Bazedoxifene: literature data and clinical evidence

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Summary

A Multidisciplinary National Panel of Experts in the management of Menopause and Postmenopausal Osteoporosis was created to determine the specific positioning of Bazedoxifene acetate (BZA), a third-generation selective estrogen receptor modulator (SERM), in the field of available therapeutic options in prevention and treatment of postmenopausal osteoporosis.
There are various therapeutic options in prevention and treatment for postmenopausal osteoporosis, but nevertheless the problem of osteoporosis and osteoporosis-related fractures is not yet resolved today.
In view of this unmet medical need, to have new treatments with efficacy and safety profile so good to therapeutically manage even larger groups of population is the conceptual basis to reduce the devastating impact of this disease on individual's morbidity and mortality, and on public health expense.
The Panel has, moreover, pointed up the need to increase the awareness about the issue "osteopenia" as a risk factor for fracture to consider in daily clinical practice and the opportunity to evaluate fracture risk using an adequate algorithm (for example, FRAX®, deFRA®), which integrates the result obtained by densitometry (Bone Mineral Density, BMD) (1, 2) and clinical risk factors, in order to consider threshold values for pharmacological intervention.
As for prevention and treatment and different groups of age in women's life, it is evident as in the group ranging in age 50 to 65 years the reference Specialist may be the Gynecologist, as the Woman's doctor, even if other Specialists could be interested (Endocrinologist, Rheumatologist, Internist, General Practitioner, or other Specialist who is seeing a patient with osteopenia/osteoporosis). The involved Specialist, necessarily, has to make preventative and/or therapeutic strategies for osteopenia/osteoporosis.
After the publication of the study Women's Health Initiative (WHI) in 2002 (3), there was a decrease in applying Hormonal Replacement Therapy (HRT) or Hormone Therapy (HT), that even if is prescribed for climacteric symptoms (hot flushes, night sweats, etc.) can prevent bone loss and reduce osteoporosis-related fracture risk. The lower use of HRT (HT) has increased and still increases the risk of developing, in postmenopausal women, osteopenia and osteoporosis, with increased fracture risk, as it is demonstrated by N.O.R.A. Study (National Osteoporosis Risk Assessment) published in 2004 (4).
On the other hand, the different treatments available for osteoporosis therapy, significantly decrease the relative risk of osteoporosis, but the percentage of non-treated or under-treated patients remains high. Thus, it is still fundamental to have at disposal further treatments with proven efficacy in preventing and treating osteopenia and osteoporosis in everyday clinical practice.

KEY WORDS: osteopenia; osteoporosis; SERMs; Bazedoxifene.

Introduction

Bazedoxifene acetate (BZA) is a third-generation Selective Estrogen Receptor Modulator (SERM) (Figure 1); its molecule was developed based on raloxifene's model, replacing benzothiophenic core with an indolic ring (5). BZA can interact with estrogen receptors (ERs) alpha and beta, in all tissues that contains them, as bone, breast, uterus, vessels, and liver; the binding affinity is slightly greater for ER-alpha versus ER-beta (6). Mean half-life is

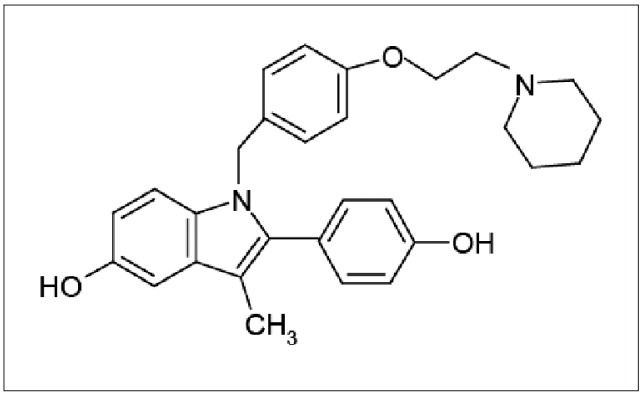

Figure 1 - Chemical structure of Bazedoxifene.

28 hours and maximum concentration (Cmax) is reached in 1-2 hours after oral administration; BZA is mainly excreted by feces (84.7 %), while renal excretion is negligible (7); the main metabolic pathway is glucurono-conjugation; steady-state is reached after about 2 weeks of oral administration.

SERMs (8) are compounds acting as an estrogen on some tissues (for example, bone tissue) and as an antiestrogen on other tissues (for example, breast, uterus), based on relative distribution of subtypes of ER (alpha and beta) and on ER-associated co-regulatory proteins (co-activators or co-repressors) activity depending on interested tissue. Moreover, the activation of different DNA sequences, the so-called Estrogen Response Elements (EREs), imply a different response, based on involved ligand (for example, estradiol, or a SERM, as BZA), also due to a different conformational changes of ligand-receptor complex, with a differentiated, subsequent, and tissue-selective agonist or antagonist effect.

