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The use of Raloxifene in osteoporosis treatment

Abstract

Introduction Osteoporosis is a common disease characterized by the occurrence of fragility fractures. Major osteoporotic fractures are associated with decreased quality of life and high costs.

Areas covered This review summarizes clinical data on raloxifene (RLX), a second generation selective estrogen-receptor modulator (SERM), currently approved for the treatment of postmenopausal osteoporosis. RLX has estrogen effects on bone and lipid profile, whereas has anti-estrogen effects on uterus and breast cells. Its main side effects are hot flushes and venous thrombo-embolism.

Literature searches were conducted to retrieve articles reporting RLX clinical trial data. For comparison of safety and efficacy, post-marketing studies on RLX were included.

Expert opinion RLX is effective in reducing vertebral fracture risk in osteoporotic women, it is safe and its ability to prevent breast cancer have to be considered in the analyses of cost/effect and of the ideal candidate to this treatment. RLX has to be avoided in patients with previous history of venous thrombo-embolism.

Keywords

Fractures, Osteoporosis, raloxifene, selective estrogen receptor modulator (SERM).

1.0 Introduction

Primary osteoporosis is characterized by low bone mass and increased fracture risk. Major osteoporotic fractures are a social and economic burden: in developed countries, the lifetime risk for osteoporotic fractures at the wrist, hip or spine is 30% to 40%, very close to that for coronary heart disease. We recently reported a prevalence of 33.67% of osteoporosis [1] and a prevalence of major osteoporotic fractures of 34% in a cohort of 4000 Italian women [2].

An estimated 1.5 million fragility fractures occur every year, costing \$20 billion and leading to significant morbidity and mortality [4], these data are expected to increase in the near future. Pharmacological treatment reduces fracture risk by between 30% and 70% for vertebral fractures and 16% and 25% for non-vertebral fractures [4,5]. nevertheless many women at risk for, or diagnosed with osteoporosis are not receiving appropriate therapy [6,2].

Currently approved pharmacologic prevention and/or treatment options for osteoporosis include bisphosphonates, selective estrogen-receptor modulators (SERMs), parathyroid hormone, strontium ranelate (outside of North America), and denosumab.

1.1 Introduction to the compound

SERMs are a class of compounds that exhibit estrogen receptor (ER) agonist or antagonist activity depending on the tissue they are targeting. An 'ideal' SERM would act as an ER agonist by exerting a protective effect on bone and improving lipid parameters, while also acting as an ER antagonist by maintaining breast and endometrial safety.

Raloxifene (RLX) is a second generation SERM that blocks uterotrophic action in response to estrogen in the rat [7] and has a greater binding affinity for estrogen receptors than estrogen in the uterus and breast [7,8].

In an ovariectomized rat model, RLX displays beneficial bone and cardiovascular effects without significant uterine effects [9].

1.2 Chemistry

RLX is a benzothiophene non-steroidal derivative that binds to the estrogen receptor [10, 11], it is classified as a SERM.

Basic data on the drug are shown in Box 1.

1.3 Pharmacodynamics

RLX is similar to tamoxifen, it produces estrogen-like effects on bone and lipid metabolism, while antagonizes estrogen on breast and uterine tissue. RLX differs chemically and pharmacologically from endogenous estrogens, synthetic steroidal and non-steroidal compounds with estrogenic activity, and anti-estrogens.

Estrogen deprivation is associated with increased parathyroid hormone levels.[12] and decreased bone mass [13, 14]. Estrogens regulates gene expression: when estrogen binds to a ligand-binding domain of the estrogen receptor (ER), biologic response is initiated as a result of a conformational change of the receptor, leading to gene transcription through specific estrogen response elements on target gene promoters. The activation or repression of the target gene is mediated through two transactivation domains of the receptor: AF-1 and AF-2 [15]. The ER also mediates uses different response elements and other signaling pathways [16]. Moreover estrogen deficiency increases osteoclasts formation and activity indirectly through the up regulation of immune system, and of inflammatory cytokines [17, 18].

