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Pharmacological management of osteoporosis in postmenopausal women: The current state of the art

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ABSTRACT

Osteoporosis is a common disease that increases fracture risk. Fragility fractures bring heavy consequences in terms of mortality and disability, with burdensome health and social costs. In subjects with clinical bone fragility, the first goal is to identify the secondary forms of osteoporosis, especially in young subjects, in males and in patients who recently experienced a fragility fracture. In addition, before considering any sort of treatment, it is fundamental to check for adequate calcium and vitamin D intake, since their deficiency is the most common reason for drug failure.

In the last decade of the 20th century, several molecules have been developed and proved to be effective in achieving the true goal of any antiosteoporotic drug: fracture prevention.

In this article, we considered the most commonly prescribed antiresorptive drugs (hormonal therapy, bisphosphonates, and denosumab), the anabolic agents (teriparatide), the dual-action drugs (romosozumab), and the drugs characterized by an unclear mechanism of action (strontium ranelate) to provide physicians with useful insights for their clinical practice. We discussed the main criteria for the appropriate choice selection and management of each treatment. Finally, we addressed the current controversies related to treatment discontinuation, sequential, and combination therapy.

Keywords: *osteoporosis; bone metabolism; bone mineral density; bisphosphonates; teriparatide; alendronate; zoledronate; risedronate; clodronate; hormonal therapy; TSEC; denosumab; romosozumab; strontium ranelate; combination therapy; sequential therapy*

Osteoporosis is a chronic disease characterized by decreased bone mineral density (BMD) and a deterioration of the bone micro-architecture that leads to an increased risk of fragility fractures.[1] This condition is mainly found in postmenopausal women, but it can also affect men, patients with other comorbidities or who are receiving treatment with drugs that affect bone health (secondary osteoporosis). The definition of osteoporosis in clinical practice is based on BMD measurement assessed by dual-energy X-ray absorptiometry (DXA); the diagnosis is made when the T-score at the femoral neck or spine is 2.5 standard deviations (SD) or more below the young adults mean.[2]

In 2010, 22 million women and 5.5 million men were estimated to be affected by osteoporosis in Europe,[3] with 3.5 million new fragility fractures in the same year (610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures, and 1,800,000 other fractures).

Fragility fractures are associated with heavy consequences in terms of mortality and disability, with burdensome health and social costs.[4] Their recovery is usually slow and often incomplete.[5] For these reasons, a large proportion of fractured individuals is destined to lose function and independence and to suffer from persistent pain and decreased quality of life.[5]

Due to the progressive aging of the general population, the annual incidence of fragility fractures is expected to rise from 3.5 million in 2010 to 4.5 million in 2025.[2]

In the last three decades, pharmacological treatments of osteoporosis have shown to be effective and able to reduce the fracture risk by about 50%, with consequent benefits on the patients' health status.[4] Unfortunately, only a small proportion of them is presently receiving adequate treatment.[4]

In this article, we summarized the most relevant data regarding the requirements for treatment, different drug options, and the rationale of sequential and combination therapy. We focused on postmenopausal osteoporosis, which currently is the most studied and common form of bone fragility, with the aim of providing physicians with useful insights for their clinical practice.

This article is a narrative overview on the pharmacological treatment of postmenopausal osteoporosis. When appropriated, the personal opinions of the authors will be added in the text and explicitly pointed out as such.

We used as sources MEDLINE/PubMed, EMBASE, and Cochrane Library, from inception to 2019.

In addition, we hand-searched references from the retrieved articles and explored a number of related web sites. After discussion, we chose 68 relevant papers.

REQUIREMENTS FOR THERAPY

A careful diagnosis of the nature of osteoporosis is fundamental for a correct treatment. A large and increasing number of diseases and drugs can contribute to bone fragility[6] and these conditions often require specific treatment. For these reasons, the first goal of the physician should always be to identify the secondary forms of osteoporosis, especially in young subjects, in males and in people with recent fractures. Referral to a qualified specialist might be needed as well.

Another key requirement for therapy is an adequate vitamin D status. Recently, some large trials and meta-analyses concluded that vitamin D supplementation has no beneficial effects neither on bone health, fracture risk nor falls,[7] but these statements require a critical analysis that cannot be limited to the raw results. As a matter of fact, most of these studies investigated the effects of vitamin D supplementation in healthy (nonosteoporotic) subjects, not at significant risk for falling and, overall, without any vitamin D deficiency. In such a scenario, data suggesting positive results would be indeed unexpected. In any case, these recent papers criticized the usefulness of vitamin D supplementation with the goal to maintain or

improve musculoskeletal health in the general population, but its role in patients receiving treatment for osteoporosis is an entirely different topic. It is well-known that, in these patients, adequate calcium and vitamin D intake are essential, and their deficiency represents the most common reason for lack of response to any treatment,[5,8,9] This observation has been confirmed also in a recent large retrospective study based on Italian administrative databases.[4] The study showed once again that pharmacological treatments for osteoporosis are associated with a lower risk for both refracture and all-cause mortality to a greater extent when they are administered in combination with calcium and vitamin D.[4]

DRUGS FOR THE TREATMENT OF OSTEOPOROSIS

The main goal of the treatment for osteoporosis is to decrease fracture risk. This often implies the reduction of systemic bone loss and the stabilization or the increase of BMD.

