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Review

Rebalancing immunity: The emerging role of selective estrogen receptor modulators in immunity and autoimmunity

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ABSTRACT

Selective estrogen receptor modulators (SERMs) are tissue- and context-specific regulators of estrogen receptor (ER) signaling, originally developed to treat breast cancer and osteoporosis. Increasing recognition of the roles of ERα and ERβ in modulation of immune cell development, tolerance, inflammation and antiviral defense has led to growing interest in SERMs as potential therapies for autoimmune disease. This review summarizes current mechanistic, preclinical, and clinical evidence on SERMs and related ER-directed agents across autoimmune and immune-mediated conditions. Preclinical studies demonstrated that select SERMs can generate anti-inflammatory or tissue-protective effects of endogenous estrogen without negatively impacting reproductive tissue. In inflammatory arthritis, SERMs reduced synovial inflammation, modulated Th17-associated responses, and protected against bone loss in murine models. In systemic lupus erythematosus (SLE), where estrogen signaling contributes to disease susceptibility and activity, SERMs and SERDs showed variable but encouraging findings: raloxifene improved bone mineral density without increasing lupus flares, bazedoxifene preserved trabecular bone in lupus-prone mice, and fulvestrant reduced disease activity and T-cell activation markers in a randomized trial. In multiple sclerosis, ERα-dependent mechanisms mediate estradiol's protective effects in experimental autoimmune encephalomyelitis (EAE), illustrating the broader immunologic relevance of estrogen pathways. Given the high burden of glucocorticoid exposure, premature ovarian insufficiency, and osteoporosis among individuals with autoimmune diseases, SERMs may offer dual benefit as both immunomodulatory and bone-protective agents. However, available human studies remain small and short-term. Future work should define cell-specific ER signaling in human immunity and autoimmunity, identify patient subgroups most likely to benefit, and evaluate long-term safety in adequately powered clinical trials.

KEYWORDS: selective estrogen receptor modulators, SERMs, estrogen receptor alpha, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, autoimmune disease, dehydroepiandrosterone, fulvestrant, antiviral therapy.

1. INTRODUCTION

1.1. Early history

The concept of using a chemical to treat or even prevent disease has been a consistent endeavor dating back to at least the 1930s. Professor Antoine Lacassagne's work in mouse models of mammary cancer implicated estrogen as a potential target, noting, "*If one accepts the consideration of adenocarcinoma of the breast as a consequence of a special hereditary sensibility to the proliferative action of oestrone, one is led to imagine a therapeutic preventive for subjects*

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predisposed by their heredity to this cancer, to stop the congestion of oestrone in the breast" [1]. In 1958, the first non-steroidal antiestrogen ethamoxytriphetol (MER-25) was discovered [2]. As time went on, additional studies highlighted the tissue specificity and the variability with which this estrogen antagonist functioned. Publications ranged from MER-25's effect on behavior and body weight regulation [3] to its impact on fertility [4]. Subsequently, clomiphene citrate was the first SERM approved for use in humans in February 1967 as a treatment for ovulatory dysfunction in healthy women desiring to conceive, but was found to have genotoxic, cytotoxic, and teratogenic issues making it unsuitable for other women's health issues [5-7]. It was another ten years before tamoxifen citrate was approved in December 1977. As with the studies on MER-25, tamoxifen was also found to have tissue site-selective estrogenic and antiestrogenic actions prompting further research in the field as to the potential applicability of SERMs as therapies for many disease processes, most notably cancer, osteoporosis, infertility, and menopausal symptoms [8-10].

1.2. Biological basis of estrogen receptors and SERMs

To better understand the function, targets, and variability of designer SERMs, we first need to appreciate the complexity of estrogen action. Estrogens are sex steroid hormones encompassing multiple structural forms, the dominant form being 17β-estradiol (E2). In addition to being essential for the function of the female reproductive system, estrogens play a role in most tissue types, and are protective in the cardiovascular, skeletal, and neurological systems [11-13]. However, aberrant levels of estrogens are also implicated in numerous disease states including cancers [14-16], osteoporosis [17], cardiovascular diseases [18], and autoimmunity [19-21]. Estrogen receptors (ERs) are part of the nuclear receptor superfamily and bind estrogens along with other endogenous chemicals and many man-made compounds, following which conformational changes occur that lead to transcriptional regulation. There are two main estrogen receptors, Estrogen Receptor alpha (ERα) and Estrogen Receptor beta (ERβ). Functional differences between the two can be partially traced to the differences in the Activating Function 1 (AF-1) domain located in the amino terminus of the ER. The AF-1 domain is poorly conserved, with only 18% homology between the two receptors, which contrasts from AF-2 which differs by only one amino acid within the C-terminus of the ligand binding domain, sharing 97% homology [22]. Together, AF-1 and AF-2 serve important roles in the response to estrogen and similar ligands to induce or suppress transcription [23]. The differences in transcriptional activation of target genes by ERα and ERβ is thought to be secondary to the independent activation of AF-1 and AF-2, working together or independently to facilitate recruitment of transcriptional co-regulator proteins. The co-regulator proteins physically interact with the liganded or unliganded ER and modulate gene expression [24]. Co-activator proteins, such as p300 and SRC3, or co-repressor proteins, such as NCoR or SMRT, function to activate or repress transcriptional activity, respectively. Following ligand binding, ERα and ERβ primarily bind to specific estrogen-responsive DNA elements (EREs) through the DNA-binding domain (DBD), regulating classical gene transcription. There is also evidence that ERα can tether to other DNA elements through transcription factors (ex. AP-1, NFκB), resulting in non-classical transcriptional regulation [25].