Scientific evidences

a. **BZA effects on bone tissue**. In a study by Komm (9), it was demonstrated that BZA administered in different doses in rat is able to increase bone mineral density (BMD) measured by peripheral Quantitative Computed Tomography (pQCT) at tibia, with a significant difference in comparison with ovariectomized, vehicle-treated rat ($p<0.01$); moreover, BZA has showed to preserve normal bone histology, significantly different if compared to trabecular deterioration found in ovariectomized animal, but not different in comparison with bone tissue obtained from animal with ovaries. Finally, BZA increased compressive strength of vertebral body (a surrogate for a decrease in fracture incidence), with a significant difference in comparison with ovariectomized animal, and with better or equivalent value to animal with preserved adnexa.

b. **Prevention of bone loss in postmenopausal women.** In a 2-year study on prevention of bone mass loss (10), BZA was administered in postmenopausal women of mean age (± standard deviation, SD) 57.6 (± 6.5), [postmenopausal years 10.8 (±8.8)], with a lumbar or hip BMD T-score -1.0 to -2.5 (osteopenia), or with clinical risk factors for osteoporosis. Women were randomized to one of the following treatments: bazedoxifene 10, 20 or 40 mg/die, placebo, or raloxifene 60 mg/die. All patients received a supplementation with calcium (600 mg/day). Efficacy parameters evaluated included changes in comparison to baseline after 24 months of observation in vertebral (lumbar), total hip, femoral neck and trochanter BMD, and changes in bone metabolism markers. As for the results, all doses of BZA and RLX prevented lumbar and femoral bone loss, while in placebo group a significant loss in BMD at all observed sites was found. All treated groups showed significant differences in comparison to placebo group ($p < 0.001$). A significant decrease in osteocalcin and C-telopeptide plasma levels compared to baseline and placebo was observed in active-treatment groups since third month of observation and throughout the study ($p<0.001$). Adverse effects incidence, even serious, and drop-out rate due to adverse events were similar among all groups, with no significant differences between active-treatments groups and placebo group. The authors of this study concluded that a 24-months treatment with BZA prevent bone loss and decreases bone turnover in a similar way to RLX, and was generally well tolerated in postmenopausal women with normal/low BMD. Important to notice, in this study, the ability of BZA to preserve bone mass and reduce bone turnover in a population of women in the early period of postmenopause and of relatively young age (mean age: 58 years).

c. **Fracture prevention in postmenopausal women with osteoporosis.** In a 3-year study, the effect of BZA on new osteoporosis-related fracture was evaluated (11). Postmenopausal women with osteoporosis, mean age (± SD): 66.4±6.7, postmenopausal years: 19.5±8.7, were treated with BZA 20 or 40 mg/day, RLX 60 mg/day, or placebo. All subjects received a supplementation with calcium (until to 1200 mg/day) and vitamin D (400-800 units/day). Primary end-point of this study was the incidence of new vertebral fractures after 36 months of treatment; secondary end-points were non-vertebral fractures, and changes in BMD and bone turnover markers. Following the treatment, in the intention-to-treat population (n= 6847), new vertebral fracture incidence was significantly lower with BZA 20 mg/day (2.3%), BZA 40 mg/day (2.5%), and RLX 60 mg/day, in comparison to placebo (4.1%), with a relative risk reduction by 42 % (HR, 0.58; 95% CI, 0.38–0.89), 37% (HR, 0.63; 95% CI, 0.42–0.96), and 42% (HR, 0.58; 95% CI, 0.38–0.89), respectively ($p<0.05$ for all active-treatment groups vs placebo). There were no statistically significant differences between BZA-treated groups and RLX-treated group. Effect of treatment was similar between both in subjects with and without prevalent fracture. As for incidence of non-vertebral fractures, there were no significant differences among groups treated with BZA, RLX, or placebo in the general study population (n= 7492). In a post-hoc analysis on a high-risk for fracture sub-group (n= 1772), with known risk factors (femoral neck T-score ≤ – 3.0 and/or ≥ 1 mild or severe vertebral fracture or multiple mild vertebral fractures), BZA 20 mg/day showed to reduce non-vertebral fracture risk by 50% in comparison with placebo ($p=0.02$; HR, 0.50; 95% CI, 0.28-0.90), and by 44% in comparison with RLX 60 mg/day ($p=0.05$; HR, 0.56; 95% CI, 0.31-1.01). As for BMD changes, after 36 months of observation, and even since 6th months and throughout the study, groups with BZA 20 and 40 mg/day showed a BMD value significantly higher to that with placebo ($p < 0.001$), both at lumbar spine and hip. Groups treated with BZA showed decreases in bone turnover markers (osteocalcin and C-telopeptide) significantly greater than those with placebo ($p < 0.001$).

