

Role of raloxifene in the management of postmenopausal osteoporosis of rheumatoid arthritis patients

Original Paper

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Abstract Objective : Due to the severe side effects of long-term treatment using hormone replacement therapy, Raloxifene (RLX) is introduced with beneficial effects on rheumatoid arthritis (RA) for postmenopausal women. This review was conducted to collect data from the available literature on RLX for the management of postmenopausal women suffering from RA. Method: All studies published up to 2019 were searched in four databases, including Google Scholar, PubMed, Scopus, and Medline. All articles were searched using several keywords, including "Raloxifene" or "Evista" in combination with "Rheumatoid Arthritis" or "Autoimmunity". Finally, six studies were selected for the review analysis of this study. In all studies, 60 mg/day RLX was administered for postmenopausal subjects. The majority of the studies showed that the use of RLX was effective in postmenopausal women who underwent corticosteroid therapy. No severe complications were reported after RLX therapy in patients with RA. Result: Based on the obtained results, RLX is a selective estrogen receptor modulator that its short-term anti-arthritis effects are proven in the treatment of postmenopausal osteoporosis. It was well tolerated without serious adverse events. Conclusion : It seems that RLX is a promising treatment candidate in postmenopausal RA due to its anti-arthritis and anti-osteoporotic effects and based on the outcomes of experimental postmenopausal arthritis in animal and human studies.

Keywords autoimmunity – Raloxifene – rheumatoid arthritis – Osteoporosis – Postmenopausal

INTRODUCTION

Rheumatoid arthritis (RA) is a progressive systemic autoimmune debilitating disease with focal joint erosions and generalized osteoporosis. The prevalence of RA is between 0.5% and 1%, and its male to female ratio is estimated at 1:3 [1]. The incidence of RA in women peaks around menopause [2]. The destruction of joint cartilage and periarticular bone occurs due to chronic inflammation. Generalized bone loss is another consequence of inflammation. Commonly, osteoporosis is observed in more than 50% of postmenopausal subjects with RA [3].

The association between the long-term use of estrogen (sex hormone) and the enhanced risk of breast cancer and thrombosis is proven in human studies [4, 5]. Menopause hormone therapy (MHT) is used to prevent postmenopausal osteoporosis. MHT is also applied to ameliorate RA progression; however, long-term MHT is associated with serious side effects [6, 7]. On the other hand, consumption of glucocorticoids, which are one of the optional treatments for RA, increases the risk of fracture secondary to osteoporosis [6, 8]. In this regard, selecting an effective combination of

RA medication and estrogen with minimal side effects has significant importance.

There is considerable evidence for the involvement of estrogens in the pathogenesis of several inflammatory diseases, including systemic lupus erythematosus (SLE) and RA [9]. With the onset of menopause in women with RA, in addition to the inflammatory nature of the disease, a lack of sex hormones (estrogen) can lead to osteoporosis [7]. Selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene (RLX) are examples of compounds that exhibit tissue-specific estrogenic activity [10]. Although raloxifene is an estrogen receptor agonist in the bone and uterus, it is an antagonist in the breast and exhibits greater agonist activity in the bone and less in the uterus [11]. Raloxifene is an SERM considered prophylaxis for invasive breast cancer [12]. Collagen-induced arthritis (CIA) is a well-established mouse model of human RA, which the result of extensive studies on the impact of sex steroids on inflammatory disease has been extensively studied by several groups. Other effects include reducing the severity of the disease and preventing decrease

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in bone mineral density (BMD) [7]. The prophylactic effects of RLX in postmenopausal osteoporosis were confirmed in the USA in 1997 [13], and the short-term antiarthritic effects of RLX have been suggested for the treatment of postmenopausal osteoporosis in patients with RA [7, 14].

Therefore, achieving a useful drug with no side effects of MHT for the prevention and treatment of osteoporosis in postmenopausal women with RA seems essential. In this regard, evidence has been presented about the effectiveness of RLX and the absence of serious side effects during its use. We aimed to study the effect of RLX in the management of osteoporosis in postmenopausal women suffering from RA. Hence, the available evidence has been reviewed:

- *Evidence supporting the use of RLX for postmenopausal osteoporosis in RA patients*
- *Effect of RLX on the immune system and fibrinolytic components of RA synoviocytes*
- *Complications of RLX therapy in postmenopausal patients with RA*

MATERIALS AND METHODS

This narrative review was carried out on the effects of RLX for the treatment of osteoporosis in postmenopausal women suffering from RA. The present study was performed based on the Cochrane Handbook for Systematic Reviews. Data regarding eligibility criteria, searching databases, removal of unrelated articles, quality assessment, data extraction, and discussion were gathered [15]. Google Scholar, PubMed, Scopus, and Medline databases were searched for published articles up to December 20 in 2019.