From the last decade of the last century, several molecules have been developed and proved effective in achieving these goals.[10,11] The mechanism of action of the various drugs is defined by their relation to the bone cells on which they act (Table 1).

Hormonal Therapy

The physiologic decline of estrogens in women begins from 1 to 2 years before menopause and reaches its plateau about 1 to 2 years after the menses cessation.[12] The drop in estrogens explains the quick rise in the rate of bone resorption and therefore of bone loss, with an increase of the risk of osteoporosis.[13] In young women in whom premature menopause is induced by surgery or cancer treatments, the estrogen drop can be particularly marked and its adverse effects (AEs) on bone loss and fracture risk are therefore greater.[14,15]

Estrogens are key determinants of skeletal health due to their specific effects on bone metabolism. For instance, they inhibit bone resorption by decreasing the signaling of the receptor activator of nuclear factor-κB (RANKL), they induce gene expression and synthesis of osteoprotegerin (OPG), and they block osteoclastogenesis and promote osteoclasts' apoptosis.[15] In addition, estrogens inhibit bone remodeling and decrease the development of new basic multicellular units, probably by limiting osteocytes' apoptosis and their production of sclerostin,[15] a key inhibitor of the Wnt pathway that is involved in the pathogenesis of osteoporosis.[16]

Hormone replacement therapy (HRT) was routinely prescribed for primary prevention of osteoporosis (independently of the presence of menopausal symptoms) before the publication of the Women's Health Initiative (WHI)[17] and of the epidemiological UK-based Million Women Study.[18] The results of these studies reported an association between HRT and an increased risk of breast and ovarian cancer. However, recent evidence showed that estrogen-alone therapy was not associated with any increase in mortality[19] or

TABLE 1. Drugs Available for the Treatment of Osteoporosis Classified by Mechanism of Action

Antiresorptive drugs: reducing the osteoclastic bone resorption
• Estrogens and selective estrogen receptor modulators (SERMs)
• Bisphosphonates
• Denosumab
Anabolic drugs: increasing the osteoblastic bone formation activity
• Teriparatide
Dual-action drugs: increasing the osteoblastic bone formation activity and reducing the osteoclastic bone resorption
• Romosozumab
Drugs with unclear mechanism of action
• Strontium ranelate

in the risk of breast cancer, even in the women who carry the BRCA1 gene mutation.[20]

We need to remember that, in females who carry the BRCA1 mutation, the cumulative risk of ovarian and breast cancer by age 80 is over 40 and 70%, respectively.[21] Prophylactic salpingo-oophorectomy is currently the only strategy able to reduce the risk of both cancers. Unfortunately, the premature withdrawal of ovarian hormones induced by this surgery causes long-term AEs that can be avoided, or at least limited, with HRT without a significant increase in cancer incidence.[14,20] For this reason, there is now a large scientific consensus that hormonal therapy at menopause represents an effective prevention strategy for osteoporosis and fragility fractures, with an overall favorable benefit to risk ratio when it is started before 60 years of age and within 10 years from the last menses.[15]

The hormonal options available for the treatment and prevention of postmenopausal bone loss are HRT, tibolone, and SERMs.

The efficacy of HRT in reducing the incidence of both vertebral and nonvertebral fractures has been confirmed for almost 20 years.[22] The analysis of the intervention and postintervention phases of large clinical trials showed a different benefit to risk profile when we compare the data of estrogen plus progestin to estrogen-alone treated subjects.[23,24] These two hormonal treatments granted similar protection from fractures and similar improvement in BMD between them when compared to placebo, with a better safety profile in women with prior hysterectomy receiving the estrogen-alone treatment both during the pharmacological intervention and in the posttreatment follow-up period. Furthermore, the breast cancer and cardiovascular (CV) disease findings tended to be worse in the arm treated with the estrogen-progestin combination, while no difference was found between the placebo arm and the patients treated with estrogen alone.[24]

Tibolone, after oral ingestion, is metabolized into three active molecules: two with estrogenic action and one with androgen and progestin activities.[25] Tibolone was shown to be as effective as an estrogen–progestin combination treatment in preventing postmenopausal bone loss and it can also increase muscle strength and lean body mass due to its androgen action.[15] Similar to HRT, tibolone is recommended only in subjects under 60 years of age, because the study that involved older women (age range 60–80 years) was prematurely stopped due to the evidence of an increased risk of stroke in the treated arm.[26]

