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Anti-resorptives in the management of osteoporosis

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Antiresorptive (or antiresorptive) drugs are the cornerstone of osteoporosis treatment. For decades, they have been considered the first step in treating this disease, although more recently some have been discontinued as indication. Others do not always have to be used as the first therapy in the current sequential treatments supported by the main scientific societies. There are five classes of purely antiresorptive drugs: bisphosphonates (BF), estrogen, selective estrogen receptor modulators (SERMs), calcitonin, and monoclonal antibodies against the activating receptor for nuclear factor κB ligand (RANKL) such as denosumab. For its part, a dual-action antiresorptive and osteoforming drug (strontium ranelate) was widely used from 2004 until its marketing cessation in 2017 in Europe for the reasons that will be detailed later. The treatments to be developed here are based on studies in postmenopausal women, although they can be extrapolated to men and to glucocorticoid-induced osteoporosis, although with less evidence[3].

While some of the antiresorptive agents alter bone remodeling markers by acting on the RANK-L pathway (estrogens, SERM, denosumab and tibolone), others have direct effects on osteoclasts as we will now see (calcitonin and bisphosphonates).

Concerns about the safety of antiresorptive drugs have increased in recent years due to the appearance of osteonecrosis of the jaw (ONJ) and atypical fractures of the femur in BF treatments, thromboembolic venous events and fatal strokes in those treated with raloxifene, fractures Multiple vertebral bodies after discontinuing treatment with denosumab and some other adverse events that have led to the suspension of the drug (strontium ranelate and estrogen therapy). Many of these adverse effects depend on the duration of therapy and the presence or absence of adequate sequential therapy.

Here we list and describe the main antiresorptive drugs used in routine clinical practice:

Table 1. Grade of anti-fracture evidence of antiresorptive drugs according to the grades of recommendation of the Oxford Center for Evidence-Based Medicine

Drugs	FV	FNV	FC	Special features
Alendronate	A	A	A	
Risedronate	A	A	A	
Etidronate	A	No	No	No indication
Ibandronate	A	B*	No	In Spain only v.o
Zoledronate	A	A	A	
Denosumab	A	A	A	
Raloxifene	A	No	No	
Bazedoxifene	A	B*	No	
Calcitonin	A	No	No	Retired for OP
Strontium	A	A	A	Retired. Dual action
Estrogens	A	A	A	No indication

A: highest grade of recommendation based on consistent randomized CT; B: second grade of recommendation, based on a cohort or case-control study; *: post hoc studies.
Modified from Sosa et al.[2]

Calcitonin

This is a peptide hormone derived from parafollicular or C cells of the thyroid that inhibits the activity of osteoclasts. It was discovered in 1961 by Copp et al. by considering its hypocalcemic effect in cattle. Synthetic or recombinant human or other animal species (eel, pig or salmon) have been used, of which salmon is the most powerful and therefore most used. The mechanism of action is through the inhibition of osteoclastic resorption and the homeostasis of Ca^{2+}, a powerful hypocalcemic agent. Although at present there is no indication for the use of this hormone in treating osteoporosis in its intranasal presentation (it only slightly increases the number of tumors when used over a long time period), preparations for subcutaneous administration can continue to be used in patients to prevent bone loss associated with prolonged immobilization. For this reason, it has a place in this section. Other uses of the subcutaneous form include treatment of Paget's disease of the bone and hypercalcemia of tumor origin. The recommendations are that the time of use be limited to the shortest possible period.

Tibolone

It is a synthetic hormone that can act as estrogen, progestin and testosterone in different body tissues[5]. It is not more effective than hormone replacement therapy in terms of bone effects or climacteric symptoms and prevents bone loss while maintaining skeletal integrity in postmenopausal women. Its safety is questioned because it increases the risk of breast cancer in women who have already suffered from this. It increases the risk of stroke in women over 60 years of age.

Estrogens *(Hormone replacement therapy)*

Estrogen deficiency (ES) is a key factor in the pathoge-

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nesis of postmenopausal osteoporosis (PMO). ES play an important role in the functioning and maintenance of the skeleton, acting on the induction of osteoblastic cells and inhibiting the production of pro-resorptive cytokines such as IL-1 and IL-6, the activating receptor for nuclear factor kappa-b (RANK) and osteoprotegerin (OPG) by osteoblast cells. They reduce the number of osteoclasts in vivo, suppressing their precursors.