Inclusion and exclusion criteria

The eligibility criteria were chosen based on Participants–Intervention–Comparison–Outcome–Study design. Studies on human samples were selected, and the articles containing a clear description and insufficient data on the efficacy of RLX for the treatment of postmenopausal women suffering from RA due to the effect of SERM were chosen. Animal studies, meta-analyses and review articles, expert opinions, editorial letters, case reports or case series, consensus statements, and qualitative investigations were excluded from the present process. In addition, the articles that focused on other therapeutic approaches in patients with no autoimmune disease were excluded from this review. We included all types of nonrandomized, nonblinded, and retrospective studies due to the limited number of studies in assessing the use of RLX for the treatment of postmenopausal women with RA.

Literature search

In this study, four electronic databases including Google Scholar, PubMed, Scopus, and Medline were searched from October 20 to December 20 in 2019. The keywords were

“Raloxifene” or “Evista” in combination with “Rheumatoid Arthritis” or “Autoimmunity”

Study selection, data extraction, and study design

This narrative review focused on the effects of RLX for treating RA caused due to the effect of SERM in postmenopausal women. Firstly, four above-mentioned databases were searched over the period by using the selected keywords. In the next step, the titles and abstracts were carefully studied, so several unrelated articles were screened. Hence, the studies were chosen based on the eligibility criteria.

It is notable that papers that were not found to meet our objectives on assessing the title and abstract were removed. The full-text versions of the selected articles were collected for scanning. All of the study phases were performed by two researchers, who were continuously in contact with each other. Meanwhile, they consulted about the extracted data, agreed on the eligibility criteria, and discussed the study objectives to exchange the required information. Finally, the relevant data was extracted and recorded in a checklist. Figure 1 depicts a PRISMA flow diagram showing the process of article selection.

Risk of bias and quality assessment

The risk of bias was assessed in the included studies based on Cochrane’s risk of bias tool. Several domains including bias due to confounders, selection of participants, measurement of intervention, missing data, selective reporting, measurement outcome, departure from intended intervention, and other sources were investigated in this study [16]. The criteria of the risk of bias were classified as low, unclear, and high. On assessment of the risk of bias, the low and high risks of bias were marked as “Yes” and “No,” respectively. “Unclear” was considered for the unclear or unknown risk of bias. Figure 2 illustrates the quality assessment of the selected articles.

RESULTS

In total, 447 scientific articles were identified in the first step, of which 362 papers were found to be irrelevant to our objectives. Among the 85 remaining articles, 18 papers were duplicates in the preliminary investigation, which were removed. Furthermore, 26 articles focusing on the effect of RLX on nonautoimmune diseases or other autoimmune diseases, except RA, were excluded from the study. In addition, all the 15 studies investigating the effects of RLX on animals, 11 articles assessing MHT in postmenopausal patients, two books, three narrative articles and reviews, and four case reports were excluded from this study. Eventually, six papers remained to be included in this review (Figure 1). No randomized, double-blind clinical trial was reviewed in this study. All papers were retrospective or prospective case–control studies. The selected studies were conducted in three

