

Estrogen and raloxifene in experimental arthritis and osteoporosis

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ABSTRACT

In postmenopausal rheumatoid arthritis (RA), both the estrogen deficiency and the inflammatory disease contribute to the development of generalized osteoporosis. This leads to an increased risk of fracture, with high morbidity and mortality. More than 50% of women with postmenopausal RA suffer from osteoporosis. Hormone replacement therapy (HRT) is used to treat postmenopausal osteoporosis. HRT has also been shown to ameliorate RA, with decreased joint destruction, reduced inflammation, increased bone density and better patient health assessment. Unfortunately, longterm hormonal treatment is associated with severe side effects, and is no longer recommended.

The aims of this thesis were to establish a murine model for studies of osteoporosis in postmenopausal RA. To investigate the relative contributions of estrogen deficiency and inflammation to osteoporosis development in arthritic disease. To examine whether treatment with raloxifene, a selective estrogen receptor modulator, would have the same beneficial anti-arthritic and anti-osteoporotic effects as estrogen. Furthermore, we wanted to compare the mechanisms for these effects between estrogen and raloxifene.

We found that lack of endogenous estrogen and arthritic disease contributed equally and additively to osteoporosis development in collagen-induced arthritis, a murine model of human RA. Arthritic ovariectomized mice lost 55% of their trabecular bone mineral density (BMD) compared with cycling healthy mice.

Raloxifene potently decreased the frequency and severity of arthritis, protected the joints from erosions, and preserved the BMD. These effects were sustained when treatment was given both as prophylaxis and in established disease, and during longterm treatment.

Raloxifene down-regulated the expression of TNF α and RANKL mRNA in the spleen. These molecules are important mediators of bone loss after menopause and in RA. In contrast to estrogen, raloxifene did not affect the effector phase of the disease, as demonstrated in collagen-antibody induced arthritis.

Many estrogenic effects are mediated via the classical estrogen receptors and binding to the estrogen response elements, which regulate gene transcription. We found that raloxifene activated this pathway at 1/4 of the intensity of estrogen.

In conclusion, our results show that estrogen deficiency and inflammation contribute equally to bone loss in arthritis. Furthermore, raloxifene has potent anti-arthritic and anti-osteoporotic effects, and is possibly a valuable addition to conventional treatment of postmenopausal RA.

Key words: rheumatoid arthritis, osteoporosis, estrogen, raloxifene, mice

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- I. **Caroline Jochems, Ulrika Islander, Malin Erlandsson, Margaretha Verdrengh, Claes Ohlsson and Hans Carlsten.** Osteoporosis in experimental postmenopausal polyarthritis: the relative contributions of estrogen deficiency and inflammation.
Arthritis Research & Therapy 2005, 7:R837-R843
- II. **Caroline Jochems, Ulrika Islander, Anna Kallkopf, Marie Lagerquist, Claes Ohlsson and Hans Carlsten.** Role of raloxifene as a potent inhibitor of experimental postmenopausal polyarthritis and osteoporosis.
Arthritis & Rheumatism 2007, 56:3261-3270
- III. **Caroline Jochems, Marie Lagerquist, Cecilia Håkansson, Claes Ohlsson and Hans Carlsten.** Longterm anti-arthritic and anti-osteoporotic effects of raloxifene in established experimental postmenopausal polyarthritis.
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- IV. **Caroline Jochems, Cecilia Håkansson, Marie Lagerquist, Claes Ohlsson, Kutty Selva Nandakumar, Rikard Holmdahl and Hans Carlsten.** Effects of estradiol and raloxifene on collagen-antibody induced arthritis and osteoporosis.
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