Update on bazedoxifene: A novel selective estrogen receptor modulator

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Abstract: In the elderly population, osteoporosis is a significant clinical problem leading to disability and even death. Many patients remain untreated, despite effective therapies, because of patients’ unwillingness to take current therapies or inability to tolerate the therapies. For this reason, ongoing research continues to search for more effective and tolerable osteoporosis agents. Bazedoxifene is a selective estrogen receptor modulator (SERM) currently in development for osteoporosis prevention and treatment. A new drug application (NDA) for postmenopausal osteoporosis prevention was recently submitted to the FDA. Preclinical and clinical studies with bazedoxifene demonstrate more tissue selectivity than other SERMs. In particular, bazedoxifene has minimal if any agonist activity in the uterus and is able to antagonize effects of estrogen on the uterus. Animal studies and early clinical studies suggest effects in the bone similar to other SERMs with prevention of postmenopausal bone loss. Until more data on efficacy and safety are published, however, its role in osteoporosis is unknown.

Keywords: osteoporosis, bazedoxifene, selective estrogen receptor modulator, postmenopause, prevention

Management of osteoporosis

Osteoporosis, most often resulting from accelerated bone resorption, leads to low bone mass and increased susceptibility to fragility fracture (Biskobing 2003). As the number of elderly increases in our population the prevalence of osteoporosis increases. In the United States, 8 million women and 2 million men have osteoporosis (National Osteoporosis Foundation (NOF) 2006). Osteoporosis poses a significant health problem worldwide; a 50 year old postmenopausal woman has a 40–50% risk of having an osteoporotic fracture in her lifetime (NOF 2006; Epstein 2006). Osteoporotic fractures can lead to significant morbidity and mortality. Hip fractures have the most substantial consequences, resulting in loss of independence in up to 50% of patients (Schurch et al 1996; NOF 2006). In addition there is up to 24% mortality in the first year after a hip fracture (Chrischilles et al 1991; Myers et al 1991; Block and Stubbs 1997). The cost to the health care system of treating hip fractures alone is substantial. Treatment of osteoporosis, thus, is aimed at preventing osteoporotic fractures, especially hip fractures. Management of postmenopausal osteoporosis to prevent fractures includes lifestyle changes, weight bearing exercise (McClung et al 1996; Henderson et al 1998), calcium and vitamin D supplementation (Epstein 2006), and pharmacologic therapy.

The majority of pharmacologic agents for osteoporosis are antiresorptives, acting to inhibit osteoclast development or action. Current antiresorptives for osteoporosis treatment include bisphosphonates, the selective estrogen receptor modulator (SERM) raloxifene, hormone replacement therapy (HRT), and calcitonin. The only available anabolic agent is teriparadite (recombinant PTH 1–34). Bisphosphonates are potent antiresorptives and currently are the mainstay of osteoporosis therapy. Both alendronate
states that stimulates bone formation. Teriparatide has been presently the only osteoporosis agent available in the United nonvertebral fractures (Chestnut et al. 2000). Teriparatide is vertebral fractures 33% but did not demonstrate a decrease in Osteoporotic Fractures trial nasal calcitonin decreased ver-
disease and breast cancer, HRT is not routinely recommended including increased thromboembolic disease, cardiovascular
But because of potential adverse outcomes noted in WHI, decreased 34–39% and vertebral fractures decreased 38%. In two Vertebral Efficacy with Risedronate Therapy (VERT) studies risedronate decreased vertebral fractures 41–49% after 3 years of treatment (Harris et al. 1999; Reginster et al. 2000). Nonvertebral fractures decreased 30%–40% after 3 years therapy in the VERT study (Harris et al. 1999) and a separate hip fracture study (McClung et al. 2001). Ibandronate is the newest bisphosphonate approved for prevention and treatment of osteoporosis. Phase III studies demonstrated a significant 50% reduction in vertebral fractures with either daily or intermittent dosing (Chestnut et al. 2004; Delmas et al. 2004). However, in the overall group, no reduction in nonvertebral fractures was seen. In the group at highest risk for hip fracture, with a femoral neck T score less than –3, daily treatment led to a 69% decrease in nonvertebral fractures (Delmas et al. 2004). Oral bisphosphonates, however, are hampered by poor gastrointestinal absorption and risk for esophageal irritation or ulceration (Epstein 2006). Because of the poor absorption and to avoid prolonged esophageal exposure, patients are required to take bisphosphonates fasting, in an upright position, with a full glass of water. These requirements often hamper compliance. Ibandronate has been approved for intravenous administration and can be used in those unable to tolerate or absorb oral bisphosphonates (Epstein 2006). In the Women’s Health Initiative (WHI) HRT was shown to be an effective treatment for osteoporosis (Ros-souw et al. 2002; Anderson et al. 2004). Hip fractures were decreased 34–39% and vertebral fractures decreased 38%. But because of potential adverse outcomes noted in WHI, including increased thromboembolic disease, cardiovascular disease and breast cancer, HRT is not routinely recommended for osteoporosis treatment. In the Prevent Recurrence of Osteoporotic Fractures trial nasal calcitonin decreased vertebral fractures 33% but did not demonstrate a decrease in nonvertebral fractures (Chestnut et al. 2000). Teriparatide is presently the only osteoporosis agent available in the United States that stimulates bone formation. Teriparatide has been shown to significantly decrease vertebral and nonvertebral fractures by 65% and 53% respectively (Neer et al. 2001). Teriparatide use is currently approved by the FDA for 2 years of therapy (Epstein 2006). Product labeling for teriparatide currently includes a black box warning due to development of osteosarcoma in rats exposed to lifelong therapy (Forteo package insert).