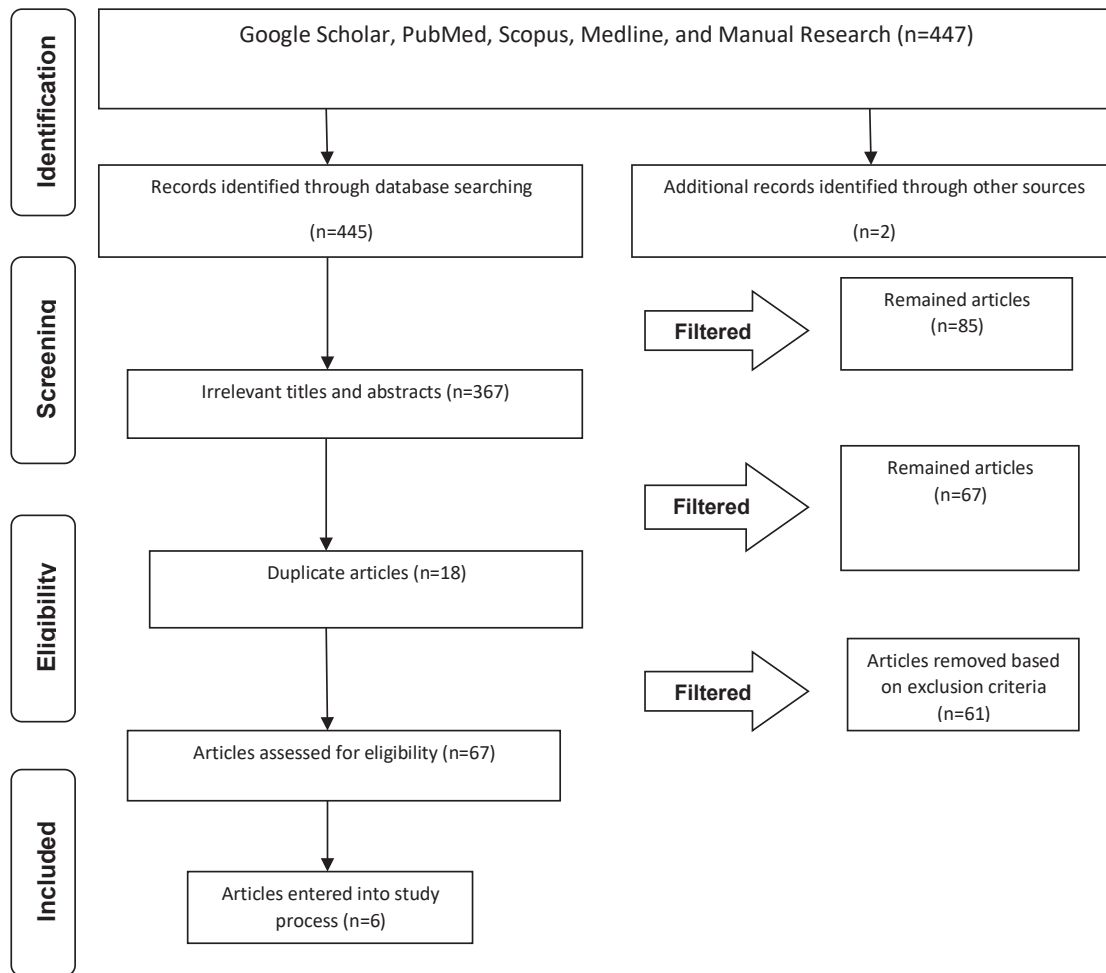


Figure 1. PRISMA flowchart representing the study selection process.

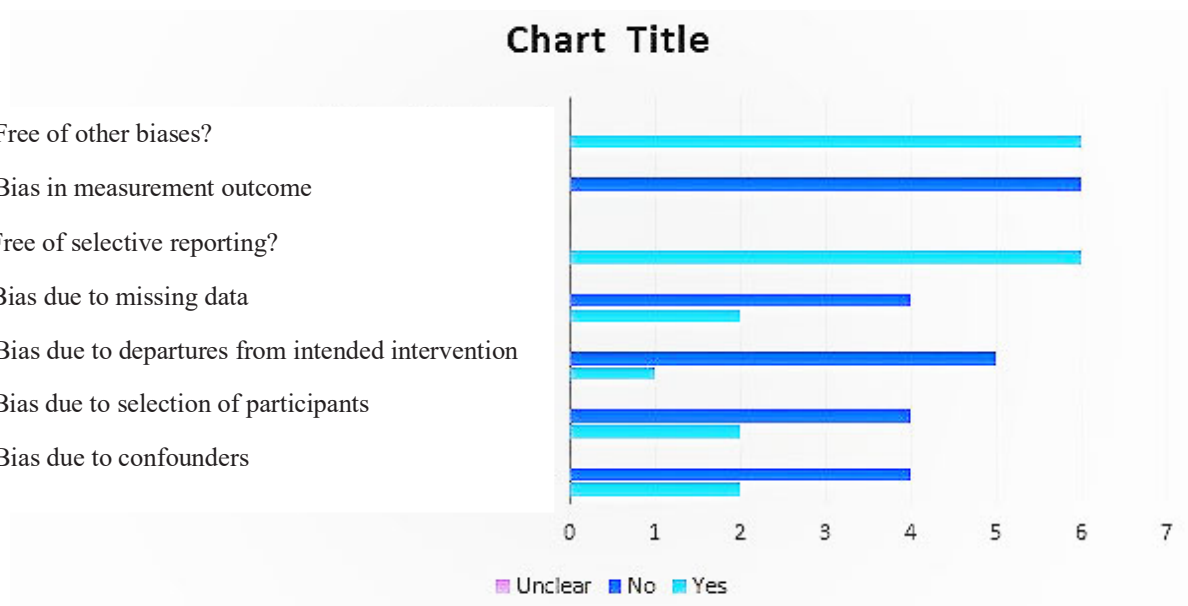


Figure 2. Quality assessment of the entered studies in the review.

different regions: most (50%) of them were conducted in the Far East (South Korea: 1, China: 1, Japan: 1), two studies (33%) in the European countries (Romania: 1, Italy: 1), and one study was performed in North America (16%). There was no study conducted in South America and Africa. It was observed that the studies were carried out on 588 subjects, of whom 218 were treated with RLX. The average age of the subjects who entered the studies was within the range of 55–72 years. The reported severity of RA varied from low to severe. Most patients were treated with long-term corticosteroids.

In all studies, the prescribed dose of RLX for postmenopausal patients was 60 mg daily. In the majority of studies, the administration of RLX had been reported effective. In this regard, Lee et al. showed that RLX was well tolerated by patients with postmenopausal osteoporosis caused by RA and other autoimmune diseases. Over the 12 months of the study, patients, both RLX users and nonusers, receiving corticosteroids had a remarkable increment in the lumbar spine and total hip BMD, while this index was decreased in the femoral neck of both groups [17]. Similarly, studies of Mok et al. and Stoica et al. showed that RLX consumption leads to increase in spinal and hip BMD after 12 months of treatment in RA postmenopausal women [18, 19]. A significant difference in serum undercarboxylated osteocalcin (ucOC; marker of the risk of hip fracture in elderly women) level was reported in patients receiving RLX compared to control group in the study of Mokuda et al. [20]. An *in vitro* study confirmed higher levels of plasminogen activator inhibitor, lower levels of urokinase-plasminogen activator (u-PA), and lower levels of u-PA receptor in RA patients treated with RLX in comparison to the control group [21].