Adding further complexity to their regulation, ERα and ERβ have cell and promoter-specific differences in transcriptional activity as evidenced by studies using chimeras of ERα and ERβ [26]. Tissue-specific expression of these receptors also serves as an important determinant of tissue responses to estrogen with variable degrees of responsivity and function seen in bone, brain, liver, and of course, reproductive tissues. For example, in mammary gland and breast cancer cells, ERα generally has a proliferative role, while ERβ serves an anti-proliferative role [27]. Interestingly in bone, the central nervous system, and the cardiovascular system, ERα and ERβ have been shown to have equally abundant expression and can impact each other's functions as well as work in coordinate fashion. Within individual tissues there is also cell-specific distribution.

For example, in mammary tissue, ERα is expressed throughout, while ERβ is mainly present in epithelial cell nuclei. In testes, ERα localizes to Leydig cells while ERβ is in Sertoli cells [28]. It is also worth noting that there is a high degree of sequence homology within the DBD of ERα and ERβ with both able to bind EREs with high affinity as homodimers, or an ERα/ERβ heterodimer.

1.3. Types of SERMs and their current medical applications

A. First generation SERMs

Research into the utility of SERMs was largely catalyzed by the repurposing of a once orphaned drug, tamoxifen, as an adjuvant therapy in ER-positive breast cancer. Two SERMs, tamoxifen and toremifene, are triphenylethylene types utilized in the treatment of breast cancer [29, 30]. Tamoxifen can also prevent breast cancer recurrence, reduce fracture risk in individuals with osteoporosis, and lower cardiovascular disease risk [31-33]. Unfortunately, tamoxifen has detrimental side effects as well, especially in women older than 50, increasing the risk of stroke, deep vein thrombosis, and endometrial cancer [31, 34]. Toremifene was developed for clinical use in hopes that it would have less genotoxic effects than tamoxifen. It has similar efficacy in breast cancer treatment as tamoxifen, but there is conflicting data on whether the adverse effects are decreased compared to tamoxifen [35-38]. Although toremifene remains a strong, comparable alternative, tamoxifen is still more widely utilized. Clomiphene, a chloroethylene type, is a first-line therapy for infertility, especially within the setting of polycystic ovarian syndrome (PCOS), with a demonstrated 5.8-fold increase in pregnancy rates over placebo, although a small study indicates that prolonged use, > 1 year, may increase ovarian tumor risks [39, 40].

B. Second generation SERMs

Benzothiophene type SERMs were created in the hopes of reducing the uterine effects of first generation SERMs. Raloxifene is the proto-type second generation SERM; it is an ER agonist in the skeletal and cardiovascular systems and an ER antagonist in breast and endometrial tissue. Raloxifene is approved in the U.S. for the treatment of osteoporosis and the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial and Continued Outcomes of Raloxifene Evaluation (CORE) trial demonstrated that raloxifene increased bone mineral density (BMD) and reduced fracture risk while also reducing breast cancer risk in postmenopausal women with osteoporosis; no significant effects on the uterus were observed [41-43]. Unfortunately, although raloxifene treatment reduced markers of cardiovascular risk (low density lipoprotein (LDL), fibrinogen, etc.), the Raloxifene Use for The Heart (RUTH) trial observed no decrease in coronary events compared to placebo and demonstrated an increase in stroke and venous thromboembolic events [44, 45].

C. Third generation SERMs

The search for an “ideal SERM,” one with estrogenic effects on bone and lipids, neutral effects on uterine tissue, and antiestrogenic effects in breast tissue, continued with third generation SERMs. Lasofoxifene is the only naphthalene type SERM currently in clinical use. In an early clinical study, lasofoxifene increased BMD and reduced LDL cholesterol levels compared to raloxifene and placebo [46]. The Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) trial observed a reduced risk of vertebral and non-vertebral fractures, ER+ breast cancer (total and ER+ invasive), coronary heart disease, and stroke at 0.5 mg dose [47, 48]. A 0.25 mg dose tested in the trial demonstrated a reduction in vertebral fractures and stroke only and a small increase in all-cause mortality compared to placebo. Both doses created minimal endometrial changes which did not increase the risk for cancer or hyperplasia compared to placebo [49]. Unfortunately, a documented increase in deep venous thromboembolism (DVT) and pulmonary embolism (PE), along with the increase of all-cause mortality at the lower dosage, kept the FDA from approving lasofoxifene for postmenopausal osteoporosis use in the United States, but it has been approved in Europe [47, 50].

Bazedoxifene is an indole type SERM. A 3-year randomized placebo- and active (raloxifene)-

controlled study demonstrated that bazedoxifene, like raloxifene, decreases the relative risk of vertebral fracture and increases BMD compared to placebo. It also significantly reduced risk of non-vertebral fractures in high-risk individuals compared to both placebo and raloxifene [51]. No cardiac events (coronary occlusion, myocardial infarction, etc.), stroke, or transient ischemic attack (TIA) differences were seen among treatment groups. Venous Thromboembolism (VTE) events were comparable between bazedoxifene and raloxifene groups and both significantly increased over placebo group. It had similar endometrial and breast tissue effects as placebo and raloxifene [52]. A two-year extension study, which discontinued the raloxifene aim, observed that most findings were consistent with the original three-year trial observations. The researchers did note that the higher risk of VTE over five years was driven by a significantly increased risk of DVT compared to placebo, with both groups having similar risks for PE and retinal vein thrombosis (RVT) [53]. Bazedoxifene appears most effective when combined with conjugated estrogens (CEs) into a tissue selective estrogen complex (TSEC) that joins the anti-endometrial behavior of bazedoxifene with the bone density benefits and menopause symptom reduction of CEs. The TSEC has been demonstrated to increase BMD, decrease in vasodilation (hot flashes), and have no endometrium stimulation, cardiovascular differences, or VTE compared to placebo [54, 55]. It is approved in the US and Europe for the prevention of postmenopausal osteoporosis and menopause symptoms.