Raloxifene is the only SERM currently FDA approved for prevention and treatment of osteoporosis. SERMs have been developed to have estrogen agonist effects at the bone with antagonist effects at the breast and uterus (Miller 2001). The effects of raloxifene on bone density and metabolic bone markers are generally more modest than that seen with bisphosphonates. This raises the question of whether SERMS have selective effects on trabecular versus cortical bone (Epstein 2006). In the large osteoporosis fracture study, Multiple Outcomes of Raloxifene Evaluation (MORE), vertebral fractures were decreased 37% after four years of raloxifene, 60 mg daily (Delmas et al. 2002). A decrease in nonvertebral fractures was not seen; however, the study was not powered to detect an effect on hip fractures. Raloxifene is generally well tolerated, however there is an increase in hot flushes associated with its use. In addition, there is a 3-fold increase in venous thromboembolic events associated with raloxifene use (Epstein 2006). Recent results of the Raloxifene Use for the Heart (RUTH) trial confirmed the results of the MORE trial with a 35% decrease in vertebral fractures but no significant effect on nonvertebral fractures (Barrett-Connor et al. 2006). The RUTH trial did demonstrate a 33% lower incidence in breast cancer. However, there was no significant effect of raloxifene on any cardiovascular outcome despite improvement in the lipid profile. In addition there was a 44% higher rate of venous thromboembolic events in the raloxifene group. Finally, the rate of fatal strokes was increased 49% in the raloxifene group. The decision to use raloxifene for management of osteoporosis has to weigh the beneficial effects on vertebral fractures and breast cancer against the risk for venous thromboembolic events or fatal stroke.

Numerous SERMS besides raloxifene are in development including arzoxifene, bazedoxifene, and lasofoxifene (Biskobing 2003). SERMs function by binding to the ligand binding domain of the estrogen receptor, but because of conformational differences have varying effects on coregulatory proteins associated with tissue-specific gene transcription (Miller et al. 2001). By altering the side chains on SERMs, binding and selectively are affected. In September 2005, the FDA gave Pfizer a non-approvable letter regarding...
lasofoxifene for postmenopausal osteoporosis prevention and in December 2005 gave a non-approvable letter for treatment of vaginal atrophy (Pfizer financial statement 2005). A new drug application (NDA) for bazedoxifene was submitted to the FDA in June 2006.