None of the studies reported significant side effects of RLX treatment. Table 1 contains information on the studies reviewed, including the time and place of the study, sample size, age, RA severity, RLX dosage, status of bone density, and outcomes. It is notable that the risk of bias of the entered studies was assessed in the present study. Figure 1 shows a small possibility of bias, according to the method of removing the effect of confounders and the method for selecting participants. This finding indicates that selecting the subjects and assigning them to groups in addition to confounding variables had low effects on the outcome of the entered studies. A high risk of bias was observed due to differences between the intended and actual interventions in one study (17%). Moreover, the risk of bias was low in terms of measurement outcome, selective reporting, and missing data subtypes.

DISCUSSION

Evidence supporting the use of RLX for postmenopausal osteoporosis accompanied by RA

The main causes of osteoporosis development are the lack of estrogen, inflammatory diseases, and exposure to

corticosteroids. Estrogen deficiency and inflammatory diseases could lead to generalized bone loss in postmenopausal women with RA [7, 14]. Most postmenopausal RA patients with asymptomatic vertebral fractures had received long-term glucocorticoid therapy that resulted in an increase in the risk of fragility and fractures due to osteoporosis [22–24]. Due to the side effects of the long-term use of glucocorticoids and the high risk of osteoporosis in rheumatic patients, it is important to be cautious in the prescription of these drugs. [25].

In a study carried out by Ozmen et al., a significant decrease was observed in the severity of osteoporosis in postmenopausal patients who were treated with RLX for 3 months [26]. In a large trial on postmenopausal women, an increase in BMD of the femoral neck and lumbar spine was reported after RLX therapy for 3 years. The results revealed that the risk of incident vertebra in patients using RLX was lower in comparison to the control group [27].

Some studies indicated preservation of the bone and a decrease in the severity of CIA by RLX [14, 28]. Animal model studies demonstrated that RLX hampered the progression of arthritis and was beneficial in the long-term treatment of established CIA. Moreover, RLX and estradiol could prevent the loss of BMD [14, 29]. In the present study, there were five articles which evaluated the effect of RLX in the treatment of postmenopausal patients with RA.

Lee et al. performed a study to determine the efficacy of RLX in disease activity and BMD in 130 postmenopausal women with osteoporosis, RA, and other autoimmune diseases. The patients who were entered into the above-mentioned study suffered from RA, lupus, Sjogren's syndrome, scleroderma, and Behcet's disease. The majority of them underwent glucocorticoid therapy for a long time. RLX were administered at a dose of 60 mg/day in addition to elemental calcium (1200 mg/day). Based on Disease Activity Score, the scores of the lumbar spine and total hip BMD were higher in patients receiving glucocorticoids in the 12th month; however, femoral neck BMD decreased in both groups. No side effect was reported due to receiving RLX. This agent was well tolerated in postmenopausal women with RA who had an inactive disease and those with unidentified hypercoagulability. Total hip and lumbar spinal BMD scores increased due to using RLX [17].

The results of Lee et al.'s research were similar to those of the study by Mok et al., which was focused on determining the efficacy of RLX in prevention of BMD loss in women who were on long-term use of glucocorticoids. The femoral neck BMD decreased with no difference between the RLX (60 mg/day) and placebo groups. They showed that use of RLX led to decrease in bone formation markers by 19%, including serum osteocalcin and procollagen type I N-terminal, after 12 months.

Moreover, a reduction in resorption markers (i.e., urine deoxypyridinoline and type I collagen) was reported by 44%.

Table 1. Characteristics of evaluated studies.