An independent re-analysis (12) of fracture data from this study on osteoporosis treatment was carried out about findings of patients treated with BZA (20 and 40 mg combined) or placebo, using FRAX® as a tool for evaluation (13), an algorithm that calculates 10-year risk for hip and major osteoporotic fractures (vertebra, wrist, humerus) based on hip BMD and clinical risk factors. Results from this re-analysis showed that BZA significantly reduced the risk of developing radiographic vertebral fractures in women with 10-year probability of fracture ≥ 6.9% and the risk of all clinical fractures in women with a 10-year probability of fracture ≥ 16%, thus demonstrating that BZA's efficacy appears to increase in parallel with the increase in fracture probability; moreover, this re-analysis showed the ability of BZA to significantly decrease non-vertebral fracture risk in comparison to placebo in women with a 10-year fracture risk ≥ 20% (14). Data from a 2-year extension (with a 5 year of total observation) (15) have confirmed 3-year results, with a sustained anti-fracture effect of BZA on new vertebral fracture in postmenopausal women with osteoporosis and on non vertebral fracture in the high-risk subgroup. Data from a subsequent 7-year extension study confirm antifracture efficacy at vertebral level with BZA 20 mg/day (16), with relative risk reduction by 30.4 % in comparison to placebo ($p<0.022$).

d. **Effects on reproductive tissues**. In the study by Ronkin et al. (17), the endometrial effects of different doses of BZA(2.5-5.0-10-20-30, and 40 mg) were evaluated in postmenopausal women in comparison to placebo. Women treated with doses ranging 2.5 to 20 mg/day did not show any change in endometrial thickness (evaluated by transvaginal ultrasound at baseline and after 6 months of treatment) significantly diffe-

rent in comparison to placebo group, while, in groups treated with 30 and 40 mg/day, the changes were significantly lower in comparison to placebo; moreover, endometrial thickness variations were inversely and significantly related to dosage; finally, no endometrial biopsy (performed at baseline and after 6 months of treatment) showed hyperplasia. Analysis of endometrial data from prevention and treatment studies showed a safe BZA use. The study by Pinkerton et al. (18) assessed safety profile of BZA about endometrium, ovary, and breast in women at risk for osteoporosis (population from the prevention study) (10), with transvaginal pelvic ultrasound (to study endometrial thickness, ovarian volume, and possible occurrence of ovarian cyst); moreover, endometrial biopsies were performed, and, finally, adverse events were recorded. Data showed that BZA intake did not lead to significant changes in endometrial thickness after 24 months in comparison to baseline. Moreover, the percentage of subjects showing an endometrial thickness or an increase in endometrial thickness greater than 5 mm was similar for all treated groups; finally, there were no endometrial hyperplasia or carcinoma in groups treated with BZA, and the rate of endometrial polyps was very low. As for the ovary, no differences among groups about ovarian volume, cysts (number and size) and cancer incidence were reported. Mastodynia and breast cancer were reported in a low number and evenly distributed among groups. The conclusion of this study was that BZA showed a favourable safety profile after 2 years of treatment in healthy, recently postmenopausal women at risk for osteoporosis. Another study (19) evaluated the effect on reproductive tissues through the observation of the population from the 3-year study (a treatment study by Silverman about treatment with BZA in osteoporotic women) (11). No significant difference in mean variation of endometrial thickness with BZA in comparison with placebo was reported after 36 months of observation. Raloxifene 60 mg/day showed a significant increase in endometrial thickness in comparison to placebo at 12 months. Reports of endometrial hyperplasia or carcinoma were rare (<1%), and similar in frequency in all groups. There were no significant changes in number and size of ovarian cysts in comparison to baseline. Incidence of breast pain, cysts and carcinoma was low, and not significantly different among groups. BZA was associated with a lower number of breast fibrocystic disease cases than raloxifene (11, 19). A retrospective analysis of a series of mammograms at baseline and after 2 years showed that BZA did not increase breast density in comparison to raloxifene or placebo (20).

e. **BZA's effect on lipid pattern.** In the 2-year study on osteoporosis prevention (6), BZA administration was associated, in comparison to placebo, to a significant reduction in low-density lipoprotein (LDL)-cholesterol ($p<0.05$) level and to a significant increase in high-density lipoprotein (HDL)-cholesterol ($p<0.05$). In the 3-year treatment study (11) BZA has increased, with a statistically significant difference in comparison to placebo, HDL-cholesterol level ($p<0.001$), while has decreased total and LDL-cholesterol ($p<0.01$ for both parameters compared with placebo in regard to baseline levels). Triglycerides levels did not show any significant differences among groups.