RLX binding to ER and the alteration of the receptor structure are different as respect to estrogens. This lead to differential transcriptional effects [19,20]. Multiple receptor subtypes, differential subtype activation and antagonism and selective tissue expression of ER may also account for the differences in the actions of estrogens and SERMs. Estrogen-receptor exists in two distinct forms α and β [21,22]. The two kinds of receptors expression varies in different tissues: receptor α has been detected in the uterus, testes, adrenal glands, kidneys, and pituitary; receptor β has been detected in the ovaries, testes, prostate, spleen, and thymus [23,24]. Estrogens and SERMs affect each of these receptors differently [25].

Other mechanisms that may explain the unique pharmacologic effects of SERMs include interaction with different co-activators and co-repressors in gene transcription, interference of proteins with the estrogen receptor, and estrogen-receptor-independent non-genomic effects [23-25].

RLX is effective on bone mineral density (BMD) and lipid profile, whereas it does not affect uterus.

1.4 Mechanism of action

RLX binds to ER, and produces estrogen-like effects on bone, reducing resorption and increasing bone mineral density in postmenopausal women. RLX and estrogens help maintaining bone mass, in part, through the regulation of the gene encoding transforming growth factor- β 3 (TGF- β 3), a bone matrix protein with antiosteoclastic properties. RLX also binds to the ER and acts as an estrogen agonist in pre-osteoclasts, inhibiting their proliferative capacity. Other mechanisms include the suppression of the bone-resorbing cytokine interleukin-6 promoter activity [26]. RLX also antagonizes estrogen effects on mammary tissue and uterus. RLX prevents the transcriptional activation of genes containing the estrogen response element in reproductive tissue. As well, RLX inhibits the estradiol-dependent proliferation of human mammary tumor cells in vitro [27]. RLX mechanism of action has not been fully determined, but evidence suggests that the drug's tissue-specific estrogen agonist or antagonist activity is related to the structural differences between the raloxifene-ER complex (specifically the surface topography of AF-2) and the estrogen-ER complex [28]. Also, the existence of 2 ER may contribute to the tissue specificity of RLX.

1.5 Pharmacokinetics and metabolism

Approximately 60% of an oral dose is absorbed, but presystemic glucuronide conjugation is extensive. Absolute bioavailability of RLX is 2.0% with a protein binding percentage of 95%.

RLX metabolism is hepatic, it undergoes extensive first-pass metabolism in the form of glucuronidation, it is not metabolized by cytochrome P450 pathways, and is primarily excreted in feces, less than 0.2% is excreted unchanged in urine [29].

2.0 Clinical efficacy

Phase I studies show that RLX is safe at a dosage of 200 to 600 mg/day: it does not induce vaginal bleeding or alter endometrium histology. The safety analysis showed no significant findings related to RLX except for vasodilation which was most common in the 600 mg group [30].

Phase II studies show that RLX is as effective as estrogen in short-term suppression of bone turnover, significantly lowers total serum cholesterol and LDL-C and increases the HDL-C: LDL-C ratio without effects on uterus. The phase II studies did not indicate an increased incidence of hot flashes during RLX therapy at 60 mg/day [11,31,32]

The Multiple Outcomes of Raloxifene Evaluation (MORE) study, a multicenter, randomized, blinded, placebo-controlled trial enrolled 7705 women aged 31 to 80 years in 25 countries who had been postmenopausal for at least 2 years and having osteoporosis. The study had up to 36 months of follow-up for primary efficacy measurements and non-serious adverse events and up to 40 months of follow-up for serious adverse events. In MORE study osteoporosis was defined as low BMD or vertebral fractures at X ray. Prior to randomization, patients were stratified to one of the two study groups: with (5064 patients) or without (2641 patients) vertebral fractures. Within each sub-study, women were randomly assigned to treatment with RLX 60 or 120 mg/day or placebo for 3 years; in addition, all women received supplemental calcium and cholecalciferol.

The data from this study show that RLX is effective in lowering the incidence of vertebral fractures both in patients with pre-existing vertebral fractures (about 30% of fracture risk reduction) and in patients with no prevalent vertebral fractures at baseline (about 50% of fracture risk reduction); the reduction was slightly higher in patients receiving 120 mg/day. As regards non-vertebral fractures, RLX significantly reduces only ankle fractures.