Author (years) Reference	Country	Type of study	Sample size	Age (years)	RA ¹ severity	Diseases	Dosage	Lumbar spine	Hip BMD ¹⁰	Treatment duration	Glucocorticoids therapy duration	Outcome
Lee et al. (2014) [17]	South Korea	Clinical trial case-control study	130 RLX:86 C:44	RLX:60.1 C:59.3	Low to severe RA	RA: 86 SLE ⁶ : 7 Sjogren's syndrome: 15 Scleroderma: 11 Behcet's disease: 11 Other rheumatic diseases: 5	RLX (60 mg/day) plus elemental calcium (1,200 mg/day)	+0.9±0.7%; P=0.04 vs. +0.4±0.1%; P=0.05	+1.1±0.5%; P=0.03 vs. 1.5±0.7%; P=0.04	12 months	Long-term corticosteroid therapy	Total hip and lumbar spinal BMD scores increased due to using RLX.
Mok et al. (2010) [18]	China	Parallel-group randomised double-blinded placebo-controlled trial	114 RLX:57 C:57	55.3	Low to severe RA	SLE: 62 RA: 31 IM ⁹ : 9 Others: 28	60 mg/day	+1.3±0.4%; P=0.004	+1.0±0.4%; P=0.01	12 months	Prednisolone received for 62.2 months (6.7 mg/day)	RLX leads to increasing the spinal and hip BMD after 12 months of treatment.
Mokuda et al. (2012) [19]	Japan	Cross-sectional study	RLX:30 ALN ⁴ :50 C:20	RLX:72 ALN:74 C:76	Low RA disease activity (DAS28 ⁷ ≤3.2)	RA	60 mg/day	--	--	--	--	A significant difference in serum undercarboxylated osteocalcin levels was reported between RLX and control groups.
Solomon et al. (2002) [20]	USA	Retrospective chart review	236 MHT ⁵ :51 RLX:7 A: 45 E ⁶ : 5 Calcitonin: 23	60.3		RA	--	--	--	--	15.4 months	RA patients taking oral glucocorticoids did not undergo bone densitometry and/or receive prescription medications for osteoporosis.
Stoica et al. (2013) [21]	Romania	Clinical trial case-control study	30	Range: 55-64		RA	60 mg/day	--	--	--	Long-term corticosteroid therapy	Raloxifene significantly increased spinal and hip BMD after 12 months of treatment in RA postmenopausal women.
Guiducci et al. (2005) [22]	Italy	In vitro case-control study	RA:4 C:4	Matched between two groups	--	RA	--	--	--	--	--	Higher levels of plasminogen activator inhibitor-1, lower levels of urokinase plasminogen activator, and lower levels of urokinase plasminogen activator receptors were reported in RA patients treated with RLX in comparison to those reported in the control group.

1- Rheumatoid Arthritis; 2-Raloxifene; 3- Control; 4-Alendronate; 5- Menopause hormone therapy; 6- Etidronate; 7- Disease Activity Score; 8- Systemic Lupus Erythematosus; 9- Inflammatory Myopathy; 10- Bone mineral density

They concluded that the lumbar spine and total hip BMD scores (1.3% and 1.0%, respectively) were better in patients receiving RLX in the 12th month. In general, they showed that RLX suppressed the markers of bone turnover in comparison to placebo [18].

In another study, a higher reduction in vertebral fracture rate in comparison to the report on lumbar spine BMD was observed after treatment with RLX. It suggested the role of RLX in improvement of bone density, because RLX decreases the production of tumor necrosis factor- α (TNF- α) and interleukin (IL)-6 and inhibits osteoclastic restorative activity [30]. Consequently, RLX can decrease the levels of all bone turnover markers by 30%–40% in the premenopausal period [27].

Based on a controlled trial carried out by Delmas et al., the effectiveness of RLX in reducing bone turnover markers including bone-specific alkaline phosphatase, osteocalcin, and C-terminal telopeptide collagen degradation product of type 1 collagen was confirmed [31]. Another study was performed by Mokuda et al. to determine the risk factors changing serum ucOC level in postmenopausal subjects with RA. They showed a significant difference between the RLX and control groups in serum ucOC levels, which was similar to the results obtained by Mok et al. [20].

Considering the antiarthritic and antiosteoporotic characteristics of RLX and its effectiveness in the long-term treatment of CIA, the agent can be used in human studies for the treatment of inflammatory characteristics of RA. Although the effect of RLX in the treatment of postmenopausal patients with RA is confirmed, there is insufficient perception of the involvement mechanisms in the protection against arthritis [17–19]. Further studies in these areas are recommended.

Effect of RLX on the immune system and fibrinolytic components of RA synoviocytes

The results of animal studies showed that estradiol has beneficial effects on the development of arthritis and osteoporosis related to ovariectomy [32–34]. SERMs are nonsteroidal molecules demonstrating estrogen-like effects in some tissues, while they have antagonistic effects on other tissues. Recently, SERMs have been used for the prevention and treatment of postmenopausal osteoporosis [35]. Only three SERMs including tamoxifen, RLX, and ICI 162780 are applied in clinical practice. RLX acts as an estrogen agonist in bone and on serum lipids and binds with a high affinity to estrogen receptors. It decreases the risk of fractures in postmenopausal patients with osteoporosis. It also prevents bone loss and decreases bone turnover [36, 37].

Estrogen affects the immune system by several ways. Estrogen might play a role in increasing autoimmune diseases [9]. The response to infections is better among women in comparison to men due to their stronger humoral and cell-mediated immune responses, although women have less-potent innate immune responses [38]. In spite of the fact that estrogen

inhibiting T-cell-dependent immune responses could increase the production of antibodies by mature B cells. [39]. A similar effect of RLX and estradiol on B lymphopoiesis was shown in a study carried out by Erlandsson et al. However, unlike estradiol, RLX had no effect on the delayed-type hypersensitivity reaction [39]. A decrease in the serum levels of IL-6 in arthritic mice was observed due to using RLX. Nevertheless, it did not affect IL-6 in nonarthritic mice [7]. RLX had a beneficial effect on the serum osteoprotegerin levels and the serum levels of bone turnover markers in postmenopausal women with osteoporosis [40]. Hence, it can be recommended for the treatment of postmenopausal osteoporosis [13].

