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CHEMISTRY
Review Article

Raloxifene: An Effective Selective Estrogen Receptor Modulator

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Received: September 16, 2015; **Published:** November 06, 2015

Abstract

In recent past, women at risk of breast cancer have got some hope to get their disease managed effectively with the help of molecules termed as Selective Receptor Modulators (SERMs). Statistically, one in eight women gets diagnosed with breast cancer. Many breast cancers are sensitive to the hormone estrogen. It is established that an anomaly in estrogen level causes the breast cancer. Such cancers have estrogen receptors on the surface of their cells. They are called as ER (estrogen receptor) positive cancer. Medicines that block the effects of estrogens have been shown to reduce the risk of breast cancer in women. There are two medicines namely, tamoxifene and raloxifene, approved by FDA for the treatment of breast cancer. While, tamoxifen is already approved for breast cancer treatment and its risk reduction in women who are at high risk of the disease for long, lately, raloxifene, originally approved for the prevention and treatment of osteoporosis has also got approval for breast cancer risk reduction in postmenopausal women with osteoporosis.. Although there are many medicines available in the market but it is yet to access ideal selective estrogen receptor modulator (SERM) that finds a critical balance with anti-cancer and anti-osteoporotic properties.

Keywords: *Raloxifene; Tamoxifene; SERM; Breast Cancer; Bone*

Introduction

Raloxifene, [6-Hydroxy-2-(4-hydroxyphenyl)-1-benzothiophen-3-yl] {4-[2-(piperidin-1-yl) eth-oxy] phenyl} methanone hydrochloride (Figure 1), is an estrogen agonist/antagonist, commonly referred as a selective estrogen receptor modulator (SERM) [1,2] that has benzothiophene heterocyclic moiety.

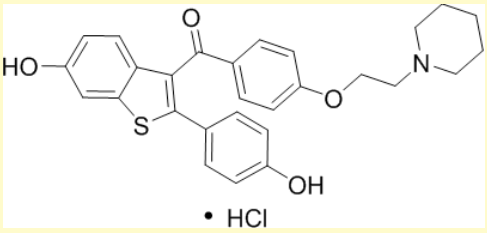

Figure 1: *Raloxifene Hydrochloride.*

It is the most extensively investigated SERM that partially mimics the effect of estrogens in bone and cardiovascular system, while functioning as an anti estrogen in endometrial and breast tissue. It has been approved for osteoporosis prevention and reduction in risk of fragility fracture [3-6].

Classification	Genitourinary & reproductive tissue	Skeletal, CVS & CNS	Examples
Agonists	Yes	Yes	Diethyl stilbestrol, hexasterol
Partial agonist/antagonists	Yes/No	Yes	Tamoxifen, Clomiphene
SERMs	No	Yes	Raloxifene, CP-336156
Antagonists	No	No	ICI-182, 790, ICI-164, 385

Table 1: *Classification of estrogen receptor modulators.*

Thus, by administering estrogen antagonist, an effect of functional deficiency of an estrogen is also created in the body depriving all the beneficial effects of the hormone.Thus the prime requisite of targeted drug discovery is to achieve critical balance of agonist/antagonist action in a molecule that may minimize or eliminate estrogenic activity in non-targeting tissues, optimize beneficial estrogenic effect in target tissues and eliminate the formation of carcinogenic metabolites [7,8].

The current approach in the development of newer therapeutic agents is to identify compounds that may elicit tissue specific effects. Many anti estrogens (Table 1) like EM-800, CP-336156, arzoxifene, raloxifene etc. are being developed as selective estrogen receptor modulators (SERMs), showing agonist actions at CNS, cardiovascular and skeletal systems while antagonist action at breast and uterus[9-13].

The clinical success of these molecules for the treatment of estrogen dependent diseases, such as osteoporosis, coronary artery disease, depression, Alzheimer's disease etc., coupled with the novel finding of tissue specificity has intrigued chemists and biologists to think about developing such agents. Recent exciting discoveries related to the structure and function of estrogen receptor has greatly enhanced the prospects for the development of novel ligands that may function as tissue selective estrogen receptor modulators [14,15].

As a new era has been entered with the demonstration of multifunctional biological profile of synthetic non-steroidal selective ER modulators, in not too distant future there will be a selection of modulators and the choice of modulators will be tailored to meet the need of specific tissues and risk profile of the individual therapy providing better treatment options for endocrine dependent disorders. Noticeably, this class of compounds shows promise for the treatment and prophylactic pathologies associated with estrogens, by which novel estrogen pharmaceuticals can be developed as tissue-selective drugs in the new millennium.

The search for ligands that can confer tissue-selective effects showing advantages of estrogens on non-traditional target tissues while mitigating some of the disadvantages, particularly concerns over estrogen agonist action led to emergence of novel group of compounds showing pounced subtype ER alpha and ER beta selective differences in binding affinity and transcriptional efficacy and elicit agonist/antagonist responses depending on target tissue and hormonal milieu. This awareness has led to the development of the molecules which could antagonize the effects of estrogens on uterine and breast tissues, while mimicking the effects of estrogens on bone and cardiovascular system. The term 'Selective Estrogen Receptor Modulators' have been coined to describe these agents [16,17].