They were used for many years as a treatment for estrogen deprivation symptoms in menopause. In Spain they are indicated in the prevention of PMO with a high risk of fracture in women in whom other types of therapies are contraindicated.

HRT has been a first-line treatment due to its efficacy in preventing VF and CF. However, the WHI (Women's Health Initiative) clinical trial conducted in the United States to verify the risks and confirm the benefits of hormone replacement therapy, was interrupted after 5 years (it was designed for 8.5 years), since in women treated with a certain type of combined hormonal therapy (equine estrogens and medroxyprogesterone), provided evidence that the benefits (decrease in colorectal cancer and hip fractures) did not outweigh the risks (increased risk of invasive breast cancer, cerebrovascular accidents, coronary heart disease and thromboembolic disease[13]).

They have shown potential in VF, FNV and hip. As side effects, cardiovascular complications, thromboembolic phenomena and an increased risk of breast cancer stand out, which has led to discourage its use in both prevention and treatment.

Bisphosphonates

Bisphosphonates (BF) have been known for many years. At first, its use was limited to avoiding the deposit of calcareous salts in the pipes. Many years passed until they were used in humans. They all have in common the chemical structure of pyrophosphate (carbon atom sandwiched between two phosphorus atoms). The first to be used, almost 40 years ago, were the first generation bisphosphonates (etidronate, pamidronate and clodronate), their common characteristic is that they do not have any nitrogen atom, which is why they are also called non-amino BF. Most of them are no longer in use today.

Subsequently, BF with an incorporated nitrogen atom (amino-BF) were developed with a potency 100-100,000 times higher than etidronate. Alendronate, risedronate, ibandronate and zoledronate belong to this group.

The mechanism of action of all of them is by reducing bone resorption by inhibition of osteoclasts (Oc) and increasing intestinal calcium reabsorption. On the Oc they produce an inhibition of their differentiation and an increase in their apoptosis. Likewise, they inhibit the integrins that are responsible for sealing the wavy edge of the Oc on the bone surface, thus producing an equalization of the pH and blocking its destructive action on the bone. In particular, amino-BFs activate an enzymatic system derived from proteases (caspase) that induces an early apoptosis of Oc. It also has a cross effect with statins by interfering with the metabolic chain of mevalonic acid, a precursor of cholesterol.

Regarding their pharmacokinetic properties, BFs are absorbed in a very small proportion (around 1%) of the administered oral dose, therefore they should not be administered with any type of food or drink that interferes with their, already erratic, absorption. Recently, a gastro-resistant formulation of risedronate has been marketed that does not need to be administered on an empty stomach. The plasma half-life is short (approximately 1 hour) and 20% of the drug is incorporated into bone tissue and the rest is eliminated in the urine. The incorporation into the bone is very strong, calculating about 10 years of apposition to the bone tissue, which may condition some of its secondary effects due to increased secondary mineralization to the detriment of the primary one.

They also have effects on the osteocytes responsible for the response to mechanical stimuli and the early detection of microfractures, preventing apoptosis induced by glucocorticoids, which is the action that contributes most significantly to the fragility and fractures of patients under steroid treatment.

BPs are the most widely used therapeutic group in the treatment of osteoporosis and can be administered orally or intravenously. They have a powerful antiresorptive effect that generates a positive balance that stops the process of bone loss. The effect of bone mineral density is most powerful in the first months of treatment. In those of oral administration they should be taken on an empty stomach accompanied by non-mineral water and should remain fasting between 30-60 minutes after taking it depending on the BF used. More recently the galenic of some of them has been modified, making fasting administration unnecessary. Even all their absorption is erratic, reaching a poor 1% under ideal conditions. The intravenous presentations do not have the gastrointestinal limitations of the previous ones, although all of them have been associated with important (although infrequent) side effects in the form of osteonecrosis of the jaw (ONJ) and atypical fractures of the femur. Always in relation to the duration of the treatments. In general, they should be avoided with glomerular filtrations below 35 ml/min[1].

The main action of the BF is on the osteoclasts that internalize the BF by endocytosis and depending on the type of BF the action is different. Non-amines are metabolized and induce apoptosis of osteoclasts. While amino BFs are not metabolized and act by enzymatic inhibition, reducing the concentration of isoprenoids and the subsequent alteration of the osteoclast brush border, preventing their tight union to the bone with equalization of the pH and alteration of their action.

