Lasofoxifene in Osteoporosis and its Place in Therapy

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ABSTRACT

Selective estrogen-receptor modulators (SERMs), which have estrogen-like effects on bone and “antiestrogen effects” on other tissues, have been in development for osteoporosis prevention and treatment in postmenopausal women as a safer alternative to long-term estrogen. We conducted a literature review of the skeletal and extraskeletal effects of lasofoxifene, a new generation SERM approved by the European Commission for osteoporosis treatment. Published data on the effects of lasofoxifene are based on 23 clinical pharmacology studies with over 10,000 participants from 17 phase 2 and 3 randomized controlled trials (RCTs). In RCTs, lasofoxifene decreases bone turnover markers (BTMs), increases bone mineral density (BMD) at the spine and hip, and decreases the incidence of vertebral and nonvertebral nonhip fractures compared with placebo. Compared with raloxifene, lasofoxifene gave greater decreases in BTMs, and greater increases in lumbar spine BMD. Lasofoxifene also decreased the risk of breast cancer, major coronary heart disease events, and stroke, but—similar to raloxifene—there was an increased risk of venous thromboembolism. In one trial, endometrial hypertrophy and uterine polyps were more common with lasofoxifene than with placebo, but endometrial cancer and hyperplasia were not. Lasofoxifene is probably most appropriate for use among women in their early or middle menopausal years (age 55-65) who have, or are at risk of developing, osteoporosis and in particular vertebral fractures. At the time of publication, lasofoxifene is not approved for use by the US Food and Drug Administration, and as such is not used in North America.

Keywords: lasofoxifene, osteoporosis, postmenopausal women, selective estrogen-receptor modulators
INTRODUCTION

The precipitous decrease in estrogen that characterizes menopause may be associated with accelerated bone loss and fractures. One way to prevent fractures is to identify and treat those at high risk. Estrogen replacement therapy can be used, but long-term use—required for fracture prevention—is associated with an increased risk of breast cancer and cardiovascular disease. Alternatives to estrogen include selective estrogen-receptor modulators (SERMs), which have estrogen-like effects on bone and “antiestrogen effects” on the breast, and thus may be safer than estrogen for long-term use. Raloxifene was the first SERM approved for prevention and treatment of osteoporosis. Randomized controlled trials (RCTs) demonstrated that, compared with placebo, raloxifene prevents bone loss, and reduces the incidence of vertebral fractures and breast cancer. However, there are no data that demonstrate raloxifene is able to decrease nonvertebral and hip fractures. Further, raloxifene is associated with an increased risk of venous thromboembolism (VTE) (hazard risk ratio [HR] 1.44; 95% confidence interval [CI] 1.06, 2.95) and fatal stroke (HR 1.49; 95% CI 1.00, 2.24), which prompted the development of other agents. Lasofoxifene is a new generation SERM approved by the European Commission in March 2009 for treatment of osteoporosis in postmenopausal women at increased fracture risk. Lasofoxifene has not received approval from the US Food and Drug Administration (FDA) for prevention and treatment of osteoporosis. (Pfizer has submitted several New Drug Applications [NDAs] to the FDA. Both NDAs submitted in 2004, one for the prevention of postmenopausal osteoporosis and one for the treatment of vulvovaginal atrophy [VVA] in postmenopausal women with low bone mass, were not approved by the FDA due to risks related to endometrial cancer and invasive gynecological procedures. In 2009, the FDA responded to Pfizer’s 2007 NDA and requested for additional information.) This paper will review the mechanism of action of lasofoxifene, RCT data on skeletal and other organ systems, and the role of lasofoxifene in osteoporosis.

Most of the RCT trial data that reports on skeletal effects of lasofoxifene describes changes in bone turnover markers (BTMs) and BMD in response to therapy and while both BTMs and bone mineral density (BMD) are accepted outcomes for clinical trials, they serve only as surrogates for fracture. Indeed, recent meta-analyses demonstrate that the reductions in vertebral and nonvertebral fracture risk with antiresorptive therapy is greater than that predicted by the change in BMD. As well, and in contrast, posthoc analyses of the Multiple Outcomes of Raloxifene Evaluation (MORE) study demonstrate that the increases in BMD seen with raloxifene was not associated with a proportional decrease in fracture risk. Therefore, as we discuss the skeletal effects of lasofoxifene, it is important to remember that fracture risk is always the most clinically meaningful effect, and the degree to which BTMs or BMD have changed in response to therapy may be only weakly correlated with the magnitude of fracture risk reduction.

MECHANISMS OF ACTION

SERMs and Lasofoxifene

Estrogen receptors (ER), both alpha and beta isoforms, uniquely enable the biological activity of estrogen and are the targets of SERMs. Differences in ER expression in target tissues, ER conformation with ligand binding, and the expression and binding of coregulator