Salient features of SERMS

1. They can be used in the prevention and treatment of osteoporosis as they have been shown to cause:
    a. Substantial increase in bone mineral density (BMD).
    b. Prevention of bone loss and decreases in fracture incidences.
2. Through their agonists effects they can also be used in the prevention and treatment of the cardiovascular diseases as they have shown following effects:
    a. Inhibit biosynthesis of cholesterol.
    b. Reduce serum fibrogen and serum cholesterol [primarily low density lipoprotein; cholesterol (LDL-C)].
    c. Reduce aortic lipid accumulation and carotid initial thickness in case of injury.

d. Inhibit lipid peroxidation and decreases membrane fluidity.

e. Inhibit progression of coronary artery arthrosclerosis.

3. Through their antagonistic properties they can be used in prevention and treatment of estrogen responsive cancers and they have shown following properties:
    a. Anti-breast cancer properties.
    b. Antagonistic effect at uterus showing no stimulation of endometrial hyperplasia.
    c. Reduction in the risk of lever carcinogenesis.
4. They have been shown to improve cognitive function of brain and palliation of Alzheimer's disease and postmenopausal depression through agonist effect.

Importance of Raloxifene

Raloxifene retards the re-sorption of bone by reducing the biochemical markers of bone turnover in the premenopausal population [18-20].

Raloxifene hydrochloride also lowers the chance of developing a certain type of breast cancer (invasive breast cancer) in postmenopausal women [21,22].These effects on bone are established as reductions of bone turnover markersin the serum and urine levels and decrease in the incidence of fractures.

Evista (Raloxifene), administered in a 60 mg dose once daily, increased spine and hip bone mineral density (BMD) by 2 to 3%. This medicine found to decrease the incidence of the first vertebral fracture from 4.3% for placebo to 1.9%.

Breast cancer is more commonly found in women over age 60 they get maximally benefitted from Evista. This is also useful to women who have a family history of breast cancer or who has a genetic predisposition may benefit. Other factors that can increase risk of developing invasive breast cancer include a previous lobular carcinoma *in situ* diagnosis, a history of frequent breast biopsies, first child delivery later age, or starting menstrual cycle at a later age.

Mechanistically, Evista works by blocking estrogen in the breast tissue of women at high risk. This medication helps prevent the spread of tumors that require estrogen to grow. Evista is found to be not effective in women who currently have invasive breast cancer or who have had invasive breast cancer. It neither prevents cancer in these women nor will it treat cancer once it appears.

Although Evista can reduce the likelihood of invasive breast cancer, it's important to be aware of its serious side effects e.g. increased chances of blood clots in the lungs and legs along with increased chance of stroke in women with coronary artery disease. The FDA advises that women with the following conditions must not take Evista:

1. Who are pregnant or planning to become pregnant,
2. Individual with present or past blood clots in the eyes, lungs, or legs,
3. Someone on cholestyramine, a cholesterol-lowering drug,
4. Someone on supplemental estrogen, and
5. Who are in pre-menopausal stage.

Comparison with Tamoxifen

Evista and tamoxifen, another SERM, have similar results and side effects in preventing invasive breast cancer, although Evista had less uterine cancers involved with its use.

In the last decade, several studies investigated the effects of Evista and tamoxifen in more than 37,000 women. For instance, one study that involved more than 19,000 women at high risk of developing breast cancer found that both medications had similar results in reducing invasive breast cancer. Unlike tamoxifen, however, Evista was not shown to reduce *noninvasive forms* of breast cancer. Noninvasive forms include ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) [22,23].

Both Evista and tamoxifen may increase the risk of developing blood clots and strokes. Some findings suggest that Evista might be less likely to cause clots, pulmonary embolisms, and strokes than tamoxifen. But other studies say there is no difference. Both raloxifene and tamoxifen carry risks. Because of the possible side effects, doctor should cautiously weigh the benefits and risks of using either drug to prevent invasive breast cancer.

Considering the outcome of comparative studies of Evista and tamoxifen it can be manifested that Evista is the choice of medicine in the management of invasive breast cancer and osteoporosis.

Conclusion

A number of SERMs are being developed as drugs and several patents have been published claiming their use in various pathological conditions. Out of the two medicines namely, tamoxifen and raloxifene, prevalent for the treatment of breast cancer, the medicine, raloxifene appears to be a near perfect selective estrogen receptor modulator. Although, these two medicines share similar chemical properties and functions, each one of these have different associated risks and side effects. It is clinically proven that raloxifene has about ten times more binding affinity for the estrogen receptor in breast tissue than tamoxifen. It binds strongly to the receptor site, practically eliminating the possibility of any estrogen interacting with a receptor and giving rise the undesired effect of the hormone estrogen. Also, tamoxifen increases the risk for venous thromboembolic and incidence of cataracts more than raloxifene. It is also found that tamoxifen but not raloxifene increases risk for endometrial cancer. These harmful effects have greatly been seen with older women.

An understanding of the pharmacology and structure of such agents has suggested their safer clinical effects in treating number of pathologies related to estrogens. Identification of such compounds with novel and therapeutically useful properties can thus plausibly be exploited in making an active pharmaceutical agent. As a new era has been entered with the demonstration of multifunctional biological profile of synthetic non-steroidal selective ER modulators, in not too distant future there will be a selection of modulators and the choice of modulators will be tailored to meet the need of specific tissues and risk profile of the individual therapy providing better treatment options for estrogen dependent disorders Noticeably, this class of compounds shows promise for the treatment and prophylactic pathologies associated with estrogens, by which novel estrogen pharmaceuticals can be developed as tissue-selective drugs in the new millennium.

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Volume 2 Issue 1 November 2015