In 2005, a series of patients with VNF considered "atypical" were described for the first time in patients treated for a long time with alendronate (>7 years). These are fractures of the femur after a minimal impact in the diaphyseal or subtrochanteric location and of oblique or transverse distribution. As a background, some patients developed pain in the area. The etiopathogenesis, although not clear yet, could be related to the sustained suppression of bone turnover.

Regarding ONJ, it is a complication of treatment with BP that was initially described in cancer patients receiving treatment with ev BP (zoledronate or pamidronate) but which, subsequently, has also been described in patients with OP treated with oral BP (although much less prevalent). It is a rare but potentially serious complication defined as exposed necrotic bone in the mandible, maxilla, or both for more than 8 weeks in the absence of metastasis or radiation to the area. Its incidence in cancer patients varies according to the series of 1-11% depending on the dose, duration of treatment and previous

dental status. In non-cancer patients the incidence drops to 1 case in every 10,000 patients treated. The etiopathogenesis is not entirely clear, it is postulated that it could be due to the direct effect of the BF on the tooth or to an excessive suppression of the turnover that would prevent the repair of the lesions produced by invasive dental procedures (implants, extractions, etc.). Spanish authors have described a polymorphism of the gene related to cytochrome P450-2C8 that is associated with an increased risk for ONJ in patients with multiple myeloma treated with ev BF[12].

In recent years, a trend of opinion has developed according to which, in patients with a certain number of years in treatment with BP, the suspension of these should be considered in order to avoid the two complications described above. There are several scientific societies that support this measure, based on the study of the clinical factors associated with the appearance of these complications and reaching the conclusion that the use of BP for more than 5 years could be one of those causes[2].

Several studies have shown that adherence to the different treatments for osteoporosis is low, with a 30-50% dropout in the first year. As it is an asymptomatic disease, the patient does not have a feeling of improvement and is more prone to abandoning it. The periodicity of the intake also influences compliance, it seems that those that are taken more widely are those with the best compliance rates. Thus, in the PERSIST study, adherence was compared for 6 months in women who took monthly ibandronate versus weekly alendronate, observing better compliance in those who took it monthly (56.6% versus 38.6%). Other drugs such as denosumab and zoledronate administered biannually and annually, respectively, have changed both non-compliance and patient preferences.

The half-life of circulating BFs is quite short, ranging from 30 minutes to 2 hours; however, once they have been incorporated into bone tissue, they can persist for more than 10 years. The absorption of oral BP is 1% if the patient has eaten or drunk anything other than plain water for up to two hours after treatment. They should not be used by patients with a history of gastrointestinal and esophageal diseases, inability to stand between 30-60 minutes after taking it, hypocalcaemia and patients with kidney disease (they should be used with caution in GFR <30 ml/min for risedronate and ibandronate and <35 ml/min for zoledronate and alendronate). Intravenous BP can produce acute febrile-type reactions and muscle aches, therefore, in the case of zoledronate, the patient must be abundantly hydrated before and after the infusion and paracetamol can be used for general symptoms.

Other reported side effects of BPs are; atrial fibrillation, conjunctivitis and uveitis, hypocalcemia, gastroesophageal disease, acute phase response, mesenteric panniculitis[14].

Ibandronate
It was the first BP for monthly oral use, although there is also a quarterly intravenous preparation for hospital use. It is approved for vertebral fractures, although a post-hoc study provided the reduction of non-vertebral fractures in a subgroup of patients with a T-score <-3. Compared with weekly alendronate, monthly ibandronate was equipotent in increasing bone mineral density and without differences in safety profiles[4]. The available studies limit the use of ibandronate to 3 years, and there are no efficacy or safety data after 3 years. Likewise, the effects observed in the bone when the drug is discontinued have not been published.

Zoledronate
Approved for postmenopausal, steroid, and male osteoporosis. A dose of 5 mg is administered annually in a 15-minute infusion. Reduces the risk of vertebral, non-vertebral and hip fractures. It is a safe drug, in the first infusion there may be general symptoms of malaise, myalgia and fever in up to 30% of cases, which is significantly reduced in the following infusions. There are published studies on its safety and efficacy up to 6 years[6]. It has also been shown in a study that it reduces the possibility of suffering a second hip fracture in patients who have already developed a previous one[7]. There have only been cases of osteonecrosis of the jaw in cancer patients in whom the doses used are much higher. There are published studies of up to 6 years with VF-lowering effects compared to those women who had discontinued the drug before.

