



Indian Menopause Society

Guideline Number 7: February 2011

Use of SERMs in Menopause

Background

Apart from the uterus and breasts – the main reproductive organs, oestrogen also acts on other tissues of the liver, brain, heart and bones.

It acts on target tissues by binding to the oestrogen receptors which are located in the cell nucleus. The estrogen-receptor complex then binds to specific DNA sites and then to coactivator proteins and nearby genes become active. The active genes produce molecules of messenger RNA, which guide the synthesis of specific proteins. These proteins can then influence cell behavior in different ways, depending on the cell type involved and the organ tissue involved. Thus it causes production of proteins in some tissues e.g.: liver and also causes cell proliferation in others e.g.: breast and endometrium.

Hormone Replacement Therapy (HRT) offered to postmenopausal women for relief from menopausal symptoms and protection from long term consequences brought with it some undesirable complications in the form of Ca breast and Ca endometrium.

The need for an ideal drug which proves beneficial in some organs and avoids the undesirable effects on other organs has resulted in the development of Selective Estrogen Receptor Modulators (SERMs) that could confer all the benefits of estrogen without any of its risks. These compounds exhibit selective agonistic or stimulatory effects (i.e. estrogenic) on one organ system and neutral or antagonistic (i.e. antiestrogenic) effects on other organ systems.

TYPES of SERMs – Synthetic & natural SERMs are available.

Synthetic SERMs: Belong to 5 chemical groups: triphenylethylenes, benzothiophenes, tetrahydronaphthylenes, indoles and benzopyrans.

Natural SERMs: These are phytoestrogens, plant derived substances that are structurally and functionally similar to estrogens and are found in many foods. They exhibit estrogenic activity in the body by acting on estrogen receptors. They too have both weak estrogenic and anti- estrogenic activity.

Effects of Estradiol and SERMs

Agent	Brain	Uterus	Vagina	Breast	Bone	Cardiovascular System
Estradiol	++	++	++	++	++	++
Pure antiestrogen	—	—	—	—	—	—
Ideal SERM	++	—	++	—	++	++
Tamoxifen	—	+	—	—	+	+
Raloxifene	—	—	—	—	+	+
Isoflavones	+	—	+ —	—	+	+

SERMs widely used:

1. **Clomiphene** - which is used for ovulation

2. **Tamoxifen** - used for the treatment of ER-positive breast cancer and chemoprotection for women at risk of breast cancer
3. **Toremifene** - a Tamoxifen derivative, indicated for the treatment of ER-positive breast cancer
4. **Raloxifene** - used for the prevention and treatment of osteoporosis.

SERMs in Menopause Management

As the risk of osteoporosis increases once women reach menopause, prevention as well as treatment is necessary for them. Raloxifene is a first-line drug for prevention and treatment of postmenopausal osteoporosis.¹

Osteoporosis is predominantly a disease of women. The burden of morbidity from osteoporosis has significant medical, social and financial implications. In addition, fractures of hip are associated with 20% excess mortality. Though osteoporotic fractures are preventable, they are often diagnosed only after the event. The effective treatment strategies currently available for this disease mandate that osteoporosis be diagnosed and treated much before the occurrence of complications like fracture. By conservative estimates India has nearly 30 million women with osteoporosis.²

Identifying Women at risk

It is essential to evaluate the risk of osteoporosis in all postmenopausal women for the development of osteoporosis.

The World Health Organization (WHO) defines osteoporosis as bone density 2.5 SD below the mean for young adult women. It is recommended that treatment for osteoporosis should be initiated according to the results of the 10-year absolute fracture risk assessment.³ The risk factors help determine which patients should be evaluated for osteoporosis with Bone Densitometry. These are

- Adults with vertebral, rib, hip or distal forearm fractures
- Women aged 65 years and older
- Corticosteroid (glucocorticoid) use
- Early menopause or surgical menopause before age 40
- Family history
- Older patients who lose a significant amount of body weight (i.e. 5%)

Those women found to be at risk should be evaluated by performing Bone Densitometry by Dual-Energy X-ray Absorptiometry (DEXA).

Prophylaxis needs to be planned for women with BMD T-scores below -2.0 SD in the absence of risk factors and in women with T-scores below -1.5 SD if other risk factors are present.

Women aged older than 70 years and who have multiple risk factors (especially those with previous fractures) are at enough risk for fracture to begin treatment without BMD testing.

Treatment with Raloxifene

Raloxifene has been approved for the prevention of postmenopausal osteoporosis in 1997 and the treatment of postmenopausal osteoporosis in 1999.

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial found that treatment with raloxifene 60 and 120 mg/ day for 3 years significantly reduced vertebral fracture risk by 30% and 50% compared with placebo respectively, in postmenopausal women with osteoporosis. The MORE trial showed that among women who had no fractures at the start of the study 4 years earlier, Raloxifene produced a 49% reduction in vertebral fractures. In the cohort with existing vertebral fractures at study entry, there was a 34% reduction.⁴

Apart from its skeletal effects, Raloxifene also provides some other beneficial effects too-

Action on uterus - A big advantage lies in the fact that Raloxifene does not stimulate endometrial proliferation which is beneficial for women with a uterus. In studies, a statistically significant increase in endometrial thickness was seen with raloxifene compared with placebo after 3 years of therapy in the MORE trial, although there was no increase in the risk of endometrial cancer.⁵

Action on breast tissue- In the MORE Study of 5,129 postmenopausal women with osteoporosis treated with raloxifene, a 76% overall reduction of breast cancer and a 90% reduction in estrogen receptor-positive breast cancer were noted in comparison with placebo.⁵

A head-to-head comparative Study of Tamoxifen and Raloxifene (STAR) showed that the drug raloxifene, currently used to prevent and treat osteoporosis in postmenopausal women, works as well as tamoxifen in reducing breast cancer risk for postmenopausal women at increased risk of the disease.⁶

Action on Lipids and Cardiovascular System : In an analysis of MORE data, raloxifene decreased total cholesterol (8.5%) and LDL cholesterol (15%) without significant changes in HDL and triglycerides. Homocysteine and lipoprotein a (Lp(a)) levels were also found to decrease significantly.⁷

The Raloxifene Use and The Heart (RUTH) study was designed to investigate possible cardioprotective effects of raloxifene in elderly women with CAD or at risk for CAD. Results demonstrated a neutral effect on CAD risk during 5.6 years of follow-up.⁸

Action on brain - Its beneficial effects on the brain, such as the cognitive benefits associated with estrogen use are yet unknown, although raloxifene does not appear to impair cognition or affect mood in postmenopausal women.

Adverse Effects: Raloxifene may induce hot flushes and leg cramps. It is not beneficial for vaginal atrophy.

Raloxifene increases the risk of Deep Vein Thrombosis (DVT) to a degree similar to that observed with estrogen. Venous thromboembolic events occurred in 1.0% of women who received Raloxifene, compared with 0.3% of women who received placebo.⁴

Contra-indications

Pre-menopausal women
Post-menopausal women with vasomotor symptoms
Women who have had thrombophlebitis/DVT
Hepatic & renal impairment

Dose : A single oral dose of 60mg/day. It can be taken with or without food. Use should be commenced at least one year after the menopause.

Efficacy and safety have been determined for up to 40 months.

Conclusion : Raloxifene is a useful drug in the prevention and treatment of osteoporosis in postmenopausal women who do not have vasomotor symptoms. In addition, it has beneficial effects on reducing the occurrence of breast cancer.

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