Selective estrogen receptor modulators (SERMs) are compounds with estrogen agonistic activities on some tissues (i.e., on bone) and antagonistic actions on other tissues (i.e., on breast and uterus), based on their different effects over different estrogen receptors subtypes whose distribution is specific for each target tissue.[27] At present, raloxifene (RLX), bazedoxifene (BZA) and lasofoxifene (LSX) are the SERMs with documented evidence of efficacy for postmenopausal osteoporosis.[15,28] They prevent bone loss and reduce the incidence of vertebral osteoporotic fractures in postmenopausal women.[15,28]

To date, RLX has not been demonstrated to reduce the risk of hip fractures at currently approved doses, while BZA (20 mg/die), in a post hoc analysis on a subgroup at high fracture risk, succeeded in reducing the risk of nonvertebral fracture both versus placebo and versus RLX (60 mg/die).[29] The post hoc nature of this analysis called for caution in the interpretation of the results until the publication of the 2-years extension of the same study.[30] At its conclusion, the trial confirmed the protective effect of BZA on new vertebral fractures in postmenopausal women with osteoporosis and on nonvertebral fractures in the high-risk subgroup.[30] In addition, two meta-analyses performed an indirect comparison of the protective effect of BZA versus oral bisphosphonates (BPs) and estimated a

similar efficacy on vertebral fractures and, in the subgroup at higher fracture risk, also on nonvertebral events.[31,32]

LSX has been approved in Europe for the treatment of postmenopausal osteoporosis after a 5-year placebo-controlled randomized clinical trial (RCT) showed its efficacy in decreasing the risk of both new vertebral and nonvertebral fractures (but not hip fractures).[33]

Similar to HRT, SERMs can increase the risk of venous thromboembolism (primarily deep vein thromboses), but, differently from HRT, due to their antagonist activity on the breast, SERMs may decrease the risk of breast cancer.[28] This was shown to be true particularly for RLX, which in the United States is also approved for the prevention of breast cancer.[28,34] No effect on endometrial proliferation is reported with RLX and BZA, whereas an increase of endometrial thickness, although without a real clinical significance, is associated with LSX.[33]

In our opinion, SERMs are preferable to HRT due to their better safety profile in the long-term and can be considered a viable second-line treatment for patients AEs related to oral BPs, particularly for women under 65 years of age at risk for vertebral fractures and at some risk for breast cancer.

SERMs represent also a possible first-line therapy after menopause for younger subjects who are expected to receive treatment for many years. Unfortunately, this opportunity is often difficult to seize, because hot flushes are a common AE of these drugs, especially in younger postmenopausal women within the first year of treatment.[34] For this reason, SERMs are not recommended in women with vasomotor symptoms and HRT is preferable instead.

The observation that SERMs (particularly BZA) inhibit the effects of conjugated estrogens in the uterus and mammary glands has opened the way to a new strategy for the prevention of systemic bone loss and the treatment of climacteric symptoms: the SERM-estrogen combination, now defined "tissue selective estrogen complex" (TSEC).[15,28] This strategy is noteworthy because the addition of SERMs makes the progestin unnecessary. Therefore, TSEC merges the positive clinical effects of estrogens alone (as already seen, they do not increase the risk of breast cancer), with the efficacy and improved tolerability of SERMs that antagonize their endometrial effects. Presently, the combination of BZA (20 mg/day) with conjugated estrogens (0.45 mg/day) is the only one approved in the class of TSEC. The positive clinical outcomes of large RCTs support the use of this combination therapy that can decrease the frequency and severity of hot flushes, improve symptoms of vulvar and vaginal atrophy and prevent bone mass loss, independently of the number of years from menopause.[15,34]

Bisphosphonates

BPs are the most widely used drugs for the prevention and treatment of all kinds of osteoporosis. They are approved, in both males and females, also for the treatment of glucocorticoid-induced osteoporosis (GIOP) and of antihormonal therapy-associated bone disease (i.e., androgen deprivation therapy and treatment with aromatase inhibitors).[33,35] These compounds have been used for more than 25 years and several millions of patients have been treated with BPs, and their excellent safety profile is now well established.[2,33,36] It is therefore quite unlikely that new unexpected side effects may be discovered in the future.