Etidronate
It was the first BF to demonstrate anti-fracture efficacy in patients with osteoporosis. They produce an increase in bone mass with a reduction in the number of vertebral fractures without proven efficacy in reducing non-vertebral fractures (including the hip). It was also the first to be used in combination with hormone replacement therapy, inducing increases in bone mineral density greater than those of each drug alone, with a certain tendency to a possible greater decrease in the incidence of vertebral fractures[8]. Its uncomfortable regimen of administration in cycles (400 mg daily for 2 weeks followed by 74 days of rest and repeat) together with its lack of effect on non-vertebral fractures, led to its abandonment in clinical practice, although it still retains its indication.

Alendronate
It was the first amino-BF recorded for the treatment of postmenopausal OP. The FIT clinical trial demonstrated a significant reduction in VFs and currently has an indication in VF and FNV. The recommended dose is 70 mg per week[9]. The FACT study compared the improvement in BMD and the decrease in bone remodeling markers in two randomized groups of alendronate and risedronate, the results being favorable to the alendronate group, although without mentioning the reduction of fractures. Regarding the duration of treatment with alendronate, there are studies that show the advantages of continuous use for 10 years compared to 5 years. Although the concept of "therapeutic holidays" (from English drug holiday) has been intrinsically related to BP in general, there is no clear consensus regarding its usefulness and experts recommend evaluating each patient with BMD and with markers of remodeling and acting based on the changes of those surrogate markers. It has an indication in postmenopausal osteoporosis, male and glucocorticoid-induced (not in Spain) although there are studies that confirm its efficacy. The authors of a meta-analysis of 11 clinical trials that included 12,068 women demonstrated that oral alendronate (10 mg daily) reduced the RR of VF by 45%, HR by 40%, and FNV by 16% versus placebo[10].

Alendronate is a safe drug, the most frequent side effects are gastrointestinal (retrosternal burning or burning, discomfort and abdominal pain) in more serious but rare cases, GI bleeding has been described. It has a 10-year safety study and when it is suspended it has a certain residual effect that allows a "therapeutic vacation" for a period of 1-2 years after having been 4-5 years of continuous treatment.

The NNT (necessary number of cases to treat to prevent a fracture) of alendronate is 24.

Risedronate

It was the second BF recorded, it differs chemically from alendronate by the existence of a nitrogen atom that is incorporated into the pyridinoine ring. In the clinical trial (VERT) the dose used was 5 mg per day. It has an indication in VF, FNV, CF, OP of the male and induced by GC. There is a monthly dosage of 150 mg that favors therapeutic compliance. In a systematic review of 7 clinical trials that included 14,049 women, risedronate at a dose of 5 mg per day was associated with a 39% reduction in VF, 26% in PK, and 20% in FNV[11].

In turn, it has a study specifically designed for hip fracture that yielded 30% protection data for HR (RR 0.7; 95% CI 0.6-0.9). This protective effect became evident 18 months after initiation of therapy. There are 7-year safety studies. After 3 years of treatment, a reduction in the risk of fracture persists that lasts 1 year, so a therapeutic vacation could be applied for that period of time.

The NNT for risedronate is 29, somewhat higher than that for alendronate.

Ibandronate

Approved in Spain for the treatment of postmenopausal OP at a dose of 150 mg in monthly tablets. It was the first BP available for intravenous infusion on a quarterly basis (3 mg). It reduces the risk of VF without prospective studies showing reduction of VF or HR. The side effects are similar to those of the other groups of BP (except in its intravenous dosage where the GI have not been described). The studies are limited to 3 years of use, so that would be the maximum duration of treatment because there is no data beyond that, nor of the effects observed in the bone when suspending it.

