

Immune Regulation by Selective Estrogen Receptor Modulators

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Avhandlingen baseras på följande arbeten:

- I. Angelina I. Bernardi, Annica Andersson, Louise Grahnemo ,
Merja Nurkkala-Karlsson , Claes Ohlsson, Hans Carlsten and Ulrika Islander.
Effects of lasofoxifene and bazedoxifene on B cell development and function.
Immunity, Inflammation and Disease. 2014 Dec;2(4):214-225.
- II. Angelina I. Bernardi, Annica Andersson, Alexandra Stubelius, Louise Grahnemo,
Hans Carlsten and Ulrika Islander.
**Selective estrogen receptor modulators in T cell development and T-cell
dependent inflammation.**
Accepted for publication in *Immunobiology*, February 2015.
- III. Annica Andersson, Angelina I. Bernardi, Alexandra Stubelius,
Merja Nurkkala-Karlsson, Claes Ohlsson, Hans Carlsten and Ulrika Islander.
**Selective estrogen receptor modulators lasofoxifene and bazedoxifene inhibit
joint inflammation and osteoporosis in experimental postmenopausal arthritis.**
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Immune Regulation by Selective Estrogen Receptor Modulators

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ABSTRACT

At menopause, the levels of estrogen decline, leading to loss of estrogen-mediated protective effects on bone and an increased risk of osteoporosis. Hormone replacement therapy, containing estrogen, has been used for many years to prevent and treat osteoporosis in postmenopausal women. However, the estrogen receptor agonistic effects on the reproductive organs increases the risk of developing cancer. Therefore, selective estrogen receptor modulators (SERMs) have been developed, that can act as tissue-specific estrogen receptor agonists or antagonists. This enables SERMs to mediate the positive effects of estrogen on bone metabolism while avoiding side effects on the reproductive organs.

Estrogen has a number of effects on the immune system; it decreases B- and T lymphopoiesis and increases antibody production. In addition, estrogen potently inhibits T-cell dependent inflammation and suppresses synovitis and inflammation-mediated bone loss in arthritis. Similarly to estrogen, the second-generation SERM raloxifene suppresses B-cell development and ameliorates arthritis. However, raloxifene lacks effects on antibody production and T-cell dependent inflammation.

Lasofoxifene and bazedoxifene are third-generation SERMs, approved for treatment of postmenopausal osteoporosis. The bone-protective properties of these compounds are well documented; however the effects of lasofoxifene and bazedoxifene on the immune system have not earlier been assessed. Therefore, the aim of the studies included in this thesis was to investigate the immune-regulating effects of these third-generation SERMs. We found that lasofoxifene and bazedoxifene suppressed B-cell development in ovariectomized (ovx) mice, but lacked effects on antibody production and on T-cell development. Furthermore, lasofoxifene and bazedoxifene did not suppress T-cell dependent inflammation, but potently inhibited synovitis and bone loss in mice subjected to experimental postmenopausal arthritis. Phenotypic analysis of lymph nodes in arthritic mice showed that while estrogen increased a subpopulation of dendritic cells (DCs), as well as T helper 17 (Th17) cells, B cells and surface markers connected to antigen-presentation on B cells, the SERMs lacked these effects.

In conclusion, the third-generation SERMs lasofoxifene and bazedoxifene suppressed experimental arthritis and inhibited B-cell development in ovx mice, but lacked effects on T-cell development and T-cell dependent inflammation. SERMs also lacked effects on lymph node DCs, B cells and T cells in arthritic mice. Therefore, further investigation is needed to find the target for the suppressive effects of SERMs on arthritis. Nonetheless, the anti-arthritic effects of the third-generation SERMs suggest possibility for an extension of the clinical indications of these drugs to include also postmenopausal RA.

Keywords: Mice, lasofoxifene, bazedoxifene, raloxifene, estrogen, osteoporosis, B cells, T cells, rheumatoid arthritis

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