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New Selective Estrogen and Androgen Receptor Modulators

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Abstract

Purpose of Review—The present review focuses on the most significant recent findings regarding selective estrogen receptor modulators (SERMs) and selective androgen receptor modulators (SARMs). SERMs, which interact with estrogen receptor (ER)- α and ER- β in multiple tissues, continue to generate clinical interest in potential applications in as many disorders as the tissues in which the two known receptors are found. SARMs have been demonstrated to have fewer clinical applications to date, but continue to be investigated for use in multiple disorders in which androgen receptor (AR) modulation is likely to be important. Both types of compounds hold great promise for therapeutic use in multiple hormonal disorders involving tissue-specific effects mediated by estrogen or androgen receptors.

Recent Findings—While SERMs have been available for clinical use for 50 years, recent investigation has focused on large randomized clinical trials for newer indications of older agents, or smaller clinical trials of newer agents with improved clinical activity and reduced side effects in specific tissues. In particular, the large, prospective, randomized, controlled, multi-year STAR and RUTH clinical trials have recently shown interesting similarities and differences between tamoxifen and raloxifene in estrogen-responsive tissues. Lasofoxifene and arzoxifene are two newer SERMs that have recently been demonstrated to improve bone mineral density and lower serum cholesterol values compared to older SERMs in smaller clinical trials. SARMs are a newer category of drug still being investigated mostly at the basic and preclinical level, with fewer clinical trials available for review. SARMs are currently being investigated mostly for use in prostate cancer at different stages, but hold promise for multiple other applications.

Summary—Recent clinical trials indicate that selective estrogen receptor modulators are useful in treatment of disorders of bone and mineral metabolism and breast cancer, and in reduction of cardiovascular risk factors. Selective androgen receptor modulators offer important benefits for management of prostate cancer at different stages, as well as other disorders.

Keywords

SERM; SARM; osteoporosis; breast cancer; prostate cancer

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Introduction

Selective estrogen and androgen receptor modulators have continued to show significant new benefits in management of human diseases in recent years. Selective estrogen receptor (ER) modulators (SERMs) prevent fractures and reduce loss of bone mineral density (BMD) in postmenopausal women, prevent and treat ER-positive breast cancer in postmenopausal women, and regulate induction of ovulation in premenopausal women with infertility (1,2). Selective androgen receptor (AR) modulators (SARMs) have been shown to prevent and treat prostate cancer in men (3,4). Therapeutic applications for these categories of medications are still being evaluated, with potential for greater promise to come.

This review will first discuss significant new clinical trial information regarding SERMs, followed by a review of important new basic and limited clinical trial information regarding SARMs. The discussion of SERMs begins with a brief overview of the current understanding of the physiology of ER- α and ER- β , followed by a discussion of how SERMs have been used to differentially regulate these receptors in human disease. The discussion of SARMs will briefly review the physiology of the AR, followed by an overview of how SARMs have been used in management of prostate cancer and other human diseases.

Selective Estrogen Receptor Modulators (SERMs)

Selective estrogen receptor modulators directly bind to estrogen receptor (ER)- α and/or ER- β in target cells and exert estrogen- or antiestrogen-like actions in various tissues. These agents exert estrogenic benefits in certain tissues, and minimize estrogenic risks in other tissues. Once a SERM ligand binds to ER- α and/or ER- β , it is believed to cause a conformational change in the ER molecule which results in dissociation of associated heat shock chaperone proteins, and release of the monomeric receptor from the apo-ER complex. The conformational change then results in altered interactions with complexed coactivator or corepressor proteins (5), with subsequent monomeric ER translocation from the cytosol to the nucleus, followed by dimerization with a second monomeric ER before binding to specific DNA sequences in the regulatory promoter regions of target genes. Homodimeric binding of the ER to these promoter regions subsequently causes initiation or suppression of transcription of the genes (6).

McDonnell et al. have demonstrated that a series of SERM ligands formed distinct ER-bound complexes, resulting from different induced conformational changes (7). X-ray crystallography was subsequently used to quantitatively assess the conformational changes induced by agonist or antagonist binding to the ER ligand binding domain (8). Initial structural evidence for the antagonist-bound ER conformation was obtained with the SERM tamoxifen (9), showing that tamoxifen blocked ER access to nuclear receptor cofactor proteins (8). Subsequent investigation showed that ER binding of many different SERMs caused development of the classical antagonist-bound ER conformation (8). Evidence has also been presented that SERMs may produce ER modulation through non-ER pathways, such as through androgen or progesterone receptors, when combined with SERM metabolites that have non-ER binding activities (10).