Bone mineral density increased after 36 months by 2.1% and 2.6% at the femoral neck and spine in the 60-mg RLX group and by 2.4% and 2.7% at the femoral neck and spine in the 120-mg RLX group, respectively ($P < .001$).

Patients included in MORE were high risk patients, as shown by the high incidence of vertebral fractures in the placebo (Tab. 1). This could emphasize the drug effect, nevertheless no effect on hip fracture was seen in this trial. The absence of effect on hip fracture could also be due to the young age of patients enrolled.

Data obtained after 4 years of treatment (CORE study) confirm that RLX 60 and 120 mg/d decreased the cumulative risk of new vertebral fractures in postmenopausal women with osteoporosis and that the decreased risk in year 4 alone was not different from that observed in the first 3 years [47].

A small study in postmenopausal women receiving long-term glucocorticoid treatment shows that RLX is well tolerated and significantly increases spinal and hip BMD after 12 months of treatment, whereas no significant effect was seen in fracture risk reduction [48].

2.1 Breast cancer prevention.

The MORE study suggested that RLX reduces the incidence of newly diagnosed breast cancer by 66%, with a marked effect on ER-positive tumors (risk reduced by 76%) and no effect on ER-negative tumors and non-invasive cancers [33-35]. The Continuing Outcomes Relevant to Evista (CORE) trial [34] examined the effect of additional 4 years of RLX (60 mg/d) therapy on the incidence of invasive breast cancer in women in the MORE trial who agreed to continue therapy: the risk of invasive breast cancer was reduced by 69% after 4 years.

RLX is being evaluated in comparison with tamoxifen in the STAR study, a large primary prevention trial of tamoxifen 20 mg/day versus raloxifene 60 mg/day for 5 years. The study population includes postmenopausal women at high risk based on the Gail model and women with previous lobular carcinoma *in situ*. It evaluated 19,747 postmenopausal women over the age of 35 years, with a 5-year predicted breast cancer risk higher or equal than 1.66% [34], and women with lobular carcinoma *in situ*. Women were randomized to receive daily tamoxifen 20 mg or RLX 60 mg. After a median follow up of 3.9 years, no difference was found in the incidence of invasive breast cancer between arms, both decreasing the incidence by 50%. However, despite the fact that RLX did not provide protection against non-invasive carcinoma while tamoxifen decreased the incidence by half, the rate of endometrial cancer was 38% lower in the RLX group and the incidence of VTE disease was lower in the RLX group, showing a better side-effect profile for this drug [37].

2.2 SERMs other than RLX.

Other SERMs were studied in the treatment of postmenopausal osteoporosis: bazedoxifene (BZD) [45] and Lasofoxifene (LXF) [39]. The two trials showed that both BZD and LXF are able to reduce the incidence of vertebral fractures, whereas effect on hip fracture was not proven for both the compounds (Table 1). The main difference relies in the study design as the study on BZD includes patients at high risk for future fractures, whereas LXF does not. Both the compounds have extra skeletal effects similar to RLX..

2.2 Safety and tolerability

In the MORE [32] and CORE [34] studies there was a significant increase in venous thromboembolic events (VTE) including deep venous thrombosis and pulmonary embolism in the RLX group. The greatest risk for deep venous thrombosis and pulmonary embolism occurs during the first 4 months of treatment. Additional adverse events include flu syndrome, vasodilation, leg cramps, endometrial cavity fluid, and peripheral edema. There was no significant increase in vaginal bleeding, endometrial cancer, or breast pain. The safety profile of RLX after 3 years of treatment and after 4 years of treatment was similar.

Due to the results of phase III studies the main concerns in the use of this drug were related to more frequent adverse events as hot flushes and VTE, whereas the great hope was the possible use of RLX as chemoprevention for breast cancer.

Hot flushes.

The vasomotor instability syndrome is characterized by subjective feelings of warmth ('hot flashes'); objectively measurable peripheral vasodilation with cutaneous flushing, particularly in the face and upper

body ('hot flushes'); sweating; chills; and a variety of symptoms consistent with adrenergic excess, including feelings of anxiety and rapid heart rate. RLX slightly increases the incidence of hot flashes relative to placebo, but does not alter the natural course of incident hot flashes, including no alteration of the total duration until complete symptom cessation [51].

Venous thromboembolism.

