodelling rate and the potential deleterious effects of an excessive suppression given that microdamage repair could be impaired (152). Microdamage increases with age, but also negatively correlates with the rate of bone remodeling and is associated with high doses of antiresorptives in experimental animals (153,154). Therefore, the theoretical concern is that an antiresorptive agent might depress remodelling excessively (155) impairing the replacement of old bone by fresh new units. Although no fracture data support this highly controversial theory, SERMs do not suppress bone turnover to an extent that would cause such concerns. In fact, the data show that raloxifene restores bone turnover to premenopausal levels (156,157) and experimental data demonstrate that the drug actually reduces microcrack density in bone tissue (84).

It has been demonstrated that the simultaneous use of a bisphosphonate with PTH impairs the bone forming response (156,157). Preliminary data suggest the opposite when the combined drug is raloxifene (158). Furthermore, in patients previously treated with raloxifene a full response to PTH was observed (159). Altogether SERMs appear to be a better partner for anabolic agents than some bisphosphonates. Also, in young postmenopausal women raloxifene will not jeopardize an anabolic effect in case PTH should be needed in subsequent therapeutic considerations.

Future SERMs

A large number of compounds selectively regulating the estrogen receptor are under development and have been briefly reviewed in the preclinical section. Some have reached clinical research stages. Levormeloxifene

(160, 161) has been studied for its pharmacokinetics, safety, dosing and antiresorptive effects. However its development was stopped after the phase II trials when uterine safety problems where detected (162). Idoxifene has demonstrated positive effects on BMD after 12 months of treatment (163) and decreased turnover in osteopenic postmenopausal women (164). Three SERMS are currently in advanced (phase III) stages of their clinical development: bazedoxifene, lasofoxifene and arzoxifene.

EXTRASKELETAL EFFECTS OF SERMS

SERMs and the breast

Tamoxifen has a well-established efficacy for breast cancer patients (34-36). Raloxifene showed a positive effect on invasive estrogen-receptor positive breast cancer after 3 years in postmenopausal women with osteoporosis (118) and this outcome is sustained after 8 years of treatment, with no apparent loss of effect or rebound effect (165). These observational data have recently been confirmed in the recent preliminary report on the results of the RUTH trial (166). Finally, the STAR trial comparing the efficacy of raloxifene vs tamoxifen in more than 19,000 women at high risk for breast cancer has shown a similar number of invasive breast cancer cases in both raloxifene and tamoxifen groups (167). In some countries raloxifene is already approved for prevention of breast cancer and all the data suggest the efficacy of the drug for this indication. Given their positive effects on bone, this beneficial effect could extent the clinical utility of the drug. However, the results of both the RUTH and STAR trial are not fully analyzed yet and we await peer-reviewed publication documenting these early observations. Other SERMs are currently under study for this indication.

Cardiovascular effects

Tamoxifen induces a small but significant increase in the incidence of deep venous thrombosis and pulmonary embolism and in the risk of stroke (168). Similarly, raloxifene use is associated with a 1.7-fold increase in the risk of venous thromboembolic events although the overall incidence is quite low (absolute risk difference of 0.9 per 1000 woman-years) (169). What has been more extensively assessed is the effect of raloxifene on coronary and cerebrovascular events. In post hoc results for a subgroup of the MORE trial, namely, women at high risk for arterial events, raloxifene decreased the incidence of coronary events and stroke (170). However, after 8 years of treatment the incidence of overall cardiovascular, coronary or cerebrovascular adverse events did not differ significantly between the raloxifene and placebo treated groups (171). Patients at increased risk of cardiovascular events showed no evidence of a beneficial or harmful effect. The preliminary report on the RUTH trial results confirm a neutral effect on coronary events and incidence of stroke, although a small increase in the stroke-associated mortality has been reported (166). In addition, the preliminary report of the STAR trial suggests a lower incidence in deep venous thrombosis and pulmonary embolism in women receiving raloxifene vs. those treated with tamoxifen (167). Again a full analysis is needed in all these aspects of both studies.

Other health problems and SERMs

An increase in the number of hot flases limits the use of available SERMs in a number of postmenopausal women (169). Some preclinical results suggest that new SERMs might avoid this problem (172). Tamoxifen is associated with an increased incidence of endometrial carcinoma (173), vaginal bleeding (174) and uterine sarcoma (175). Raloxifene has not reported to increase vaginal bleeding, ovarian or uterine cancer (117,169,176). Analyses of the safety results from the raloxifene trials also suggest positive effects on urinary incontinence (177) with neutral effects on cognitive function (178). Points related to cardiovascular issues have already been noted.

CONCLUSIONS

SERMs have increased our understanding of hormone-receptor regulatory mechanisms. Their development has permitted a targeted efficacy profile avoiding some of the side effects of the hormone therapy. Their clinical utility relies today mostly on the effects on breast cancer and bone. Future members of this class may offer an improved risk-benefit profile and could represent an integral approach for the health problems of postmenopausal women.

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