It is suggested that the peripheral sex hormone metabolism plays an important role in immune-inflammatory local response and RA manifestations. In addition, sex hormones stimulate synovitis in RA [41]. Androgens and progesterone are natural immune suppressors, though estrogen leads to an increase in humoral immunity [42]. Functional receptors for both androgens and estrogens are observed in synovial macrophages, monocytes, and lymphocytes, which help in the metabolism of gonadal hormones [43]. Pathogenic immunosuppressive properties could decrease androgen levels. Low levels of androgen, high levels of synovial fluid estrogen, and decrease in androgen/estrogen ratio were reported in RA patients [44–46].

RLX reduces the risk of vertebral fracture; therefore, it can be used for the prevention and treatment of osteoporosis in postmenopausal women [47]. Its antiestrogen activity on the uterus and breast tissues, in addition to progesterone activity in the bone were confirmed in previous studies [48, 49]. The etiopathological role of sex hormones and their potential long-term effects on the development of RA remain unclear. There has been no sufficient information on the relation between sex hormones and fibrinolytic system in RA synovial cells.

RLX inhibits cell proliferation and chemoinvasion in a dose-dependent manner, which decreases the levels of u-PA and urokinase plasminogen activator receptor (u-PAR). Estradiol and different SERMs regulate the expression of genes encoding u-PA and plasminogen activator inhibitor-1 (PAI-1). Concentration-dependent agonistic effect on the regulation of these genes is reported in some SERMs including 4-hydroxytamoxifen and RLX [50].

The interaction between u-PA and u-PAR leads to an increase in PAI-1 level and blocking u-PA. RLX plays a role in the modulation of the growth of synovial pannus by inhibiting the migration of RA synoviocytes. Consequently, RLX consumption decreases the invasive and angiogenic potential of synovial cells via reduction of u-PA level derived from RA synoviocytes [21].

Only in one study the effects of RLX on the fibrinolytic components of RA synoviocytes were evaluated and it focused on their fibrinolytic pattern and function. The results of this study (Guiducci et al.) showed the role of RLX as an inhibitor of the fibrinolytic system. The authors reported

higher levels of PAI-1, lower levels of u-PA, and lower levels of u-PAR in RA patients treated with RLX compared to the control group [21]. RLX blocks u-PA-dependent extracellular matrix degradation and decreases cell movement that results in an increase of PAI-1. Moreover, it reduces the levels of u-PAR and u-PA that have a main role in decreasing the proinvasive and proangiogenic patterns of RA synoviocytes [50].

Complications of RLX in postmenopausal patients with RA

Due to the limited number of studies on the effects of RLX in RA treatment, the side effects of this agent in postmenopausal osteoporosis in patients with RA remain unclear.

Decrease in osteocyte apoptosis [51] and prevention of bone loss [7] after using RLX were reported in an animal study [52]. Although the role of RLX in the treatment of postmenopausal women with osteoporosis and its prophylaxis for invasive breast cancer is proven, several side effects are reported, such as increasing risk of deep venous thrombosis and pulmonary embolism. Metabolic disorders, endocrine disease, and cardiovascular disease are other probable complications of RLX [28, 53].

Results of a study showed that the risks of breast cancer, nephritis, osteoporosis, and RA were lower among patients using RLX compared to the control group. However, the risk of metabolic disorders was higher among subjects treated with bisphosphonates. Except gastroesophageal reflux and gastritis (2%–3%), gastrointestinal disorders were reported in less than 1% of patients treated with RLX [54].

No venous thromboembolism was reported among patients using RLX in Kung et al.'s study on Asian women [55]. This

finding was compatible with another study performed by Mok et al. [18]. In addition, in a study carried out by Lee et al., thromboembolism or other side effects were not observed in any patient [17]. However, due to insufficient data, it is recommended to carry out future longitudinal studies to confirm the safety of RLX in terms of thromboembolic risk and other side effects.

CONCLUSION

RLX was well tolerated without serious adverse events. It seems that RLX is a promising treatment candidate for postmenopausal osteoporosis in patients with RA due to its antiarthritic and antiosteoporotic effects and based on the outcomes of experimental postmenopausal arthritis in animal and human studies.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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References