BPs are a large family of stable analogs of pyrophosphate with a strong affinity for bone apatite. BPs reduce the recruitment and activity of mature osteoclasts and increase their apoptosis. Consequently, they act as potent inhibitors of bone resorption and this is the rationale of their use in postmenopausal osteoporosis.[2,33,36]

Several BPs have been approved for the treatment of osteoporosis, such as alendronate (ALN), risedronate (RIS), ibandronate (IBA), and

zoledronate (ZOL). All these drugs have shown not only to increase BMD and bone strength but also to be effective on a hard endpoint such as the reduction in the fracture incidence; indeed, their registration process was based on RCTs powered to detect an effect on new vertebral fractures in patients with moderate-to-severe osteoporosis.[2,33,36]

Oral formulations are available for daily (ALN, RIS), weekly (ALN, RIS), and monthly (IBA, RIS) administration. Oral bioavailability of BPs is very low, roughly 1% of the ingested dose, and it is reduced by food (especially if rich in calcium). For this reason, they must be ingested with plain water on an empty stomach and after an overnight fast, with a postdose fast of 30 to 60 minutes.[36] A more recent (but still not widely available) delayed-release formulation of 35 mg risedronate (weekly administration) can be taken before or immediately following breakfast, with a potential improvement in adherence and persistence.[2]

Two intravenous BPs have been licensed by the European Medicines Agency for the treatment of osteoporosis: IBA (administered every 3 months) and ZOL (administered yearly). These options are particularly interesting in subjects with AEs related to oral BPs and in whom adherence to chronic treatment might be an issue. To date, comparative head-to-head RCTs with fracture incidence as endpoint are not available, but if we compare the results from each RCTs that investigated each molecule, all compounds showed to approximately halve the incidence of vertebral fractures in patients affected by postmenopausal osteoporosis.[36]

On the contrary, the efficacy on nonvertebral fractures, and particularly at the hip, differs considerably across the various BPs.[36] However, this observation can be largely explained from the different statistical power of the studies.[36]

Regarding the better results obtained with i.v. ZOL once yearly, they have been attributed to the complete adherence of i.v. ZOL during the first year of treatment (100%) versus oral BPs (<85%).[36] Despite these data, oral ALN and oral RIS are still the most commonly prescribed BPs.[2] A large case-control analysis that involved more than 90,000 patients, older than 80 years and with previous history of fragility fractures, showed that ALN significantly reduces not only the hip fracture risk (−34%) but also mortality (−12%).

Unfortunately, this treatment was also associated with a 58% increase in the risk of mild upper gastrointestinal (GI) symptoms.[37] The GI side effects are the most typical AEs associated with oral BPs and may involve a large number of users (about 25%).[6] However, of this 25%, less than 1% require hospitalization due to GI bleeding.[6]

Treatment with i.v. ZOL has also shown to decrease mortality when given shortly after the first hip fracture[38] and, as expected, without GI side effects. On the other hand, i.v. aminobisphosphonates (such as ZOL), in about 30% of patients, can induce a transient acute phase reaction characterized by flulike symptoms (fever, myalgia, arthralgias, bone pain, headache, and nausea). Usually, this undesired event occurs within 24 hours after the first drug administration and can be controlled by paracetamol or nonsteroidal anti-inflammatory and improves or disappears within 3 days.[2,6]

Major severe AEs with BPs are extremely rare. Osteonecrosis of the jaw (ONJ) is a condition characterized by long-lasting (>8 weeks) necrotic exposed bone in the maxillofacial region associated with the use of antiresorptive drugs such as BPs and denosumab (DMAb). ONJ has been described in cancer patients receiving doses of BPs (and DMAb) 10 times higher than subjects with postmenopausal osteoporosis. Indeed, in this latter scenario, ONJ is extremely rare (one case every 100,000 patients/year) and its incidence seems to be only slightly higher than the general population.[2,6]

BPs and DMAb have been associated also with an increased risk of atypical femoral fractures. Atypical femoral fractures are transverse or short

cortical oblique fractures, occasionally associated with periosteal thickening. However, this particular kind of fractures may also occur in treatment-naïve subjects. The risk seems to rise with the increase in the exposure to BPs (or DMAb) and to decrease rapidly after its cessation.[2,6,33]

In addition, atypical femoral fractures are indistinguishable from those observed in patients with other bone diseases characterized by bone fragility, such as hypophosphatasia, osteopetrosis, or osteogenesis imperfect.[39,40] All these remarks emphasize the key role of a correct diagnosis in each patient with bone fragility before prescribing any pharmacological treatment and they also suggest caution before considering a longstanding antiresorptive treatment in patients with baseline low-bone turnover states.[41]

In any case, the incidence of atypical fractures is extremely low (about 3–50 cases every 100,000 patients/year), and the excellent risk to benefit ratio of this drug class is out of the question. Indeed, we need to consider the benefit of the treatment on the much more common typical hip fractures:[42] for every 100 atypical fractures prevented by BPs, an increase of one single atypical fracture has been calculated.[43]

Caution is advised also with patients at risk of kidney impairment, given that high doses of BPs administered over a short period of time could induce or worsen renal failure. Because of the very low bioavailability of oral BPs (less than 1%), the serum concentration is so low that renal damage is an issue only for the i.v. formulation.[6] For this reason, i.v. BPs are contraindicated in patients with creatinine clearance lower than 60 ml/min.[6] For safety concerns, however, in this kind of patients also the oral formulations should be prescribed very carefully.