2. DISEASE-SPECIFIC EFFECTS OF SERMS IN AUTOIMMUNE AND INFECTIOUS DISEASES

Autoimmune diseases are characterized by a dysregulated immune response that leads to loss of tolerance and targeting self-tissues resulting in chronic inflammation and organ damage. Autoimmune conditions encompass a broad spectrum of disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and many others. Intriguingly, many autoimmune diseases exhibit a pronounced sex bias, with a higher prevalence, and sometimes greater severity, in females compared to males [56]. This sexually dimorphic pattern has prompted extensive investigation into the role of sex hormones, and estrogen in particular, in disease susceptibility and expression [19-21, 57-59].

Estrogen receptors are expressed across most immune cell lineages, including B and T lymphocytes, dendritic cells, macrophages, and microglia [58, 60-62]. Estrogen signaling through ERα and ERβ has been shown to influence central and peripheral tolerance, T-cell differentiation, B-cell survival and class switching, cytokine production, and type I interferon responses [58, 60, 61, 63]. Depending on concentration, timing, and cellular context, estrogen can either amplify or restrain immune activation, contributing to the complex and sometimes paradoxical relationship between sex hormones and autoimmunity. High-estrogen states such as late pregnancy are often associated with improvement in disease like RA and MS, whereas low-estrogen states, abrupt hormonal withdrawal, or chronic dysregulation may exacerbate disease activity, particularly in conditions such as SLE [57, 64-67].

SERMs add an additional layer of nuance by acting as ligand-dependent, tissue- and cell-specific modulators of ER signaling. Unlike uniform estrogen agonists or antagonists, SERMs function as partial agonists or antagonists depending on the ER isoform expression, co-regulator availability, and promoter context within a given cell type [8, 10, 29-31, 41-46, 50]. In immune cells, this can translate into selective effects on T-helper cell polarization, regulatory T-cell function, B-cell maturation and antibody production, and innate cytokine responses. Preclinical studies across several autoimmune models suggest that SERMs can recapitulate some beneficial effects of estrogen signaling, such as anti-inflammatory or tissue-protective effects, while mitigating others that are pathogenic, particularly in diseases with strong Th17, type I interferon, or autoantibody signatures [68-77]. The following sections synthesize these observations within specific disease contexts, highlighting where SERMs, SERDs, and related endocrine strategies have already been tested and where key gaps remain, as summarized in Table 1 and Figure 1.

Table 1. Selective estrogen receptor modulators and related agents: indications, immune effects, and antiviral properties.

Agent / class	Generation / type	Primary approved indications*	Key immune / autoimmune data	Antiviral evidence	Major safety considerations
Tamoxifen (SERM)	1st gen; triphenylethylene	ER+ breast cancer treatment and prevention; breast cancer chemoprevention [29-33]	RA/arthritis models: inhibits neutrophil migration and arthritis progression; bone-protective effects in rodents [144, 145] MS models: enhances oligodendrocyte differentiation and remyelination [125]	Inhibits HIV replication and LTR-driven transcription [131]; disrupts HCV NS5B–ERα interaction and replication [132-134]; activity against Ebola virus in screens [136]; associated with lower COVID-19 mortality in breast cancer cohort [140]	Increased risk of VTE, stroke, and endometrial cancer, especially in older women [31, 34]
Toremifene (SERM)	1st gen; triphenylethylene	ER+ breast cancer treatment [30, 35-38]	Similar efficacy as tamoxifen; developed for lower genotoxicity [36, 38]	Inhibits Ebola virus entry and infection *in vitro* and *in vivo* models [130, 136]	VTE risk similar to other SERMs; lower genotoxicity vs tamoxifen but overall safety profile comparable [30, 36-38]
Clomiphene (SERM)	1st gen; chloroethylene	Induction of ovulation; first-line therapy in anovulatory infertility, esp. PCOS [5-7]	SLE: well tolerated, with rare mild disease flares and no thromboembolic events reported across treatment cycles [146]	Identified as active against Ebola virus in drug-repurposing screens; blocks viral entry [130, 136]	Ovarian hyperstimulation, multiple gestation; potential increased ovarian tumor risk with long-term use [39, 40]
Raloxifene (SERM)	2nd gen; benzothiophene	Osteoporosis treatment and vertebral fracture risk reduction; breast cancer risk reduction in postmenopausal women with osteoporosis [41-43]	RA/arthritis models: SERM analog inhibits postmenopausal polyarthritis and osteoporosis [73, 89, 90] SLE: improves BMD without worsening disease activity; modest effects on vascular biomarkers [116, 117]	Active against Ebola virus in cell-based screens [130, 136]; phase 2 trial in mild–moderate COVID-19 showed higher rate of undetectable SARS-CoV-2 at day 7 vs placebo [141]	Increased VTE and possibly stroke risk; generally neutral endometrial profile; no uterine stimulation [41-43]

Table 1 continued..

Agent / class	Generation / type	Primary approved indications*	Key immune / autoimmune data	Antiviral evidence	Major safety considerations
Lasofoxifene (SERM)	3rd gen; naphthalene	Postmenopausal osteoporosis (Europe); fracture and breast cancer risk reduction [46-49]	RA/arthritis models: attenuates arthritis severity and inflammatory cytokine expression in CIA and spondyloarthritis models [95, 96] MS models: promotes oligodendrocyte differentiation and remyelination [127]	*In vitro* anti–SARS-CoV-2 activity reported for several SERMs; lasofoxifene included in some screens [139]	Increased VTE and PE; increased all-cause mortality at 0.25 mg in PEARL; not approved for osteoporosis in US [46-49]
Bazedoxifene (SERM)	3rd gen; indole; ± TSEC	Osteoporosis treatment and fracture risk reduction; TSEC (bazedoxifene + conjugated estrogens) for menopause vasomotor symptoms and osteoporosis prevention [51-55]	RA/arthritis models: bazedoxifene reduces arthritis and osteoporosis [88, 95] SLE: TSEC protects trabecular bone in experimental lupus without exacerbating disease [118] MS models: promotes oligodendrocyte differentiation and remyelination [127]	Potent in vitro and in vivo anti–SARS-CoV-2 activity; functions as viral entry inhibitor via altered cholesterol distribution/endosomal acidification [139]	Similar endometrial and breast profile to placebo; increased DVT risk vs placebo (especially first 2 years) [51-54]
Fulvestrant (SERD)	ERα selective downregulator	ER+ metastatic breast cancer	SLE: randomized trial showed improved SLEDAI scores and decreased T-cell activation markers; reduced need for background immunosuppression [119]	Limited direct antiviral data; conceptual relevance via ERα blockade rather than SERM-like partial agonism	Injection-site reactions; menopausal symptoms; needs monitoring of bone health and standard SERD toxicities [147]

Table 1 continued..