In an international, multicenter, randomized, double blind, placebo-controlled trial of RLX in postmenopausal women with or at a high risk of coronary diseases [Raloxifene Use for The Heart (RUTH) study] [52], RLX did not significantly affect the risk of coronary heart disease, but the incidence of fatal stroke was higher in the RLX group than in the placebo group (RLX group, 2.2/1,000 person years vs. placebo group, 1.5/1,000 person-years), whereas the incidence of stroke in the RLX group did not differ significantly from that in the placebo group.

In the MORE and RUTH studies, the increases in the absolute risk of VTE induced by RLX were 1.8 and 1.2 (per 100 persons), respectively. RLX is contraindicated in women with a complication or history of VTE, long-term immobile participants, and participants with antiphospholipid antibody syndrome, who are reported to be susceptible to VTE.

The mechanism of the increase in blood coagulation with SERM treatment is currently unclear. However, some reports have indicated that SERMs have an accelerating effect on blood coagulation and reduce anticoagulation [53,54].

Large post-marketing surveillance studies [55,56] show no significant increase in stroke incidence in women treated with RLX and confirm its efficacy on bone density, persistence in RLX was 42.3 %. The most frequently reported adverse events were edema peripheral (0.65 %) and VTE (0.16 %).

2.3 Regulatory affairs

RLX is indicated for treatment and prevention of osteoporosis in postmenopausal women in Europe; in USA it is also approved by FDA for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer.

RLX is not indicated for the treatment of invasive breast cancer, reduction of the risk of recurrence of breast cancer, or reduction of risk of noninvasive breast cancer.

The main concerns regard increased risk of deep vein thrombosis and pulmonary embolism with RLX, hence women with active or past history of venous thromboembolism should not take RLX.

It has been demonstrated an increased risk of death due to stroke, hence risk-benefit balance in women at risk for stroke has to be considered before starting therapy with RLX [57].

3.0 Economic data.

Interventions targeting the prevention and treatment of osteoporosis such as bisphosphonates and RLX have been found to be cost-effective in postmenopausal women with low BMD and/or prevalent vertebral fractures [58-62]. Several studies have highlighted how absolute risk affects cost-effectiveness [63]; RLX has been proved to be cost effective also in postmenopausal women unselected for low BMD and modeled for additional conditions such as breast cancer and cardiovascular health, whereas other drugs, as bisphosphonates, are not cost effective in these patients [64, 65].

As compared to other SERMs RLX is equally cost-effective than BZD [57]. Whereas there are no economic data available on the comparison between RLX and LXF.

4.0 Conclusion

Post-menopausal osteoporosis stems from the cessation of ovarian function at menopause, RLX addresses this estrogen deficiency by activating skeletal estrogen receptors and subsequently reducing bone turnover to levels similar to those found in premenopausal women.

Clinical trials with up to 8 years of follow-up and including over 39,000 patients show that RLX is effective in increasing bone density and decreasing the risk of vertebral fractures, whereas it is not effective in reducing non-vertebral fractures.

Moreover, RLX showed invasive breast cancer risk reduction during 8 years of observation in the MORE and CORE studies.

The benefits of RLX in reducing the risks of invasive breast cancer and vertebral fracture should be weighed against the increased risks of venous thromboembolism and fatal stroke.

4.1 Expert opinion

Osteoporosis is a common disease and fragility fractures are a social and economic burden, the prevention of fractures is extremely important in order to reduce social and economic costs. The measurement of BMD by DXA is one of the end point of treatment, nevertheless the anti-fracture effect is the main goal of therapy. The effect of RLX on BMD is quite small as compared to other anti resorptives, nevertheless it has a comparable effect in lowering vertebral fractures incidence. Improvement BMD accounts only for a part of the reduction in risk of vertebral fractures observed with RLX [65], this may be attributable to improvement in bone quality. RLX increases bone mechanical competence by altering collagen fibres [66].

Treatment option for osteoporosis are wide and safe, the use of RLX has to be recommended in patients without risk factors for venous thromboembolism and has to be avoided in patients with significant vasomotor symptoms.