- [1] Doran, M.F., et al., *Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period*. Arthritis & Rheumatism, 2002. **46**(3): p. 625-631.
- [2] Goemaere, S., et al., *Onset of symptoms of rheumatoid arthritis in relation to age, sex and menopausal transition*. The Journal of rheumatology, 1990. **17**(12): p. 1620-1622.
- [3] d'Elia, H.F., et al., *Radiographic joint destruction in postmenopausal rheumatoid arthritis is strongly associated with generalised osteoporosis*. Annals of the rheumatic diseases, 2003. **62**(7): p. 617-623.
- [4] Anderson, G.L., et al., *Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial*. 2004.
- [5] Investigators, W.G.ft.W.s.H.I., *Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial*. Jama, 2002. **288**(3): p. 321-333.
- [6] D'Elia, H.F., et al., *Influence of hormone replacement therapy on disease progression and bone mineral density in rheumatoid arthritis*. The Journal of rheumatology, 2003. **30**(7): p. 1456-1463.
- [7] Jochems, C., et al., *Role of raloxifene as a potent inhibitor of experimental postmenopausal polyarthritis and osteoporosis*. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 2007. **56**(10): p. 3261-3270.
- [8] Lafage-Proust, M.H., B. Boudignon, and T. Thomas, *Glucocorticoid-induced osteoporosis: pathophysiological data and recent treatments*. Joint Bone Spine, 2003. **70**(2): p. 109-118.
- [9] Straub, R.H., *The complex role of estrogens in inflammation*. Endocrine reviews, 2007. **28**(5): p. 521-574.
- [10] Deroo, B.J. and K.S. Korach, *Estrogen receptors and human disease*. The Journal of clinical investigation, 2006. **116**(3): p. 561-570.
- [11] Fabian, C.J. and B.F. Kimler, *Selective estrogen-receptor modulators for primary prevention of breast cancer*. Journal of Clinical Oncology, 2005. **23**(8): p. 1644-1655.
- [12] Temin, S., *American Society of Clinical Oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction*. Gynecologic oncology, 2009. **115**(1): p. 132-134.
- [13] Stefanick, M.L., *Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US*

- Food and Drug Administration. The American journal of medicine*, 2005. **118**(12): p. 64–73.
- [14] Jochems, C., et al., *Long-term anti-arthritis and anti-osteoporotic effects of raloxifene in established experimental postmenopausal polyarthritis*. *Clinical & Experimental Immunology*, 2008. **152**(3): p. 593–597.
- [15] Green, S. and J. Higgins, *Cochrane handbook for systematic reviews of interventions*. 2005, Version.
- [16] Higgins, J., *Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration*. www.cochrane-handbook.org, 2011.
- [17] Lee, W., et al., *SAT0497 Effect of Raloxifene on Osteoporosis and Disease Activity in Postmenopausal Female with Rheumatic Diseases*. *Annals of the Rheumatic Diseases*, 2014. **73**(Suppl 2): p. 772–772.
- [18] Mok, C.C., et al., *Raloxifene for prevention of glucocorticoid-induced bone loss: a 12-month randomised double-blinded placebo-controlled trial*. *Annals of the rheumatic diseases*, 2011. **70**(5): p. 778–784.
- [19] Stoica, S. and G. Zugravu, *THU0402 Effects of Raloxifene for Prevention of Bone Loss in Rheumatoid Arthritis Women Receiving Long-Term Glucocorticoids*. *Annals of the Rheumatic Diseases*, 2013. **72**(Suppl 3): p. A301–A301.
- [20] Mokuda, S., et al., *Post-menopausal women with rheumatoid arthritis who are treated with raloxifene or alendronate or glucocorticoids have lower serum undercarboxylated osteocalcin levels*. *Journal of endocrinological investigation*, 2012. **35**(7): p. 661–664.
- [21] Guiducci, S., et al., *Raloxifene reduces urokinase-type plasminogen activator-dependent proliferation of synoviocytes from patients with rheumatoid arthritis*. *Arthritis research & therapy*, 2005. **7**(6): p. R1244.
- [22] Woolf, A.D., *An update on glucocorticoid-induced osteoporosis*. *Current opinion in rheumatology*, 2007. **19**(4): p. 370–375.
- [23] Angeli, A., et al., *High prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: a cross-sectional outpatient study*. *Bone*, 2006. **39**(2): p. 253–259.
- [24] Van Staa, T., et al., *Oral corticosteroids and fracture risk: relationship to daily and cumulative doses*. *Rheumatology*, 2000. **39**(12): p. 1383–1389.
- [25] De Vries, F., et al., *Use of inhaled and oral glucocorticoids, severity of inflammatory disease and risk of hip/femur fracture: a population-based case-control study*. *Journal of internal medicine*, 2007. **261**(2): p. 170–177.
- [26] Ozmen, B., et al., *Influence of the selective oestrogen receptor modulator (raloxifene hydrochloride) on IL-6, TNF-alpha, TGF-beta1 and bone turnover markers in the treatment of postmenopausal osteoporosis*. *Eur Cytokine Netw*, 2007. **18**(3): p. 148–153.
- [27] Ettinger, B., et al., *Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial*. *Jama*, 1999. **282**(7): p. 637–645.
- [28] Adomaityte, J., M. Farooq, and R. Qayyum, *Effect of raloxifene therapy on venous thromboembolism in postmenopausal women: a meta-analysis*. *Thrombosis and haemostasis*, 2008. **99**(02): p. 338–342.
- [29] Islander, U., et al., *Combined treatment with dexamethasone and raloxifene totally abrogates osteoporosis and joint destruction in experimental postmenopausal arthritis*. *Arthritis research & therapy*, 2011. **13**(3): p. R96.
- [30] Taranta, A., et al., *The selective estrogen receptor modulator raloxifene regulates osteoclast and osteoblast activity in vitro*. *Bone*, 2002. **30**(2): p. 368–376.
- [31] Delmas, P.D., et al., *Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women*. *New England Journal of Medicine*, 1997. **337**(23): p. 1641–1647.
- [32] Jochems, C., et al., *Osteoporosis in experimental postmenopausal polyarthritis: the relative contributions of estrogen deficiency and inflammation*. *Arthritis research & therapy*, 2005. **7**(4): p. R837.
- [33] Holmdahl, R., L. Jansson, and M. Andersson, *Female sex hormones suppress development of collagen-induced arthritis in mice*. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, 1986. **29**(12): p. 1501–1509.
- [34] Yamasaki, D., et al., *Effects of ovariectomy and estrogen replacement therapy on arthritis and bone mineral density in rats with collagen-induced arthritis*. *Bone*, 2001. **28**(6): p. 634–640.
- [35] Miller, P. and R. Derman, *What is the best balance of benefits and risks among anti-resorptive therapies for postmenopausal osteoporosis?* *Osteoporosis international*, 2010. **21**(11): p. 1793–1802.
- [36] Miller, P.D., et al., *Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study*. *Journal of bone and mineral research*, 2008. **23**(4): p. 525–535.
- [37] Silverman, S.L., et al., *Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial*. *Journal of bone and mineral research*, 2008. **23**(12): p. 1923–1934.
- [38] Moxley, G., et al., *Sexual dimorphism in innate immunity*. *Arthritis & Rheumatism*, 2002. **46**(1): p. 250–258.
- [39] Erlandsson, M., et al., *Oestrogen receptor specificity in oestradiol-mediated effects on B lymphopoiesis and immunoglobulin production in male mice*. *Immunology*, 2003. **108**(3): p. 346–351.
- [40] Messalli, E.M., et al., *Raloxifene therapy interacts with serum osteoprotegerin in postmenopausal women*. *Maturitas*, 2007. **56**(1): p. 38–44.
- [41] Cutolo, M., et al., *Sex hormones and rheumatoid arthritis*. *Autoimmunity reviews*, 2002. **1**(5): p. 284–289.
- [42] Cutolo, M., et al., *The role of androgens in rheumatic diseases*. *The Israel Medical Association journal: IMAJ*, 2001. **3**(10): p. 743.
- [43] Cutolo, M., et al., *Androgen and estrogen receptors are present in primary cultures of human synovial macrophages*. *The Journal of Clinical Endocrinology & Metabolism*, 1996. **81**(2): p. 820–827.
- [44] Ushiyama, T., et al., *Association of oestrogen receptor gene polymorphisms with age at onset of rheumatoid arthritis*. *Annals of the rheumatic diseases*, 1999. **58**(1): p. 7–10.