Agent / class	Generation / type	Primary approved indications*	Key immune / autoimmune data	Antiviral evidence	Major safety considerations
DHEA (endocrine modulator)	Adrenal androgen	Not licensed specifically for SLE; used off-label as adjunctive therapy in mild–moderate SLE	SLE: improves health-related quality of life and fatigue; inconsistent effects on disease activity; possible increase in BMD; limited utility in other rheumatic diseases [111-113]	No direct antiviral indication; mechanistic implication via androgen/ER crosstalk, but data limited in infectious disease	Mild androgenic side effects; acne, hirsutism; decreased HDL; uncertain long-term CV safety in high-risk patients [111-113]

*Regulatory approvals vary by region.

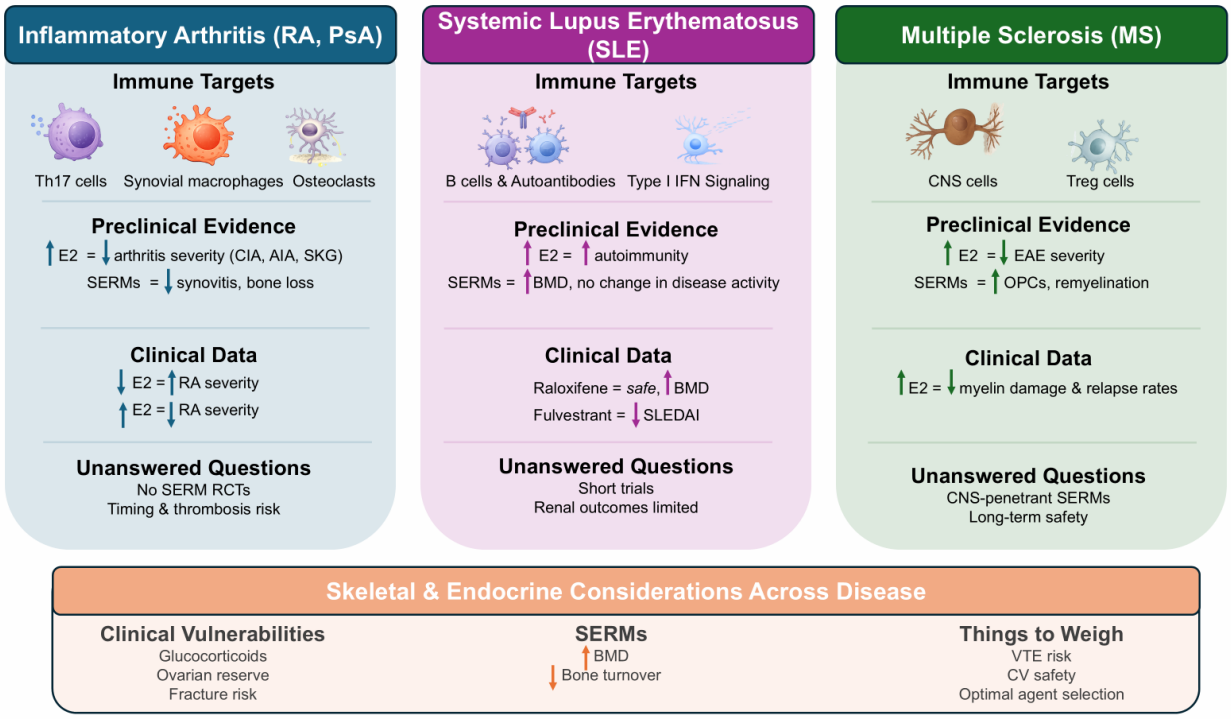

Figure 1. Overview of preclinical and clinical evidence for SERMs across inflammatory arthritis, systemic lupus erythematosus, and multiple sclerosis, highlighting key immune targets, disease-specific effects, and shared skeletal and endocrine consideration.

2.1. Inflammatory arthritis

Sex differences are a hallmark of inflammatory arthritides, particularly rheumatoid arthritis (RA), which occurs more frequently in women than in men. The role of sex hormones, particularly estrogen, in RA pathogenesis and disease progression has been extensively reviewed elsewhere [57]. In women, RA incidence has a bimodal temporal pattern with a second peak at the time of menopause, coinciding with declining estrogen levels and implicating hormonal changes in disease susceptibility [64]. In contrast, estrogen levels in men remain relatively stable across adulthood and are higher than those observed in postmenopausal women of comparable age [78]. Clinical observations further support a modulatory role for sex hormones, as a substantial proportion of women with RA experience improvement in disease activity during pregnancy, when estrogen levels are markedly elevated [65].