**Pharmacology and pharmacokinetics of bazedoxifene**

Bazedoxifene is a novel, non-steroidal, indole-based SERM currently under development by Wyeth Pharmaceuticals (Gruber and Gruber 2004). It was developed using raloxifene as a template with the benzothiophene core substituted by an indole ring (Gruber and Gruber 2004). Bazedoxifene binds to both ERα (IC₅₀ 23 ± 15 nM) and ERβ (IC₅₀ 89 ± 159 nM) with high affinity (Miller et al 2001). However, in vitro studies have demonstrated selective effects of bazedoxifene compared to estrogen. In cultured breast cancer (bMCF-7) cells bazedoxifene does not stimulate ERα mediated transcriptional activity and acts as an antagonist to estradiol (Miller et al 2001). Similar results are seen in other cell lines including CHO (ovarian), HepG2 (hepatic) or GTI-7 (neuronal) with bazedoxifene having no ERα agonist activity and acting as an antagonist to estradiol action (Komm et al 2005). However, bazedoxifene agonist activity can be seen with the hepatic lipase promoter with an EC₅₀ of 100 nM compared to estradiol which has an EC₅₀ of 26 nM. In contrast, raloxifene does not have a detectable agonist effect on the hepatic lipase promoter (Komm et al 2005). Several pharmacokinetic studies have been performed in normal women. In a study designed to evaluate the metabolic clearance of ¹⁴C)bazedoxifene, a single 20 mg dose was given to six postmenopausal women. Metabolism of the drug was via glucuronidation with the major route of excretion via the feces (Chandrasekaran et al 2003). To study the bioavailability of bazedoxifene two oral formulations, a 10 mg tablet and two 5 mg capsules, and a 3 mg IV formulation were given to 18 postmenopausal women in a 3-way crossover design. Blood samples were collected for 168 hours after each dose. Each period was separated by 2 weeks. The absolute bioavailability of bazedoxifene was 6.2% for both oral formulations (Patat et al 2003). Finally, a study evaluated the longer term pharmacokinetics of multiple doses of bazedoxifene. In a randomized, crossover study 23 postmenopausal women were given multiple doses of bazedoxifene (5, 20, 40 mg) for 14 days. Maximum concentration was achieved in 1–2 hours and t½ was approximately 28 hours. Protein binding was greater than 99%. Steady state concentrations were achieved by day 7 (Ermer et al 2003).

**Efficacy studies**

Preclinical studies have evaluated effects of bazedoxifene on the bone and the breast as well as potential adverse effects on the uterus. In an immature rat model, bazedoxifene at a dose of 0.5 mg/kg increased uterine wet weight 35% compared to an 85% increase with raloxifene at the same dose and a 300% increase in uterine weight with ethinyl estradiol at a dose of 10 µg/kg (Komm et al 2005). Despite the significant increase in uterine weight with bazedoxifene treatment, there was no evidence for epithelial cell hyperplasia or myometrial hyperplasia compared to estradiol which stimulated more than a 3-fold increase in luminal cell height. In a similar immature rat study, 10 ug and 100 ug doses of bazedoxifene did not increase uterine wet weight and also was able to prevent the increased uterine wet weight seen with administration of 1 ug of estradiol (Miller et al 2001). Further studies in ovariectomized rats have demonstrated dose-dependent effects of bazedoxifene on bone similar to estrogen (Kharode et al 2005, Komm et al 2005). Ovariectomized rats treated with 0.3 mg/d bazedoxifene displayed maintenance of bone mass and bone strength similar to effects seen with 2 µg/d ethinyl estradiol, 3 mg/d raloxifene, or sham operated animals (Komm et al 2005). In addition, total cholesterol levels were significantly lower with bazedoxifene treatment than in vehicle treated animals. To evaluate the potential effects of bazedoxifene on hot flushes, a morphine-addicted rat model of vasomotor changes and thermoregulation was used. In this model estradiol prevents a rise in tail skin temperature induced by naloxone (Komm et al 2005). Bazedoxifene does not act as an estrogen agonist in this model. With high dose bazedoxifene (10 mg/kg) the effect of estrogen is abrogated. However, with bone sparing doses of bazedoxifene there is no antagonism of estrogen effects on vasomotor instability. Further evaluation of the bone sparing effects of bazedoxifene has been done in a monkey model. Ovariectomized monkeys were treated with placebo or increasing doses of bazedoxifene (0.2, 0.5, 1, 5, or 25 mg/kg/d) for 18 months. Treatment with the highest doses of bazedoxifene resulted in maintenance of BMD at the spine and proximal femur at pre-ovariectomy levels. Biomechanical strength, mineralization, and structural parameters were not adversely affected by bazedoxifene treatment (Smith et al 2005).