f. **Safety profile and tolerability**. BZA was generally well tolerated and safe both in the 2-year study on postmenopausal women at risk for osteoporosis (10) and in the 3-year study on postmenopausal osteoporotic women (11). Overall, incidence of adverse events, serious adverse events, and adverse events leading to treatment interruption in BZA-treated groups was not different from placebo. Incidence of hot flushes and leg cramps was greater in BZA-treated and raloxifene-treated groups than placebo-group, even if the majority of events was low-moderate and did not lead to treatment interruption. In this context, a study (21) has evaluated the BZA's impact in inducing hot flushes in postmenopausal women in comparison to placebo during a 12-weeks period of observation; results showed that BZA does not increase incidence, number, and intensity of hot flushes in postmenopausal women not suffering from this symptom before the start of administration compared to placebo. Cardiovascular events (cardiac disturbances, ischemic or hemorrhagic stroke) were absent during prevention study (10), and rare during the 3-year treatment study (11), with a uniform distribution among study groups, while the incidence of venous thromboembolism was greater with BZA 20 mg/day compared to placebo, even if low in absolute terms (BZA 20 mg/day: 2.8 cases per 1000 women-year; placebo: 1.7 cases per 1000 women-year). Safety and tolerability profile from the 3-year study was further analyzed, first in an 5-year extension (22), and subsequently in another observation 7-year study (16), showing that the overall incidence of adverse events, serious adverse events and adverse events leading to treatment interruption was similar between BZA-treated group and placebo group.

Remarks about BZA effects on skeleton

In the prevention study (10), BZA appear to be able to protect bone mass and to decrease bone turnover in a population of women in their early period of postmenopause and of relatively young age (mean age: about 58 years), with a low/normal lumbar and/or hip BMD**,** and clinical risk factors for osteoporosis. Therefore, BZA appears to be able to act positively on two parameters that better can explain anti-fracture efficacy of a certain treatment: BMD and bone turnover, also bearing in mind that BMD change alone cannot entirely explain fracture relative risk reduction with a therapy, and that bone turnover is thought to be an important element of bone quality (23, 24).

According to definition of Osteoporosis by World Health Organization (25), BZA can have a positive effect on bone quantity and quality in terms of improving bone strength. BZA, actually, in postmenopausal women with osteoporosis, significantly reduced, compared to placebo, relative risk of vertebral fracture and non vertebral fracture in a sub-group of at high-risk subjects.

Points of agreement

Agreement among Panel Components was reached, as for efficacy and safety data of BZA 20 mg/day, on the following points:

a. Efficacy in significantly reducing osteoporosis' development in postmenopausal women with BMD in the range of osteopenia o normal BMD and/or with clinical risk factors for osteoporosis.
b. Efficacy in significantly reducing vertebral fracture relative in osteoporotic postmenopausal women.
c. Efficacy in significantly reducing non-vertebral fracture relative risk in a subgroup of postmenopausal women at high-risk for fracture, based on a post-hoc analysis.
d. Efficacy in significantly reducing bone turnover (as indicated by a significant decrease in bone turnover markers).
e. Lack of stimulation on mammary and endometrial tissue.
f. High profile of safety and tolerability.

Clinical use of BZA

Agreement among Panel Components was reached about following areas of use for BZA. Clinical use of BZA 20 mg/day, based on scientific and clinical data, is a valid option in the following conditions:

a. Patient in recent postmenopause, with mild or no vasomotor symptoms, with BMD value in the range of osteopenia, or with normal BMD or with clinical risk factors for osteoporosis, to prevent bone mass loss.
b. Patient in late postmenopause, with osteoporosis, at vertebral fracture risk (or at high risk for non-vertebral fracture).
c. Patient in postmenopause, with a positive family story for breast cancer, with BMD values in the range of osteopenia or with normal BMD and with clinical risk factors for osteoporosis.
d. Patient who already has taken in the past hormone replacement therapy and wishes, or needs to change strategy to prevent and treat osteoporosis.
e. Patient who cannot or does not wish to take hormone replacement therapy due to contraindications at uterus or breast or because of fear of possible effects on uterus and breast.

Conclusions

Panel agreed that BZA treatment is able to decrease fracture risk related to osteoporosis, since the first years of postmenopause, with an antiestrogenic effect on uterus.
BZA is an adequate pharmacological option for women with osteopenia/osteoporosis and at risk for fracture, since the first years of postmenopause.

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