In particular RLX is a first option treatment for osteoporosis together with bisphosphonates and strontium ranelate, in the treatment choice the physicians have to consider the risk of side effects, but also the extra skeletal effects of RLX

Differently from other anti-osteoporotic drugs, RLX has shown to be effective in reducing the incidence of ER positive breast cancer, this suggest to use this drug as first therapeutic options in osteoporotic patients at high risk based on the Gail model or with previous lobular carcinoma in situ.

An ideal candidate to RLX is a post-menopausal woman, without risk factors for VTE and significant vasomotor symptoms. The women should be both at high or low risk for fractures. Women at low risk (under 20% of major fractures within 10 years) may be treated with RLX if at high risk of breast cancer [64, 65]

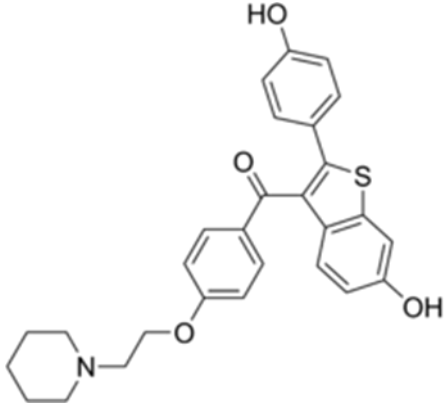
Differently from other drugs as bisphosphonates, RLX does not have long term adverse events as atypical fractures, nevertheless safety data are available for 8 years, for other treatment as alendronate and strontium ranelate we have data until 10 years [67]. Until now no safety concerns were raised to stop RLX therapy after 8 years.

Patients treated with RLX do not need specific monitoring, other than active surveillance on BMD and fractures, for side effects

The ability of RLX to lower breast cancer incidence implies also its possible use in adjuvant oncological therapy. Phase II studies on the administration of RLX together with examestane show that the co-administration did not affect the pharmacokinetics or pharmacodynamics of either agent and it is well tolerated [68].

Perhaps of greater significance are the prospects for the prevention of breast cancer together with the treatment of osteoporosis due to cancer treatment, thus, RLX may fulfil its promise to be the first prevention maintenance therapy.

Drug summary box

Drug name: Raloxifene
Phase: Launched
Indication: post-menopausal osteoporosis
Pharmacology description: C ₂₈ H ₂₇ NO ₄ S•HCl Selective Estrogen Receptor Modulator (SERM)
Route of administration: oral
Chemical structure: 
Pivotal trials: NCT00670319 (Post-menopausal osteoporosis) NCT00371956 (Glucocorticoid-induced osteoporosis) NCT00003906 (Prevention of breast cancer)

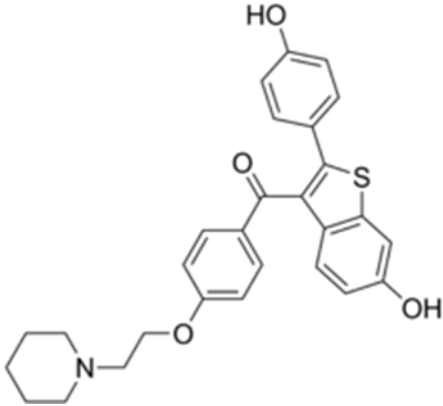


Table 1. Outcome measures for vertebral fracture over 3 years with currently available osteoporosis treatments calculated from the results of randomized, double-blind, pivotal phase III trials vs placebo.

Treatment	Study	Fracture incidence		RRR (%)	ARR (%)	NNT
		Placebo	Treatment			
Raloxifene	MORE [32]	21.2	14.7	30	6.5	16
Lasofexifene	PEARL [39]	9.5	5.7	40	3.9	26
Risedronate	VERT-NA [40][16.3	11.3	41	5.0	20
Risedronate	VERT-MN [41]	29.0	18.1	49	10.9	10
Ibandronate	BONE [42]	9.6	4.7	62	4.9	21
Strontium ranelate	SOTI [43]	32.8	20.9	41	11.9	9
Bazedoxifene	- [44]	4.1	2.3	42	1.8	56
Alendronate	FIT 1 [44]	15.0	8.0	47	7.0	15

ARR = absolute risk reduction, **NNT**= number needed to treat (over 3 year), **RRR**=relative risk reduction

5.0 Annotated bibliography

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