Every ER ligand has SERM activity intrinsic to the ligand. Tissue-specific actions of SERMs are thought to be due to unique ER conformational changes caused by SERM ligand binding, resulting in a variety of specific interactions with other proteins within a cell. However, conformational change alone may not explain all actions of SERMs on target cells. Recent work in mice with targeted deletion of the ER- α amino-terminal A/B domain suggests that stimulation of ER- α by SERMs with minimal activation of the amino-terminal activation domain AF-1 might preserve beneficial vascular effects, but minimize effects on

sexual tissues (11). Some SERMs may also exert non-genomic effects after binding to membrane-bound receptors. Functions of ER- α and ER- β have been best studied to date in bone, breast, uterine and genitourinary tissues, and brain. Because of the variable tissue effects of SERM ligands in different tissues, it is very difficult to reach conclusions about the clinical activity of a given SERM without conducting the appropriate clinical trials.

A variety of SERMs have been developed to date for different purposes, with raloxifene approved for prevention and treatment of postmenopausal osteoporosis and ER-positive breast cancer, tamoxifen for prevention and treatment of postmenopausal ER-positive breast cancer, and clomiphene for infertility treatment in premenopausal women. The initial SERMs were used as anti-estrogens beginning about 50 years ago (12), with the concept of selective estrogen receptor modulation introduced only about 15 years ago (13). A variety of SERMs with special tissue selectivity remain under clinical investigation for prevention and treatment of these and other diseases (14). SERMs may increase the risk of postmenopausal hot flashes, night sweats, leg cramps, deep venous thrombosis, or bone pain in some patients, particularly during the first few months of drug exposure.

A number of SERMs have been investigated since the first drug in this class was introduced in the form of clomiphene many years ago. Several SERMs have been discontinued from further clinical investigation due to various adverse effects or lack of efficacy compared to available SERMs. Recent published clinical trials within the last several years have focused mostly on raloxifene, lasofoxifene, and arzoxifene.

Raloxifene

Raloxifene is a polyhydroxylated nonsteroidal compound with a benzothiophene core with high affinity for both ER- α and ER- β (15), which was originally investigated for breast cancer prevention in the early 1980s. It acts as a partial estrogen agonist in bone, thereby preventing vertebral fractures and loss of bone mineral density when given at the approved oral dose of 60 mg daily (16,17). Raloxifene has been shown to be more effective than another SERM, tamoxifen, in reducing the risk of ER-positive breast cancers, but not ER-negative cancers, in postmenopausal women at high risk (18). Neither drug reduced cardiovascular risk in this trial, however. Raloxifene is approved for prevention and treatment of postmenopausal osteoporosis, reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis, and prevention of breast cancer in high-risk postmenopausal women.

The most recently published clinical trials with raloxifene include the Raloxifene Use in the Heart (RUTH) study (19) and Study of Tamoxifen and Raloxifene (STAR) study (20). The RUTH study evaluated the effects of raloxifene 60 mg daily vs placebo in 10,101 postmenopausal women with a mean age of 67.5 years and with coronary heart disease or multiple coronary heart disease risk factors over 5.6 years. This study showed that raloxifene reduced the risk of invasive breast cancer, but not non-invasive breast cancer, in these women. Raloxifene also reduced the risk of clinical vertebral fractures, but not nonvertebral or hip fractures. Unfortunately, raloxifene did not reduce the primary endpoint risk of coronary events or stroke, but was associated with a statistically significant increased risk of stroke mortality and venous thromboembolism.

The STAR study evaluated the effects of raloxifene, 60 mg daily, vs tamoxifen, 20 mg daily, in 19,747 postmenopausal women of mean age 58.5 years with high risk of breast cancer over 5 years (20). This study showed that raloxifene and tamoxifen caused similar reductions in the risk of invasive breast cancer, and that the tamoxifen group had fewer cases of cases of non-invasive breast cancer than the raloxifene group, although this

difference was not statistically significant. Neither drug reduced the risk of non-invasive breast cancer in postmenopausal women.