A possible association between BPs therapy (especially i.v. ZOL) and atrial fibrillation has been reported, but subsequent studies have produced conflicting results. Presently, the possibility of this association cannot be completely excluded.[2]

Clodronate is a relatively weak BP, widely available for the treatment of neoplastic bone disease and licensed for the use in osteoporosis in only a few countries.[2] The data about osteoporosis are not conclusive, and the evidence of its efficacy is weaker than the other BPs previously discussed.[33] Two RCTs showed the efficacy of 800 mg daily oral clodronate in both increasing BMD and reducing the incidence of vertebral fractures in women with senile, postmenopausal, or secondary osteoporosis.[44,45] In Italy, intramuscular clodronate is registered for postmenopausal osteoporosis and GIOP on the basis of few low-quality studies.[46–48]

Clodronate is usually prescribed in subjects at low fracture risk or when all the other treatments cannot be used. In conclusion, clodronate, especially when administered intramuscularly, should not be currently considered a real option for osteoporosis treatment.

Denosumab

Like BPs, DMAb belongs to the antiresorptive drugs class (Table 1). DMAb is a fully humanized monoclonal antibody that neutralizes RANKL signaling by interfering with its interaction with its receptor located on the membrane of preosteoclasts and mature osteoclasts (RANK). In this way, it impairs the recruitment, maturation, and survival of osteoclasts and leads to a stronger inhibition of bone resorption than BPs.[49] Its potency and activity at the cortical bone explain why DMAb is able to induce greater increases in BMD than BPs both at trabecular sites (i.e., at lumbar spine) and at cortical ones (i.e., hip and radius).[49] The drug is administered subcutaneously every 6 months at a dose of 60 mg. DMAb is not cleared by kidneys and therefore it can be used also in patients with renal failure.[33] DMAb is also approved for treatment in males, in GIOP and antihormonal therapy-associated bone disease.[33,35]

Long-term treatment determines sustained increases in BMD (both at the spine and at the hip), without any plateauing after 4 years of

treatment, as commonly seen with BPs. This feature could be a consequence of a greater activity on cortical bone and/or of its unique effects on Wnt inhibitors and in particular on Dkk-1.[16]

In postmenopausal osteoporosis, over 3 years of therapy, DMAb reduced the incidence of vertebral fractures (−68%), hip fractures (−40%), and nonvertebral fractures (−20%), without significant adverse events.[2,33] The yearly incidence of new fractures (both vertebral and nonvertebral) remained low also during the long extension trial that involved a subgroup of women treated for further 7 years.[2]

Due to its mechanism of action, discontinuation of DMAb therapy is associated with a rapid offset of action as soon as the drug is cleared from the plasma.[2] For this reason, the positive effects of DMAb on BMD are quickly reversible after its discontinuation, with a return to pretreatment values within 12 to 18 months, independently of the treatment duration, while bone turnover markers increase above pretreatment levels and then return to baseline values within 1 to 2 years after its discontinuation.[2]

Recently, RANKL serum levels have been shown to progressively increase after suspension of long-term DMAb treatment, and this observation may support the hypothesis of a sudden loss-of-inhibition of the resting osteoclast line after DMAb clearance.[50] This rebound effect is associated with an increase in fracture risk of vertebral fractures, while no increase in nonvertebral fracture has been reported to date.[2] Therefore, in case of DMAb discontinuation, the initiation of a different antiresorptive treatment (such as BPs) should be considered to prevent, or at least limit, this rapid bone loss.[2]

DMAb is well tolerated. Few cases of ONJ and atypical femoral fractures have been reported to date and the same considerations already discussed for BPs apply.

Teriparatide

Currently, teriparatide (TPD) is the sole anabolic drug available for the treatment of osteoporosis in Europe. TPD is the active 1–34 N-terminal fragment of parathyroid hormone (PTH) and its daily subcutaneous administration produces anabolic effects on the bone tissue. This occurs in contrast with the well-known bone catabolic consequences of chronic overproduction of PTH. As known, primary hyperparathyroidism is characterized predominantly by the overstimulation of osteoclast's activity, while daily (pulsatile) pharmacological PTH administration determines the predominance of bone formation over bone resorption due to a direct action on osteoblasts.[51] Treatment with TPD has been shown to reduce significantly the risk of vertebral and nonvertebral fractures and its use is strongly recommended in high-risk subjects and in patients with previous history of vertebral fractures.[2]

The data concerning TPD and GIOP are particularly intriguing. One clinical trial versus ALN in patients treated with glucocorticoids showed that TPD is more effective not only in improving BMD but also in reducing the incidence of vertebral fractures.[52] These results support the preferential use of an anabolic agent over a traditional antiresorptive drug in patients with GIOP. The mechanistic explanation of the clinical evidence may rely on the inhibitory effect of glucocorticoids on osteoblasts, a mechanism that, together with the increase in bone resorption, explains their severe negative effects on the quantity and quality of bone.[53] In this setting, TPD should be considered the first-line option for patients on long-term glucocorticoid treatment with low BMD or with previous history of osteoporotic fractures.

