Sosa Henríquez M[1], Cancelo Hidalgo MJ[2]

1 Universidad de La Palmas de Gran Canaria - Grupo de investigación en osteoporosis y metabolismo mineral - Hospital Universitario Insular - Servicio de Medicina Interna - Unidad Metabólica Ósea

2 Universidad de Alcalá - Servicio de Ginecología y Obstetricia - Hospital Universitario de Guadalajara

Role of bazedoxifene in the treatment of postmenopausal osteoporosis

Correspondence: Manuel Sosa Henríquez - c/Espronceda, 2 - 35005 Las Palmas de Gran Canaria (Spain)
e-mail: msosa@ono.com

Introduction. Osteoporosis. Its importance

La Osteoporosis is a disease which does not have a totally satisfactory definition[1]. Since the 50s, when Fuller Albright defined it as "too little bone"[2], an incomplete concept, since it only recognises the quantitative, and not the qualitative aspect of the disease, it has been succeeded by other definitions, such as that of the American National Institute of Health (NIH) which in 1988 referred to osteoporosis as " a condition in which bone mass is reduced, increasing the bone's susceptibility to suffer fractures"[2,3], or that agreed by the Hong Kong Consensus in 1993[4]. In spite of it not being totally satisfactory, nowadays we accept the definition published by the NIH in the year 2001, an update of the 1988 version, which considers osteoporosis to be "a disease of the whole skeleton characterised by low bone mass and an alteration in bone microarchitecture which causes bone fragility, with a consequent increase in the risk of fractures"[5].

Even though the current definition addresses the fundamental problem of osteoporosis (the existence of a greater bone fragility which results in an increase in the risk of suffering fractures), and integrates the loss of quantity (bone mass) with changes in the quality of bone (microstructural changes), this definition of osteoporosis does not have a direct clinical application, because with it we cannot use it to identify those patients who suffer from the disease. Thus in day to day care, the definition of osteoporosis most used is that derived from a densitometric finding of a T-score lower than -2.5, although this has the limitation of being based exclusively on quantitative criteria[6].

Clinical situations in which the use of bazedoxifene is indicated

Taking into account the premise that bazedoxifene is indicated for treatment of postmenopausal women with osteoporosis, we are able to profile more specifically those women in whom the drug could have a more precise indication.

a. The patient with densitometric osteoporosis

Given that osteoporosis does not have symptoms in itself, and that the clinical signs are produced as a consequence of its complications, fractures[1,7], it is necessary to identify and treat the disease before the fractures appear. At the moment we only have available densitometry, which only evaluates the quantitative, and not the qualitative components of bone. According to the World Health Organisation (WHO) densitometric osteoporosis exists when the patient has a value of T lower than -2.5 in any anatomical location where the measurement is taken[6,8,9].

There is a clear relationship between a decrease in bone mineral density and an increased risk of fracture, in such a way that it is accepted globally that for each reduction in the typical deviation the risk of fracture doubles[10]. Therefore, in a woman in whom a diagnosis of osteoporosis has been established by densitometry, it is possible to initiate treatment with bazedoxifene.

should be recommended that it be taken daily at the same time so that the patient does not forget to take it. In the case in which a dose is missed, this should be administered as soon as possible, in order to continue with the normal timetable, thus avoiding double or extra doses[27].

This ease of administration facilitates therapeutic compliance with bazedoxifene, which has been demonstrated in the different clinical trials in which the abandonment rates are similar to those of the placebo[23].

As with the other drugs used for the treatment of osteoporosis, bazedoxifene should be associated with calcium and vitamin D supplements since its efficacy in this association has been demonstrated in clinical trials[12,20-23]. The drug may be taken at the same time as the supplement, there being no interference in its absorption.

Adverse effects

In general, bazedoxifene is a well-tolerated drug. The adverse effects most frequently observed in the clinical trials were breathlessness and muscle spasms, especially cramps in the legs. Less frequent but more serious are thromboembolic episodes[20].

Other adverse effects report are dry mouth, allergic reactions, increase in triglycerides, peripheral oedema and drowsiness, and an increase in transaminases, although the frequency was similar to that produced with the placebo[20,22,27].

To whom should bazedoxifene not be prescribed?

Bazedoxifene is only indicated for the treatment of postmenopausal women. It has no indication for use in premenopausal patients. Other contraindications are[27]:

- Personal history of venous thromboembolism or of an increased risk of having this pathology.
- Allergy to bazedoxifene or some of its excipients.
- Its safety in women with endometrial or breast cancer has not been sufficiently studied. There are no data regarding its use concomitant with other treatments used in breast cancer. Its use for the prevention of breast cancer is not recommended.
- Its safety in patients with severe renal and hepatic insufficiency has not been established.
- In those women with moderate of intense vasomotor symptoms it should be born in mind that bazedoxifene does not act on these symptoms, which means that they should be treated, in addition, with other specific associated drugs (for example, estrogens).

The patient with high risk of breast cancer

In the clinical studies of bazedoxifene it has not been associated with an increase in tension or pain in the breast, benign or malignant pathology, their presence being similar to that with the administration of a placebo[28]. These results are maintained after treatment in the long term over 7 years[34].

A study with digital mammography in women treated for 2 years with bazedoxifene has indicated that the treatment does not affect mammary density and therefore, does not modify the diagnostic interpretation of the mammography[29].

In breast cancer cell lines, bazedoxifene shows a differentiated pattern of genetic expression with respect to raloxifene and lasofoxifene in more powerfully antagonising the stimulator effect of the estrogens[30].

In the phase III studies the presence of breast cancer was similar for bazedoxifene, raloxifene and placebo, and the incidence of breast cancer turned out to be low and not powerful enough to properly evaluate this aspect[31,32].

