EVOLUTION OF SELECTIVE ESTROGEN AND ANDROGEN RECEPTOR MODULATORS: STATUS OF CURRENT THERAPY AND NEW DRUG DEVELOPMENT

Gregory T. Wurz and Michael W. DeGregorio

Department of Internal Medicine, Division of Hematology and Oncology, School of Medicine, University of California, Davis, Sacramento, California

1 BACKGROUND

Selective estrogen and androgen receptor modulators (SERMs and SARMs) are compounds that can act, respectively, as either estrogen receptor (ER) or androgen receptor (AR) agonists or antagonists on a tissue-selective basis. For example, the SERM tamoxifen, which is widely used in the treatment of breast cancer, is an ER antagonist in breast tissue but has agonistic effects in the endometrium. SERMs and SARMs are diverse groups of molecules comprised of structurally unrelated compounds from several different chemical classes. The chemical structures of selected SERMs and SARMs are shown in Figures 1 and 2. Included in Tables 1 and 2 are some of the various chemical classes of SERMs and SARMs as well as some clinically approved and investigational compounds from each class.

1.1 How SERMs and SARMs Became a Focus of Drug Development

The search for new contraceptive agents in the 1950s and 1960s led to the development of the first clinically useful SERM, tamoxifen [1]. Rather than acting as a contraceptive, tamoxifen, then known as a nonsteroidal antiestrogen, was found to actually induce ovulation [2], an effect that led to the approval of tamoxifen and a related drug, clomiphene, for use as fertility agents [3–5]. Tamoxifen was later developed as a treatment for breast cancer, and it is currently approved for the treatment of all stages of breast cancer and for reducing the risk of breast cancer in high-risk women. While tamoxifen is a very effective breast cancer treatment due in part to its antiestrogenic effects in breast tissue, it was soon recognized that tamoxifen was having estrogenic effects in the endometrium, which is associated with an increased risk of endometrial cancer [6–9], on serum lipids [10, 11], and on bone [12, 13]. These observations led to efforts to develop new compounds, that is, SERMs, with the beneficial effects of estrogen on bone density and serum cholesterol [14–16] and without the negative side effects of tamoxifen and estradiol on the endometrium [6–9] and breast [17], respectively. Early SERM development was focused on breast cancer applications in an attempt to improve upon tamoxifen, but the success of raloxifene as an osteoporosis treatment [18], and the potential risks posed by long-term use of hormone replacement therapy (HRT) [17] in postmenopausal women, have generated an interest in developing new SERM compounds for the treatment of postmenopausal osteoporosis, menopausal symptoms,

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