The duration of treatment with TDP is limited to a maximum of 2 years and the decline of its positive effects on bone formation (seen after 12 to 24 months) seems to be dependent on the regulation of the Wnt pathway and the overproduction of its inhibitor Dkk-1.[54]

The most commonly reported AEs of TPD are nausea, pain in limbs, dizziness, and headache.[6] In addition, cases of moderate hypercalcemia and hypercalciuria have been reported but they are

usually asymptomatic and only rarely request the cessation of the treatment.[6]

Besides TPD, other peptides of the PTH family are abaloparatide (currently still in development) and the 1 to 84 intact molecule (whose marketing authorization has not been confirmed).[2]

Overall, all these agents are contraindicated in severe kidney impairment and in all diseases characterized by increased bone turnover and/or hypercalcemia, such as primary hyperparathyroidism, Paget's disease of bone, malignancies, or bone metastasis.[2]

Studies on rats chronically exposed to very high doses of TPD have reported an increased incidence of osteosarcoma. However, the analysis of the pivotal clinical trial and the postmarketing surveillance did not show any increased risk of osteosarcoma with the doses of TPD presently used in humans (which are much smaller by relative comparison).[2,6] Unfortunately, despite these safety data, the TPD Summary of Product still includes a warning for physicians and patients about this unproven complication.

Romosozumab

Romosozumab (RMZ) is a humanized monoclonal antibody that acts by blocking sclerostin, a molecule almost exclusively expressed by osteocytes and one of the main inhibitors of the Wnt canonical pathway.[16]

As known, this pathway plays a key role in bone metabolism. On one hand, it promotes osteoblastogenesis and directly contributes to the differentiation, proliferation, and survival of osteoblasts.[55] On the other, it enhances the expression of OPG by indirectly inhibiting osteoclast-mediated bone resorption.[55] Therefore, sclerostin is an important negative regulator of bone formation with a potential key role in the pathogenesis of disuse osteoporosis.[16] In addition to its antianabolic role, it enhances the catabolic activity on the bone tissue through the up-regulation of RANKL expression.[55]

For all these reasons, RMZ represents the first true dual-action agent: it increases osteoblastic bone formation by enhancing Wnt canonical signaling and reduces osteoclastic bone resorption by unbalancing the OPG/RANKL ratio (in favor of OPG).[49]

The dual action of RMZ was already remarkable in the phase I study, in which it showed an impressive (dose-dependent) increase in the markers of bone formation (+70 to 140%), simultaneous with a less considerable, but statistically significant, dose-dependent decrease in the markers of bone resorption (−15 to −50%).[56] This interesting dual activity can explain the extraordinary effects on BMD that overtake what seen with any other osteoporosis treatment, TPD included.[49]

The unique metabolic effect of long-term RMZ treatment is limited to the first 12 months of therapy. Markers of bone formation increase immediately after the first RMZ injection and reach their peak after the first month. Thereafter, they decrease and return to baseline within 9 months and they eventually reach values significantly lower than baseline after the 12th month.[57]

Interestingly, during the second year of RMZ, the serum levels of both bone formation and bone resorption markers remained below their baseline.[57] This may suggest that, within the first year of treatment, RMZ acts as a true dual-action drug, but later on it probably works just as a bone turnover inhibitor, without any further anabolic action.

Notably, the BMD gain, which is outstanding in the first year of treatment, is less relevant during the second year of RMZ. An increase in BMD similar to the first year of treatment has been shown only in the subgroup of women who were then randomized to receive DMAb for an additional year.[57]

For these reasons, the phase III trial (FRAME trial) investigated the effects of subcutaneous monthly injections of RMZ for 12 months versus

placebo, followed by treatment with DMAb (administered in both arms).[58] The effects on fracture incidence within these 12 months were remarkable: the incidence of vertebral fractures was reduced by 73% and of clinical fractures by 36%. At 24 months, after the switch to DMAb, the incidence of new vertebral fractures remained significantly lower in the RMZ group (−75%).