Multiple studies have shown that raloxifene reduces serum total and LDL cholesterol levels similar to estrogen, but that serum triglycerides and C-reactive protein are not affected. Raloxifene has not been shown to alter the risk of cardiovascular endpoints, cardiovascular death, or overall mortality in several studies, including the RUTH study (19).

Lasofloxifene

Lasofloxifene is a potent SERM that belongs to the naphthalene class of SERMs. Lasofloxifene improves lumbar spine bone mineral density more effectively than raloxifene, causes about the same increase in hip bone density as raloxifene, and reduces markers of bone turnover and LDL-cholesterol more effectively than raloxifene (21). The recent three-year PEARL pivotal fracture trial demonstrated that lasofloxifene increased lumbar spine and femoral neck BMD by approximately 3%, but that vertebral fractures were reduced by 42%, and nonvertebral fractures by 27%, with reduction in markers of bone turnover (22,23). Lasofloxifene did not prevent hip fractures in this trial, however.

Arzoxifene

Arzoxifene is another potent benzothiophene SERM being investigated for prevention and treatment of osteoporosis (24) and chemoprevention of breast cancer. Arzoxifene was recently shown to be less effective than tamoxifen for progression-free survival and time to treatment failure in locally advanced and metastatic breast cancer, and to cause a similar tumor response rate, clinical benefit rate, and median response duration (24). No human data have yet been published on the bone effects of arzoxifene.

Other SERMs

Small clinical trials of several other SERMs, including toremifene, ospemifene, pipendoxifene, bazedoxifene, HMR-3339, and fulvestrant are being designed or are underway for prevention and treatment of breast cancer and postmenopausal osteoporosis. Studies are also examining possible benefits of toremifene in the prevention of fractures in men undergoing gonadal suppression for the treatment of prostate cancer. Each of these SERMs has unique features which endow them with specific characteristics potentially useful for various clinical applications.

Selective Androgen Receptor Modulators

Proposed mechanisms of action of SARMs include differential tissue distribution of the ligands, potential interactions with 5 α -reductase and/or aromatase at the tissue level, ligand-specific regulation of gene expression, and/or non-genomic actions at the molecular level (25). While these mechanisms of action have been applied successfully in modeling the actions of SERMs, fundamental differences between androgen and estrogen physiology and signaling exist.

There are two forms of ER, but estrogen is the only known endogenous ligand. ER α and ER β have different structures, ligand affinities, tissue distribution patterns, transcriptional properties, and biological roles, and the presence of two ERs provides greater flexibility for regulation of estrogen action in different tissues. To date, only one AR has been identified, with two endogenous ligands, testosterone and dihydrotestosterone. 5 α -reductase is expressed in a tissue-specific distribution to convert testosterone to dihydrotestosterone. Type II 5 α -reductase is highly expressed in prostate as an androgenic tissue, but at relatively low levels in bone and muscle as anabolic tissues. This distribution of 5 α -reductase ensures

that dihydrotestosterone is the predominant androgen in prostate (26), and that testosterone is the dominant form in the circulation and in bone and muscle. Inhibition of 5 α -reductase activity results in testosterone becoming the dominant androgen in the prostate, despite testosterone having much lower potency for stimulating prostate growth.

The existing evidence with BMS-564929 and several other SARMs suggests that tissue distribution of 5 α -reductase may play a significant role in determining tissue selectivity of SARMs. Recent studies with nonsteroidal AR ligands indicate that differential tissue distribution by itself is not likely to explain differences in pharmacological responses seen in prostate and muscle (27). In addition, although AR binding involves ligand-induced conformational changes mediated via the ligand-binding domain, crystal structures of aryl propionamide and hydantoin SARMs do not show the same magnitude of conformational changes as seen with the SERM-bound ER ligand binding domain (28,29), particularly in the AF2 region (30,31). Crystal structures of testosterone- and dihydrotestosterone-bound AR ligand binding domain were virtually identical despite significant differences in their androgenic properties in the prostate (29). Although these crystal structure determinations are helpful in determining AR ligand binding mechanisms, it is difficult to model potential changes in receptor function occurring under native physiological conditions.