Bazedoxifene and the reproductive tract

Treatment with bazedoxifene over 5 years is not associated with changes in endometrial thickness, the frequency of abnormal uterine bleeding, an increase in benign endometrial pathologies such as polyps endometrial hyperplasia or malignant pathology. Nor did it interfere with cervicovaginal cytology results[27,29,33]. In an extension of the reference study to 7 years, the group treated with bazedoxifene showed an endometrial thickness similar to that with the placebo and lower incidence of endometrial carcinoma than in the placebo group ($p<0.05$), although the number of cases was very low in both groups[34].

In recently postmenopausal women at risk of osteoporosis, treatment with bazedoxifene over two years has shown no differences in relation to the placebo in the measurement of ovarian volume, the number or size of ovarian cysts or in the presence of malign ovarian pathology[35].

Preclinical and clinical studies suggest a different and favourable uterine profile for bazedoxifene compared with other SERMs. The marked antagonist effect on the endometrium has permitted the development of the association of bazedoxifene with the estrogens, since it neutralises more powerfully than raloxifene the proliferative effect induced by the estrogens in the endometrium[36], which suggest a different endometrial profile for this SERM.

Women with associated pathology

Cardiovascular pathology is the principle cause of dysfunction in postmenopausal women. Hence the effect of an intervention on surrogate markers of cardiovascular disease is seen to have great importance.

In the lipid profile, bazedoxifene has shown a significant reduction in blood cholesterol (-3.75%), cholesterol bonded to low density lipoproteins (-3.6%) and an increase in cholesterol bonded to high density proteins (5.10%), in comparison with the placebo. The effect on the triglycerides was similar to that of the placebo. This favourable effect on the lipid profile is independent of age and has been shown both in the prevention study[28] (average age 57.6 years) and in the study with women with osteoporosis (average 65.9

years)[27]. For this reason, a woman with hypercholesterolemia may be a candidate for treatment[20], with the expectation of an additional beneficial effect of an improvement in their lipid profile.

Arterial hypertension is another important surrogate marker for cardiovascular risk. Treatment over 5 years with bazedoxifene has been shown to be similar to the placebo in its effect on blood pressure. Thus, women with hypertension could use bazedoxifene since, in addition, it does not interact with anti-hypertension drugs. Nor has there been reported to be any influence on the glycemic profile in the follow up at 5 years of treatment with bazedoxifene. Women on anticoagulant treatment, and once they have be evaluated for its indication, could be treated with bazedoxifene since there is no medicinal interaction with anticoagulant drugs like warfarin.

A new approach to the treatment of osteoporosis. Sequential therapy

One of the problems which we currently find in the treatment of osteoporosis is knowing how long should be maintained.

It should be born in mind that treatment for osteoporosis does not "cure" the disease, rather it reduces the risk of the appearance of fractures. Most of the reference studies designed to demonstrate the effectiveness of drugs in achieving this last 3–5 years. Up until now the available data has been observational, usually with a very low number of patients participating in the study, which does not maintain the methodological rigor observed during the randomised clinical trial. Therefore, in order to be reasonably safe and legally protected, we are authorised to maintain the treatment for the patients for the same time as the clinical trial lasts.

However, what do we usually do with the patients when they complete the 3-5 years? We consider whether to continue with the treatment or to cancel it, this in a patient affected by osteoporosis in whom there remains a high risk of fragility fracture and in whom, by being 3-5 years older, this risk is even higher. Up until now we have adopted individualised positions, with the agreement of the patient, and in many cases the treatment has been maintained for periods longer than those of the clinical trial, due, on the one hand, to the generally good tolerance of the drug, and on the other, the absence of reported of secondary effects or significant complications. This has been the case until relatively recently when there have started to be reports of the presence of atypical diaphyseal femoral fractures in patients in whom the treatment, usually with biphosphonates, had been sustained for a long period[37]. The risk of fracture per 100 patients per year in these patients has been established by some authors at 1.46 (CI 95%: 1.11-1.88)[38], and by others at values as high as 37.4 (CI 95%: 12.9-119, $p<0.001$)[39]. The duration of treatment with biphosphonates appears to be a significant factor in the appearance of these atypical fractures, since when these drugs, especially alendronate, are maintained over 2 years 2 cases for every 100,000 patients treated per year are observed, while when the treatment is prolonged for 8 years, the risk increases to 78 cases per 100,000 patients treated per year[37].

In the light of this we need to rethink what to do in the longer term with those patients affected by osteoporosis, especially when we are going to indicate a treatment for the first time, since, with the current data, it does not seem very advisable to maintain a treatment with powerful antiresorptive drugs beyond 5 years, and besides, we already know that the indication for the anabolic drugs, PTH 1-34 and 1-84, is that they can only be maintained for 2 years. There are no data with respect to this, but in these circumstances, in a patient with postmenopausal osteoporosis, we could consider the possibility of beginning the first years of treatment with an antiresorptive drug such as bazedoxifene which is not as powerful as the biphosphonates or denosumab, in order, some years later, to continue with one of these more powerful drugs, precisely when the patient has the greater risk of fracture by being older. We do not have studies available which support this suggestion, which should be taken only as a personal opinion of the authors.

In conclusion, bazedoxifene is a selective estrogen receptor modulator whose prolonged use, for at least 5 years, produces a reduction in the appearance of new vertebral fractures and a decrease in the risk of non-vertebral fractures in those women at high risk, considered to be those who had a BMD in the femoral neck with a T-score lower than -3.0, and/or 1 severe vertebral fracture or two moderate vertebral fractures.

It is a drug with a significant long term safety profile, and has the additional advantage of not increasing the risk of breast cancer and of reducing the risk of endometrial cancer. Therefore, it is a drug which we should consider as the first choice for the treatment of osteoporosis.

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