- [45] Cutolo, M., et al., *Androgens and estrogens modulate the immune and inflammatory responses in rheumatoid arthritis*. Annals of the New York Academy of Sciences, 2002. **966**(1): p. 131-142.
- [46] Cutolo, M., et al., *Hypothalamic-pituitary-adrenocortical and gonadal functions in rheumatoid arthritis*. Annals of the New York Academy of Sciences, 2003. **992**(1): p. 107-117.
- [47] Walsh, B.W., et al., *Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women*. Jama, 1998. **279**(18): p. 1445-1451.
- [48] Khalkhali-Ellis, Z., et al., *Estrogen and progesterone regulation of human fibroblast-like synoviocyte function in vitro: implications in rheumatoid arthritis*. The Journal of rheumatology, 2000. **27**(7): p. 1622-1631.
- [49] Fuleihan, G.E.-H., *Tissue-specific estrogens—the promise for the future*. 1997, Mass Medical Soc.
- [50] Levenson, A.S., et al., *Agonist activity of antiestrogen-receptor complexes to regulate urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1) endogenous gene expression in breast cancer cells*. Cancer letters, 1998. **125**(1-2): p. 215-220.
- [51] Huber, C., et al., *Selective estrogen receptor modulator inhibits osteocyte apoptosis during abrupt estrogen withdrawal: implications for bone quality maintenance*. Calcified tissue international, 2007. **81**(2): p. 139-144.
- [52] Islander, U., et al., *Estrogens in rheumatoid arthritis; the immune system and bone*. Molecular and cellular endocrinology, 2011. **335**(1): p. 14-29.
- [53] Phillips, K., A. Aliprantis, and J. Coblyn, *Strategies for the prevention and treatment of osteoporosis in patients with rheumatoid arthritis*. Drugs & aging, 2006. **23**(10): p. 773-779.
- [54] Foster, S.A., et al., *Characteristics of patients initiating raloxifene compared to those initiating bisphosphonates*. BMC women's health, 2008. **8**(1): p. 24.
- [55] Kung, A.W., et al., *Efficacy and safety of raloxifene 60 milligrams/day in postmenopausal Asian women*. The Journal of Clinical Endocrinology & Metabolism, 2003. **88**(7): p. 3130-3136.