These epidemiologic and clinical findings are mirrored in experimental models of inflammatory arthritis. In collagen-induced arthritis (CIA) models, estrogen consistently reduces disease severity and joint inflammation [68-71]. Mechanistically, estrogen has been shown to suppress Th17 differentiation and IL-17 production in CIA mice, providing a direct link between estrogen signaling and modulation of pathogenic adaptive immune responses relevant to inflammatory arthritis [72]. In an antigen-induced arthritis (AIA) model, E2 treatment significantly reduced both synovitis and joint destruction, effects that were absent in ERα knockout mice, implicating ERα as critical for E2's protective actions [79]. Additional studies extend these findings to other inflammatory arthritis phenotypes. In the SKG mouse, a model of spondyloarthritis driven by aberrant immune activation, E2 treatment suppressed arthritis development and reduced expression of pro-inflammatory cytokines, including TNF, IFN-γ, and IL-17A [80]. Similarly, in ovariectomized mice with experimentally induced arthritis, E2 replacement improved innate immune responses and attenuated joint inflammation, effects also attributed by the authors to nuclear estrogen

receptors [81]. Earlier work supported a central role for ERα. In both mouse and rat models of experimental arthritis, selective activation of ERα recapitulated the anti-inflammatory and bone-protective effects of estrogen, whereas selective ERβ activation failed to confer similar benefit [69, 82].

Population-based data further strengthens these observations by linking lifetime estrogen exposure to disease activity and outcomes in RA. Early menopause has been associated with higher disease activity and worse patient-reported outcomes in women with postmenopausal-onset RA [83], while lower cumulative lifetime estrogen exposure correlates with increased disease severity, greater radiographic damage, and reduced likelihood of achieving remission [84]. Consistent with these findings, women with RA have also been shown to exhibit decreased ovarian reserve compared with age-match controls, suggesting earlier reproductive aging and reduced endogenous estrogen exposure even prior to menopause [85].

Beyond effects on joint inflammation, reduced lifetime estrogen exposure in women with RA has important implications for skeletal health. RA is independently associated with increased risk of osteopenia and osteoporosis, driven by chronic inflammation, glucocorticoid exposure, and decreased physical activity, with postmenopausal women experiencing particularly accelerated bone loss [86]. Estrogen deficiency further exacerbates this risk by impairing osteogenesis and accelerating bone turnover, in part through increased oxidative stress, thereby linking hormonal changes to both inflammatory and skeletal disease manifestations [87]. SERMs offer a potential strategy to address this intersection of immune-mediated joint disease and skeletal health. In a randomized study of postmenopausal women with RA receiving low-dose glucocorticoids, treatment with the SERM bazedoxifene was associated with improvements in bone mineral density and reductions in biochemical markers of bone turnover, although the change in bone mineral density did not exceed the least significant change [88]. In contrast, raloxifene treatment for 12 months was well tolerated and resulted in significant increase in both spinal and hip bone mineral density in postmenopausal women with RA receiving long-term glucocorticoids [89]. Consistent with these clinical observations, preclinical studies in estrogen-deficient models of inflammatory arthritis demonstrate that long-term raloxifene treatment can attenuate arthritis severity while preserving bone mass, supporting a mechanistic link between estrogen receptor signaling, immune regulation, and skeletal homeostasis [90].

Although the majority of mechanistic and clinical data connecting estrogen signaling to inflammatory arthritis derive from RA, emerging evidence suggests that sex hormones may also influence disease expression in psoriatic arthritis (PsA). Although the incidence of PsA is comparable between males and females, recent reviews highlight sex-related differences in disease manifestations and outcomes as well as the potential impact of hormonal fluctuations across the female life course, including fertility, pregnancy, and menopause. Clinical and translational studies have further demonstrated association between estrogen levels and key PsA-relevant cytokine pathways, including IL-12, IL-17A, and IL-23, supporting a role for sex hormones in shaping pathogenic immune responses in this disease. While the data remain more limited than in RA, they suggest that estrogen-mediated immunomodulation may extend to other IL-17-driven inflammatory arthritides, warranting further investigation [91-93].

Together, these clinical and experimental findings demonstrate that estrogen signaling, particularly through ERα, exerts broad immunomodulatory and tissue-protective effects across multiple forms of inflammatory arthritis. Building on this preclinical evidence, investigators have explored whether SERMs can recapitulate these protective effects through receptor-selective engagement. Several animal studies provide proof-of-concept for this pharmacologic approach. For example, genistein, a soy-derived phytoestrogen with estrogen receptor activity, shifted immune responses in CIA rats away from a Th1-dominant phenotype by suppressing IFN-γ production and augmenting IL-4 secretion, resulting in reduced joint inflammation and radiographic damage [94]. In an estrogen-deficient model of inflammatory

arthritis, raloxifene or its related analogs markedly decreased arthritis incidence and severity while preserving bone and cartilage integrity [73]. More recently, treatment with SERMs, including lasofoxifene and bazedoxifene, has been shown to suppress synovial inflammation and protect against bone loss in CIA models, effects associated with decreased measures of cartilage degradation and modulation of the pro-inflammatory cytokine IL-6 [95]. Consistent with these findings, studies using the SKG mouse model of spondyloarthritis demonstrated that lasofoxifene attenuated arthritis severity and reduced expression of inflammatory cytokines, including TNF, IFN-γ, and IL-17, further supporting the capacity of receptor-selective estrogen signaling to regulate immune responses across distinct inflammatory arthritis phenotypes [96]. Collectively, these data provide a strong mechanistic rationale for evaluating SERMs and related estrogen receptor-targeted agents as adjunctive or alternative therapeutic strategies in inflammatory arthritis.

2.2. Systemic lupus erythematosus

In lupus, estrogen signaling is regarded as pathogenic due to its immune-stimulatory effects, with ERα signaling serving as the predominant mediator both developmentally and functionally [58, 97]. Although ERs have not been identified in a lupus genome wide association study (GWAS) to date, a small study utilizing peripheral blood mononuclear cells (PBMCs) of patients with SLE demonstrated elevations in ERα mRNA when compared to healthy controls [98]. Another study showed increased production of anti-dsDNA antibodies and IgG in peripheral blood mononuclear cells from patients with active SLE but not in patients with inactive disease or in a normal population when treated with estradiol (E2) [99]. Consistent with these immunologic observations, several small clinical studies have explored whether sex hormone dysregulation may be associated with disease activity in SLE. While alterations in estradiol and testosterone levels have been reported, interpretation of these findings is limited by methodological constraints, including small sample sizes and reliance on indirect or metabolite-based hormone measurements [100, 101]. Consequently, while these studies raise the possibility of altered estrogen signaling in SLE, definitive conclusions regarding systemic estrogen levels remain premature.