There have also been animal studies evaluating the effects of combination treatment with estrogen and bazedoxifene. An immature rat model and 6 week ovariectomized rat model were treated with a bone sparing dose of CEE alone or in combination with bazedoxifene to evaluate effects on bone, uterus, and vasomotor instability (Komm et al 2003a; Komm...
et al 2003b). 7–10-fold the bone sparing dose of bazedoxifene was needed to inhibit the effects of CEE on the uterus (Komm et al 2003a). However, this dose of bazedoxifene did not interfere with the improved vasomotor control elicited by CEE. In a separate study ovariectomated rats were treated with CEE (2.5 mg/kg) alone or in combination with bazedoxifene (1–3mg/kg), lasofoxifene (0.1–1 mg/kg), or raloxifene (1–10 mg/kg) (Komm et al 2003b). After 6 weeks bone mineral density was similar in all groups. However, only the bazedoxifene was able to inhibit the increased uterine wet weight associated with CEE treatment.

There are no published studies on the results of clinical osteoporosis fracture trials comparing bazedoxifene to placebo. Results of a phase II study have been presented at the American Society for Bone and Mineral Research in 2001. 494 healthy, postmenopausal women were randomized to 3 doses of bazedoxifene, placebo, or raloxifene for 3 months. A significant decrease in metabolic bone markers was seen with bazedoxifene treatment compared to placebo (Ronkin et al 2001). The decrease in metabolic bone markers was comparable to the effect seen with raloxifene. A similar study in Chinese women was presented at the 2003 annual meeting of the International Osteoporosis Foundation. In this study 275 postmenopausal women were randomized to bazedoxifene (20 mg or 40 mg) versus placebo for 3 months. Both doses of bazedoxifene resulted in a significant decreases in metabolic bone markers: urine CTX decreased 37%–42% compared to 25% with placebo; serum CTX decreased 34%–38% compared to 18% with placebo; urine NTX decreased 18%–30% compared to 13% with placebo and osteocalcin decreased 20% compared to 7% with placebo (Ling et al 2003). The effect of combination therapy with bazedoxifene plus conjugated equine estrogen (CEE) was evaluated in a phase II study. Women were treated with CEE alone or in combination with 10 or 20 mg of bazedoxifene. The increase in endometrial thickness was 3mm with CEE but only 1.5 mm and 1mm with the addition of 10 or 20 mg of bazedoxifene. Furthermore, the addition of bazedoxifene to CEE did not negate the decrease in hot flashes expected with CEE therapy (Gruber and Gruber 2004). Large phase III osteoporosis prevention and treatment studies are completed but results are not yet published. In addition phase III studies evaluating a combination of bazedoxifene plus CEE for osteoporosis treatment or menopausal symptoms are currently ongoing. Combination bazedoxifene/CEE is being pursued to provide the benefits of estrogen and a SERM on bone and lipid metabolism while avoiding increased hot flashes and the potential for breast and endometrial cancer.

**Safety and tolerability**

The effect of bazedoxifene on the endometrium has been evaluated. In a dose-ranging double-blind, randomized, placebo controlled study, 600 postmenopausal women were treated with bazedoxifene doses ranging from 2.5 mg to 40 mg, 0.625 mg CEE, or placebo for 6 months (Ronkin et al 2005). Change in endometrial thickness after 6 months of treatment with bazedoxifene was not significantly different than placebo. On endometrial biopsy there was no evidence for endometrial hyperplasia. In addition, bazedoxifene was well tolerated; no women withdrew from the study due to hot flushes, leg cramps, or uterine bleeding. There was one case of superficial thrombophlebitis. Another study evaluated breast pain. 236 postmenopausal women were randomized to bazedoxifene (20 or 40 mg), or placebo for 6 months. The incidence of breast pain was not different compared to placebo in the 20 mg group and was significant lower than placebo in the 40 mg group (Boudes et al 2003).

**Conclusion**

In conclusion, bazedoxifene appears to have improved selectivity compared to other SERMs. Preclinical and clinical studies suggest little to no stimulatory effects on uterine tissue and the ability to antagonize estrogen uterine effects. In addition, from the few published clinical studies available, bazedoxifene does not appear to increase hot flashes. Similar to raloxifene, in vitro studies suggests inhibitory effects at the breast although no long term clinical data has yet been released on effects on breast cancer rates. There is currently not enough published data to assess bazedoxifene’s effect on bone metabolism in postmenopausal women or the rate of adverse effects such as venous thromboembolic events. Until more data on efficacy of bazedoxifene in osteoporosis prevention and treatment is published, its role in osteoporosis management cannot be determined.

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