AEs incidence was balanced between the groups. In the RMZ group, a single atypical femoral fracture and two cases of ONJ were reported among the 3,500 treated subjects.[58]

After the publication of the results of the RCT comparing RMZ and ALN (ARCH trial), concerns were raised about a possible increased CV risk associated with the use of RMZ.[59] The incidence of severe CV events resulted higher in the RMZ group versus the ALN group, despite a similar CV risk at baseline.[59] It should be noted, however, that RMZ was not associated with any increase of the CV risk in the previous and larger FRAME trial,[58] in which RMZ was compared with placebo. Indeed, the increase in CV events in the RMZ group might be explained by the protective CV effects of ALN (and of amino-BPs in general), as already reported several times.[60–62]

Strontium ranelate

Strontium ranelate (SrR) is an oral medication that has been approved in Europe for the treatment of postmenopausal osteoporotic women.[33] Its mechanism of action is still not completely understood, but the RCTs showed its efficacy in reducing the risk of vertebral and nonvertebral fractures respectively after 3 and 5 years of treatment.[33]

A consistent increase in the risk of venous thromboembolism has been documented in the registration trials and, during the postmarketing surveillance, rare but severe dermatological reactions were also reported, with consequent limitations to its clinical use.[6] During the long-term postapproval surveillance safety analyses, the increased risk of pulmonary embolism and myocardial infarction was confirmed and thus, in 2014, the EMA restricted its use to patients affected by severe osteoporosis who cannot be treated with different medications and in whom the risk of fracture overwhelmingly exceeds the CV risk.[6]

Treatment discontinuation

BPs, in particular ALN and ZOL, are the drugs with the most persistent "tail effect" concerning bone turnover after their discontinuation.[36] Their antifracture efficacy is only partially lost after treatment discontinuation for several months.[36] Unfortunately, the impact of the discontinuation of the other drug classes is very different.

After suspension of hormonal therapy, bone turnover and bone loss return to pretreatment levels within few weeks. Therefore, reassessment of fracture risk and of the opportunity of resuming treatment itself is strongly warranted.[63]

TPD is strongly recommended in severe osteoporosis, but the regulatory authorities limited the treatment duration to a maximum of 2 years. There is now a very large agreement about the absolute need for the start of an antiresorptive agent soon after the conclusion of the TPD treatment cycle to avoid the quick rebound on BMD.[63] Sequential administration of ALN, ZOL, or DMAb after TPD have been associated to further BMD gains; however, the effects on fracture risk reduction are to date still speculative.[33]

In patients treated with DMAb, its discontinuation is followed by an overshoot in bone turnover, with accelerated bone loss and increased fracture risk.[2] The best exit strategy to adopt after DMAb discontinuation is still unclear and large randomized and active-controlled trials are warranted to investigate this key topic. Presently, BPs are recommended by most experts as the preferable choice to prevent or at least limit the rebound effects of DMAb discontinuation.

As already discussed, RMZ has a peculiar mechanism of action and combines the stimulation of

bone formation with the inhibition of bone resorption. Unfortunately, the benefits in terms of BMD are lost after its discontinuation.[64] Hence, sequential treatment with antiresorptives is required, as it was scheduled in its RCTs.[58,59]

Sequential Therapy

In these last decades, the number of drugs available for the treatment of osteoporosis has grown exponentially. The development of novel and more potent antiresorptives (such as DMAb and ZOL), bone anabolic agents (such as TPD), and antisclerostin antibody (such as RMZ) determined a substantial growth in the field. As already discussed, the discontinuation of many of these therapies (DMAb, TPD, and RMZ) requires the initiation of another treatment in order to avoid the loss of the BMD gains. Furthermore, a treatment switch might need to be recommended also in patients who experience a new fragility fracture despite already being on osteoporosis medications, or in case of tolerability or adherence issues.

The different mechanisms of action of osteoporosis drugs strongly influence the cumulative effects of the possible sequential and/or combination approaches and should guide the physician to the choice of the correct treatment.

Hereby we will briefly discuss the different opportunities presently available for sequential therapy:

Antiresorptive agents after antiresorptive agents

Sequential treatment with different antiresorptive agents might be required when:

- a patient discontinues DMAb and there is the necessity to limit the rebound effect
- poor compliance with ongoing oral BP therapy
- occurrence of a new fragility fracture during treatment with oral BPs.

As already mentioned, to prevent or at least limit the rebound effect of DMAb discontinuation, BPs are presently considered the best choice.

Injectable treatments such as DMAb and ZOL may solve GI issues associated with oral BPs and may also improve the adherence to the treatment with their more deferred administration schedule.

In the case of new fractures occurring during treatment with oral BPs, ZOL might represent a possible choice, given its 100% adherence on the first year of therapy. DMAb might be considered as well due to its stronger inhibition of bone turnover and the greater BMD increases at all skeletal sites, even when compared to ZOL.[2]

Antiresorptive agents after agents with anabolic effects

In patients with high fracture risk, the use of anabolic drugs seems the most appropriate for its quick reduction.