Importantly, estrogen exerts context-dependent effects on immune functions that are not solely determined by circulating hormone concentrations. Estrogen has disparate effects on cell-mediated versus humoral immune responses that are influenced by hormone levels, receptor engagement, and cellular context. Low estrogen levels enhance Th1 responses and cell-mediated immunity, whereas high estrogen levels, such as those observed during pregnancy, promote Th2 polarization and humoral immune responses [102-104]. This estrogen-driven skewing toward Th2 responses is believed to be highly relevant to lupus pathogenesis, characterized by autoantibody production and immune complex formation. For example, treatment of wild-type mice with E2 induced a lupus phenotype with nephritis, along with increased production of Th2 cytokines and autoantibodies, but minimally impacted ERα KO mice [105]. Similarly, in MRL/lpr lupus-prone mice, E2 enhanced B cell activation and autoantibody production but suppressed T cell-mediated vasculitis [106]. Overall, in murine models of lupus, manipulating sex hormones via classic ovariectomy and castration experiments demonstrated clear roles for estrogen and testosterone. In wild type B6/129 mice, ERα deficiency resulted in a lupus-like glomerulonephritis [107]. Surprisingly, targeted disruption of ERα in NZM2410 and MRL/lpr female mice ameliorated the development of glomerulonephritis [108]. Similarly, in NZB/NZW F1 female lupus prone mice ERα deficiency was protective, attenuating glomerulonephritis, extended survival, and blunted the development of anti-double-stranded DNA IgG antibodies [109]. Unfortunately, the interpretation of the above animal studies is challenging, as the mouse models described were studied in the context of intact gonads for which disruption of ERα resulted in high serum levels of both E2 and testosterone (T2) in response to elevated GnRH, suggesting that increased T2, or supraphysiologic sex hormone levels, may have been responsible for the protective effects observed. Further, female lupus prone ERα null mice are not protected from lupus following

ovariectomy supporting the potential role of elevated levels of E2 and T2 as a protective mechanism in these models [110].

Given the complexity of ERα signaling and the divergent effects of estrogen in lupus models, pharmacologic modulation of estrogen pathways has been explored. Early studies demonstrated that LY139478, an analog of raloxifene, improved survival and reduced nephritis in MRL/lpr mice [74]. In addition to SERMs, adrenal androgen supplementation with dehydroepiandrosterone (DHEA) has been explored as another endocrine-modulating strategy in SLE. Across seven randomized controlled trials, DHEA demonstrated modest but clinically meaningful improvements in health-related quality of life, particularly fatigue and overall well-being in patients with mild to moderate disease [111]. However, effects on disease activity were inconsistent: in six trials reporting SLEDAI outcomes, DHEA showed no benefit over placebo in all but one study, and long-term efficacy remains unproven. A subsequent systematic review similarly concluded that while DHEA may improve quality-of-life measures, its impact on disease activity is controversial and incompletely defined. Mild androgenic side effects were also commonly reported and concerns regarding reductions in HDL cholesterol also raise questions about long-term cardiovascular safety in a population already at elevated risk [112]. A recent review on DHEA extended these observations, noting that DHEA use in SLE may modestly improve disease activity, reduce fatigue, and increase bone mineral density [113]. Together these data suggest that while DHEA may hold adjunctive value in select SLE populations, its therapeutic effects are limited, and its long-term safety requires further study.

Hormone replacement therapy (HRT) studies in SLE further highlight the nuanced relationship between exogenous hormones, disease activity, and cardiovascular risk, with mixed effects reported across trials [114, 115]. Notably, one study of 114 HRT users compared with 227 non-users found no increased risk of coronary artery disease associated with HRT use; in multivariable analysis, only age and SLEDAI were predictive of CAD risk, suggesting that HRT itself did not independently contribute to cardiovascular events in this population [115]. Together these findings underscore both the therapeutic potential and the clinical complexity of manipulating estrogen pathways in SLE, setting the stage for interest in receptor selective strategies such as SERMs and SERDs, which may offer immunomodulatory benefit with more targeted biologic effects.

Small clinical trials of the SERM raloxifene in postmenopausal women with SLE have also shown improvements in bone mineral density and potential modest effects on immunologic markers [116, 117]. Importantly, no worsening disease activity was observed. Beyond these clinical studies, SERMs have also been evaluated in lupus models specifically for their skeletal effects. In an ovariectomized MRL/lpr mouse model of postmenopausal lupus, treatment with a tissue-selective estrogen complex containing bazedoxifene protected against trabecular bone loss without exacerbating lupus disease manifestations [118]. Taken together, these clinical and preclinical data suggest that SERM-based interventions may play a beneficial role in addressing osteoporosis in SLE while maintaining disease stability.

An additional area of potential relevance for SERMs in SLE relates to the unique hormonal and skeletal vulnerabilities of this patient population. Many individuals with SLE experience substantial glucocorticoid exposure, predisposing them to rapid bone loss and increasing risk of avascular necrosis. In patients with severe organ-threatening disease, cyclophosphamide-based regimens may be required, which can lead to premature ovarian failure, abrupt estrogen deficiency, and accelerated decline in bone mineral density. Given these endocrine and musculoskeletal complications, often occurring in young women already at high fracture risk, SERMs or related receptor-targeted agents may offer therapeutic value by providing estrogenic benefits to bone while avoiding systemic estrogen exposure. Although their immunologic effects in SLE remain incompletely defined, the intersection of steroid dependence, premature ovarian insufficiency, and osteoporosis creates a clinical environment in which receptor-selective estrogen modulation could have a dual relevance for disease stability and skeletal protection.