Selective estrogen receptor modulators (SERMs)

SERMs are non-steroidal molecules that compete for estrogen receptors (ERs) which are nuclear hormone receptors that function as ligand-dependent nuclear transcription factors. There are two types of RE, alpha and beta. Alpha is almost always activating, and beta can inhibit the action of alpha by forming a heterodimer with it. Tamoxifen and raloxifene are antagonists of beta ERs, and may act as partial agonists of alpha ERs. But ERs can act in the absence of estrogens, responding to growth factors (epidermal growth factor) at their extracellular membrane receptors. This alternative mechanism is of utmost importance in resistance to tamoxifen treatment in breast cancer. Receptors for epidermal growth factor HER2 are the target of trastuzumab treatment of this breast cancer.

The mechanisms by which SERMs exert antiresorptive effects on bone are unknown. Although it is known that this mechanism of action is mediated by binding to estrogenic alpha and beta receptors in which they compete with estradiol with an agonist or antagonist effect, depending on the type of tissue. Although there are 1st and 2nd generation SERMs (tamoxifen, raloxifene), it is the 3rd generation SERMs (bazedoxifene) that have sufficient endometrial safety to recommend their use in PM women.

Tamoxifen is indicated as an adjunct to early breast cancer surgery in women with ER + with a duration of 5 years after it. It has positive effects on the bone (in postmenopausal women, BMD increases in the lumbar spine and hip, contrary to what occurs in premenopausal women) but it lacks an indication for the treatment and prevention of osteoporosis. Among the main side effects are endometrial cancer and thromboembolic problems.

Raloxifene has an indication for the prevention and treatment of OPM, as well as for the prevention of invasive breast cancer in women at high risk of suffering it. In the MORE study observed a 30% reduction in the risk of VF. The NNT was 16. The duration was 4 years. The dose of raloxifene is 60 mg per day to reduce VF as well as FNV in a subgroup of women with previous high risk of fracture. Side effects include cramps in the LES, increased risk of VTE and climacteric symptoms.

There is a presentation in Spain combining bazedoxifene with conjugated equine estrogens, indicated for the treatment of estrogen deficiency in postmenopausal women and with a uterus in whom a progestogen cannot be used, but without an indication for osteoporosis so it has no more place in this revision.

Efficacy is maintained up to 5 years according to studies and safety up to 7 years.

Denosumab

First 100% human monoclonal antibody approved for the treatment of OPM with high risk of fracture. It is directed against RANK-L (RANK ligand) which produces a reduction in the differentiation, survival and action of osteoclasts. It also has an indication in the treatment of bone loss associated with hormonal suppression in men with prostate cancer at high risk of fractures, for steroid osteoporosis and for men. In patients with bone metastases, factors released by tumor cells result in dysregulation of the RANK-RANK-L signaling pathway, leading to bone destruction. Denosumab-mediated RANK-I inhibition suppresses osteoclast development which, in turn, reduces cancer bone destruction and slows bone tumor growth. Denosumab non-reversibly inactivates osteoclasts, deactivation that lasts throughout their life. The effect of the drug lasts for 2-5 months after administration (which is semi-annual) with a half-life of 25 days.

It is used in doses of 60 mg subcutaneously every 6 months. Reduces the risk of VF, FNV and hip with studies up to 10 years. Rare side effects include cataracts, severe infections (including skin infections), eczema, dermatitis, and rashes. Cases of jaw necrosis have been described. Recently a side effect has been observed when suspending or discontinuing the drug, it is a sudden increase in bone remodeling markers, which would lead to a rapid loss of bone mass and an increased risk of fractures, especially vertebral fractures, although have been described in other locations, being able to produce multiple VFs. This effect on markers of bone remodeling was already included in the Freedom study, where the possibility of this "rebound effect" was alerted.

Strontium ranelate
It is a divalent cation made up of an organic skeleton, ranelic acid, attached to two strontium atoms. But we leave this family for last because it is not currently marketed in Spain. Its properties have been known since the 1980s when strontium chloride caused a slight increase in osteoformation and a decrease in resorption in animal models. It was a dual-action drug, with an antiresorptive and bone-forming effect, used in women with severe PMO and in men with no indication for steroids. It was effective in reducing the risk of VF and FNV in 5-year studies. And in post hoc studies it showed a reduction in HR and up to 8 years. But after an alert from the AEMPS that declared an imbalance between its risk and benefit and stopped being marketed. It increased the risk of cardiovascular and thromboembolic disease. Cases of DRESS syndrome (drug rash systemic eosinolphilia symptoms), some of which were fatal, have also been reported.

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