Various agonists and antagonists have been developed to target the AR for prevention or treatment of male hypogonadism, prostate cancer, muscle wasting, anemia, or benign prostate hyperplasia (32–34). None of these agents has been approved for prevention or treatment of male osteoporosis. Androgen receptor ligands are classified as agonists (androgens) or antagonists (antiandrogens), based on their ability to activate or inhibit the transcription of AR target genes. Androgen receptor ligands may be steroidal or non-steroidal, depending on their chemical structure.

Testosterone is the major circulating endogenous steroidal androgen, and is converted locally by 5 α -reductase to dihydrotestosterone in prostate and skin, and by aromatase to estrogen in bone, adipose tissue, and the central nervous system. Androgen effects in reproductive tissues, including the prostate, seminal vesicles, testis, and accessory structures, are considered to be androgenic effects, whereas effects in bone and muscle are designated as anabolic effects.

Clinical application of the testosterone preparations developed to date has been limited by virilizing androgenic side effects, such as acne or hirsutism in women, hepatotoxicity, adverse lipid effects, and concerns regarding stimulation of prostate disease in men. A variety of testosterone formulations, including transdermal patches, injectable esters, and steroidal analogues, including 17 α -alkylated androgens and 19-norandrogens, have been developed for clinical use. Oral nonsteroidal antiandrogens developed in the 1970s, including bicalutamide, flutamide, and nilutamide, continue to play a role in the treatment of prostate cancer. These antiandrogens have high specificity for the AR, but lack tissue selectivity, and therefore also block AR in bone, skeletal muscle, and the hypothalamus-pituitary-gonadal axis.

The concept of SARMs was first proposed by Negro-Vilar in 1999 (35). The ideal SARM was proposed to have high AR specificity, oral bioavailability and acceptable pharmacokinetics, and tissue-selective pharmacological effects. In recent years, SARMs have been developed with greater tissue selectivity in order to minimize adverse effects. Tissue-selective SARMs could potentially be used to prevent or treat osteoporosis, muscle wasting due to age-related frailty or burns, cancer, chronic kidney disease, or AIDS. These agents could be used for hormone replacement in men and women without concern related to their virilizing side effects. Tissue-selective antiandrogens could be used to prevent or

treat benign prostate hypertrophy or prostate cancer without blocking anabolic androgen effects on bone, muscle, or the CNS.

SARMs largely remain in the discovery and development stage, with a number of agents in preclinical development, and only a few drugs completing phase I or II clinical trials to date. No SARM has yet been approved for clinical use (34). Most SARMs undergoing development currently are nonsteroidal anabolic agents derived from aryl propionamides (36) or quinolines (37). SARMs of the aryl propionamide class were first shown to have tissue selectivity in 2003 (38), followed later the same year by tetrahydroquinoline SARM (39), quinoline SARM in 2006 (40), and hydantoin SARM in 2007 (29). These anabolic SARMs show tissue selectivity in castrate animals, with stronger agonist effects in anabolic tissues, such as the levator ani muscle, than in androgenic tissues, such as the prostate.

Recently reported results of the modified hydantoin SARM BMS-564929 indicate that this SARM is among the most potent and highly tissue selective SARMs to date (29). This SARM, and other SARMs, potentially suppress secretion of luteinizing hormone (LH), which results in decreased testicular production of testosterone in the dose range associated with anabolic activity. Suppression of LH secretion by SARMs remains a potential barrier to further development of this category of compounds.

Conclusion

Available data suggests that individual SERMs and SARMs have unique tissue-specific activities that require delineation in clinical trials. The clinical profiles of different SERMs are strikingly different, particularly in regard to effects on the pelvic floor and cardiovascular markers. The largest head-to-head comparison trial of SERMs to date was the STAR trial, which showed that raloxifene and tamoxifen had similar beneficial effects on invasive breast cancer and clinical fractures, and similar non-effect on ischemic heart disease and stroke. Raloxifene, however, had lower risk of venous thromboembolism, cataracts, and cataract surgery, while tamoxifen had a non-significantly lower risk of noninvasive breast cancer. The tissue-specific effects of SARMs are not yet as well established as those of SERMs, but future clinical trials will provide this information. The future of SERMs and SARMs remains rich with possibilities, but their widespread application to date has been hampered by the fact that they affect many different tissues.

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