These considerations highlight an important future direction for research evaluating SERMs and SERDs not only as immune modulators but also as potential adjunctive strategies for mitigating long-term endocrine and bone complications in SLE.

Targeted antagonism of estrogen signaling has also been explored through SERDs. In a 15-month randomized trial, fulvestrant significantly improved SLEDAI scores at 12 and 15 months compared with placebo, despite no major changes in serologic markers or bone density [119]. Patients receiving fulvestrant required reductions in background lupus medications, whereas the placebo group required stable or increased dosing. Fulvestrant also decreased T-cell activation markers, including CD154 and calcineurin. These findings suggest that ER blockade with a SERD may have therapeutic potential in moderately active SLE. However, broader application, particularly in young women, raises important feasibility and safety considerations. Fulvestrant is contraindicated in pregnancy and carries embryo-fetal toxicity risk based on animal data and mechanism of action, necessitating pregnancy testing and effective contraception in females of reproductive potential. Sustained ER degradation can also produce clinically relevant hypoestrogenic effects including vasomotor symptoms in addition to potential reproductive effects making the long-term risk-benefit in premenopausal patients less well defined.

In contrast, SERMs offer the potential to uncouple immunomodulatory benefits from global estrogen deprivation through tissue- and receptor-selective signaling. This pharmacologic distinction suggests that SERMs may provide a more feasible and safer strategy for long-term modulation of estrogen pathways in women with SLE, particularly those of reproductive age.

2.3. Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system (CNS) that results in oligodendrocyte damage, loss of myelin, and neurological dysfunction. Oligodendrocyte precursor cells (OPCs) are unable to differentiate into oligodendrocytes and disease progresses due to axon degeneration caused by remyelination failure [120, 121]. Epidemiological data indicate a role for estrogen in MS. There is an overall 3:1 female:male ratio in incidence. In high estrogen states, like late-term pregnancy, the relapse rate decreases as estriol hormone levels increase, which reduces lesions, but this protective effect disappears postpartum when hormone levels decline and lesions return [66, 67, 122]. In low estrogen states for females, usually at the onset of menopause, there is a trend of worsening disease and symptom severity. The later onset of MS in males is also hypothesized to be affected by age-related decline in testosterone levels [123, 124]. In the experimental autoimmune encephalomyelitis (EAE) MS mouse model, E2 inhibits cytokine and chemokine expression and suppresses symptoms [75]. In this mouse model, E2 acted through ERα and receptor expression was required in T lymphocytes for E2-mediated inhibition of Th1/Th17 cell differentiation and downregulation of IL-17 [76, 77].

There is limited research into the use of SERMs for MS treatment. Tamoxifen was studied as a potentially re-purposed drug that could inhibit protein kinase C alpha (PKCα) signaling. It induced rat OPCs to differentiate through both ER receptors and the GPR30 receptor, but not via the PKCα receptor, and was able to accelerate remyelination in a rat model [125]. Further clinical studies have not been conducted with tamoxifen, perhaps due to the strong adverse effects and duration of therapy with tamoxifen treatment limited to 5 years to avoid increased risk of endometrial cancer and VTEs. Recently, certain SERMs, including lasofoxifene, bazedoxifene, and tamoxifen, were identified via a high throughput selective screen of FDA-approved bioactive molecules that magnified differentiation of rat OPCs into oligodendrocytes [126, 127]. Since bazedoxifene is well-tolerated, it was further studied in a mouse model. The researchers demonstrated that it did not induce OPC differentiation through either ER receptor but seemed to work through the emopamil binding protein (EBP) in the cholesterol biosynthesis pathway [127]. One caveat to the researchers' interpretations is that the ERα knockout mouse utilized (Jackson Laboratories Strain 004744) is a functional knockout and the mouse can produce

the shorter ERα46 variant. Since all three mice (WT, ERαKO, and ERβKO) would have the shorter ERa46 variant present, this isoform may have impacted the bazedoxifene effects. A phase II clinical trial studying this SERM as a remyelinating agent was completed in June 2025, but results have not yet been published [128].

2.4. Infectious diseases

ERα (encoded by *Esr1*) is a major rheostat of viral replication [129]. Consequently, SERMs have been investigated for their broader potential to inhibit viral replication through non-classical ER signaling pathways. Early studies focused on HIV, hepatitis C virus (HCV), and Ebola virus, with more recent work expanding to include activity against SARS-CoV-2 [130]. In HIV models, tamoxifen (TAM) emerged as a disruptor of viral replication during chronic infection and an inhibitor of HIV-associated transactivation. Notably, TAM suppressed HIV replication in non-stimulated, HIV-infected lymphocytes through mechanisms independent of its anti-estrogenic activity, likely involving interference with targets of the NF-κB pathway [131]. TAM also exhibits anti-viral activity against HCV, where it disrupts the interaction between ERα and the viral polymerase NS5B, reduces replication complex formation, decreases viral protein expression, and protects against HCV-induced cytopathic effects [132, 133]. Additional work shows that TAM can act at multiple stages of the HCV lifecycle including attachment, entry, replication, and release, with a similar multistep inhibitory profile reported in HSV-1 models [134, 135].

Building on these observations, a 2013 drug-repurposing screen identified several SERMs with activity against Ebola virus, including clomiphene, toremifene, tamoxifen, raloxifene, as well as the clomiphene stereoisomers enclompihene and zuclomiphene [130, 136, 137]. These SERMs demonstrated *in vitro* antiviral activity across multiple Ebola strains and have shown survival benefits in murine infection models, although efficacy appears sensitive to dose-dependent toxicity. Mechanistic studies indicated that clomiphene and toremifene inhibited Ebola virus entry through effects on GP1,2-containing viral particles [136]. These antiviral properties positioned SERMs as attractive candidates for repurposing efforts during the COVID-19 pandemic, prompting investigation into their effects on SARS-CoV-2 infection and host-cell entry pathways. Preclinical studies highlighted notable sex-based disparities in coronavirus susceptibility: in transgenic mouse models, male mice showed greater vulnerability to SARS-CoV infection with higher mortality and more severe symptoms, whereas female mice were protected through ER signaling. This protection was lost after ovariectomy or treatment with ER antagonists, underscoring the role of ER pathways in modulating disease severity [138]. Experimental antiviral screening further broadened this concept; evaluation of 18 SERMs demonstrated that several including clomiphene, tamoxifen, toremifene, and bazedoxifene exhibited potent anti-SARS-CoV-2 activity *in vivo*, reducing viral load, inflammatory markers, and weight loss in infected hamsters. Mechanistically, bazedoxifene acted as a viral entry inhibitor by altering cholesterol distribution and endosomal acidification, supporting SERMs as multipronged antiviral agents [139]. Population-level clinical data also reinforced this potential: in a cohort of nearly 23,000 breast cancer patients in Italy, tamoxifen users exhibited the lowest COVID-19 hospitalization rate among endocrine therapies and an exceptionally low mortality rate (0.02%), emerging as the only agent associated with a significantly reduced standardized mortality rate compared with the regional female population [140]. These findings suggested that SERM-based therapies may mitigate COVID-19 severity. Complementing these observations, a phase 2 multicenter, randomized, placebo-controlled trial of the second generation SERM raloxifene in adults with mild to moderate COVID-19 demonstrated a higher proportion of participants achieving undetectable SARS-CoV-2 levels after seven days of treatment at both dosing regimens, without differences in serious adverse events, although effects on oxygen requirements were not observed [141].

3. CONCLUSIONS AND FUTURE DIRECTIONS

SERMs occupy a unique intersection between endocrinology, immunology, and host defense.

Originally developed for hormone-sensitive malignancies and osteoporosis [29-33, 41, 42, 46], SERMs are now recognized as context-dependent regulators of estrogen receptor signaling in immune cells. Preclinical studies across multiple autoimmune models, including inflammatory arthritis, systemic lupus erythematosus, and multiple sclerosis, demonstrate that modulation of ER pathways can alter disease onset, severity and tissue damage [68-77, 105-107, 110]. In many of these settings, ERα emerges as a central mediator of both protective and pathogenic estrogenic effects, with SERMs capable of partially reproducing beneficial actions while avoiding the systemic consequences of exogenous estrogen [58, 69, 79, 82, 101].

Clinical investigations of estrogen-pathway modulation in autoimmunity remain limited but informative. Small trials of raloxifene in SLE demonstrate improvements in bone mineral density without increased disease activity [116, 117], while fulvestrant has shown reductions in SLEDAI scores and T-cell activation markers in a randomized study [119]. Beyond classic autoimmune models, emerging preclinical studies suggest that SERMs may also confer tissue-protective effects in related immune-mediated connective tissue disorders; for example, raloxifene reduced fibroblast proliferation and extracellular matrix production and ameliorated skin fibrosis in an iPSC-derived and bleomycin-induced model of systemic sclerosis, pointing to broader therapeutic potential of SERM-class agents in fibrotic autoimmune pathology [142]. These findings indicate that estrogen pathway modulation is feasible in autoimmune disease populations, although the magnitude and durability of immunologic benefit remain uncertain.

Beyond autoimmunity, SERMs exhibit antiviral activity with multiple common pathogens, including HIV, HCV, Ebola virus, and SARS-CoV-2, acting at the level of viral entry, replication, and host inflammatory signaling [130-139]. Clinical data from breast cancer cohorts receiving tamoxifen suggested potential mitigation of COVID-19 severity [140], and early randomized evidence with raloxifene supported antiviral effects in SARS-CoV-2 infection [141], underscoring the broad biologic reach of these agents.

Despite these encouraging signals, substantive limitations temper immediate clinical application of SERMs as disease-modifying therapies. Existing human studies are small, short-term, and heterogeneous, limiting conclusions about risk, disease progression, and long-term safety outcomes (e.g. thromboembolism). The complex nature of estrogen signaling, capable of amplifying or suppressing immune pathways depending on dose, context, and receptor biology, also raises the possibility of divergent effects across disease and patient subgroups [19, 20, 58, 97].

Future research should prioritize mechanistic studies defining cell type-specific actions of ERα and ERβ in human immune subsets, as well as how SERMs, SERDs, and tissue-selective estrogen complexes reshape transcriptional programs in synovium, kidney, CNS, spleen and bone marrow. Clinically, adequately powered trials are needed that stratify patients by sex, menopausal status, hormone levels, antiphospholipid antibody positivity, glucocorticoid exposure, and thrombotic risk. Given the high burden of glucocorticoid-induced bone loss, cyclophosphamide-associated premature ovarian insufficiency, and fracture risk in SLE and other autoimmune conditions [118, 143], special attention should be given to evaluating SERMs as dual-purpose agents addressing both immune activity and skeletal protection and possible cardiovascular protection.

In summary, SERMs and related estrogen receptor-directed therapies represent a promising but incompletely defined class of agents at the interface of endocrine modulation, immune regulation, and antiviral defense. Current evidence supports their use for established indications such as osteoporosis in select autoimmune populations and provides biologic rationale for further exploration of receptor-selective strategies in RA, SLE, MS, and infectious disease. Realizing their full potential will require coordinated mechanistic and clinical investigation designed to leverage tissue specificity while minimizing thromboembolic and cardiovascular risks.

CONFLICT OF INTEREST STATEMENT

The authors declare that no conflict of interest exists.

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