As already discussed, treatment with drugs characterized by anabolic effects is limited to 12 (RMZ) or 24 months (TPD), and their benefits can be preserved only through the initiation antiresorptive agents as soon as possible after their discontinuation.[2] Therefore, prompt treatment with antiresorptives after bone anabolic agents is recommended.

Anabolic agents after antiresorptive agents

The choice of an anabolic agent as the first-line therapy is not often possible due to its high cost, but it is recommended in patients who experience a new fragility fracture despite BPs therapy. Unfortunately, there is some evidence suggesting that the effectiveness of anabolic medications might be impaired when started after prolonged exposure to antiresorptive drugs.[65] Indeed, when patients on long-term potent antiresorptive treatments are switched to TPD, hip BMD tends to decline for at least 12 months, especially when the antiresorptive is DMAb.[66] Therefore, the switch from antiresorptive drugs to an anabolic agent, a quite common scenario in clinical practice, is not currently supported by much evidence. How can we manage these patients? Combination therapy might be an answer.

Combination Therapy

The dual action of RMZ demonstrates the effectiveness of the association of strong stimulation on bone formation with powerful inhibition on bone resorption. Currently, no other drug administered alone can act in this manner, but a similar therapeutic framework could be obtained by combining two different treatments and there is evidence to support this possibility. An interesting comparison between patents who switched from ALN to TPD versus those who added TPD to ongoing ALN, showed a greater benefit of combination therapy on BMD and strength at the hip.[65]

Another small study compared the changes of bone turnover markers in patients treated with DMAb versus TPD versus a third therapeutic scheme: TPD added to ongoing DMAb (TPD was started 3 months after DMAb).[67] The results showed that the effects of TPD on bone turnover markers were not blunted by prior and concurrent DMAb administration. In the combination arm of the study, the increase in markers of bone formation was observed quite earlier than the increase in the ones of bone resorption.[67] This remark supported the hypothesis of a consequent wider anabolic window of the concurrent treatment than TPD alone.[67]

The favorable metabolic profile of the combination therapy (DMAb plus TPD) found confirmation in the DATA-Switch study.[68] This study compared the effects on BMD of three different therapeutic schemes: DMAb administered after TPD, TPD after DMAb, and the combination of the two medications given concurrently for 2 years, followed by DMAb alone.[68] The results confirmed that TPD to DMAb sequential therapy is significantly superior than DMAb to TPD. At the end of the study, the TPD to DMAb arm achieved similar BMD benefits at the lumbar spine compared to TPD plus DMAb combination therapy, but the latter reached the BMD peak 12 months earlier than sequential treatment. Besides, if we consider the BMD gains at total hip, the combination arm showed the greatest benefits overall.

Obviously, these results regard only BMD measurements and currently there is no data on fracture incidence. However, it is noteworthy that maximum BMD effects can be reached with an anabolic agent (such as TPD or RMZ) followed by an antiresorptive and that the combined DMAb plus TPD regimen seems to provide the greatest skeletal benefits to patients with established osteoporosis.[65] Like RMZ, combination therapy of DMAb plus TPD should be considered for patients with severe osteoporosis who are at the highest risk of imminent fragility fracture.

NEW DIRECTIONS FOR FUTURE STUDIES

Our recent improvements in the knowledge of the RANK/RANKL/OPG and the Wnt/beta-catenin pathways have led us to the development of DMAb and RMZ.

In our opinion, RMZ represents a new era and, as previously discussed, it is likely to open a new scenario in the management of the imminent fracture risk, a concept that could be considered born and raised with RMZ itself. It cannot be excluded that further biotechnological agents interfering with the inhibitors of the Wnt/beta-catenin pathway (i.e., Dkk-1) will be developed in the future. However, preclinical studies evaluating the effects of monoclonal antibodies to Dkk-1 as potential treatment for osteoporosis have not shown encouraging results to date.[69]

Other possible approaches in the future might include stem cells transplantation, antisenescence agents, and drugs that target specific osteoblast pathway but, unfortunately, the relating research is still in its very early stages.[9]

In our opinion, the low costs and the good effectiveness of many currently available therapies (i.e., BPs) will not encourage large investment in the field of osteoporosis. For this reason, the drugs that are going to be developed in the future will be likely limited to a small proportion of

patients affected by the most severe form of osteoporosis.

On the contrary, we hope that the reduction in the costs of TPD (due to the expiration of its patent) is going to encourage clinicians to prescribe both the sequential and the combined approach.

CONCLUSION

Several pharmacological treatments are available for osteoporosis. The challenge is to identify the optimal treatment for each patient. Indeed, all the different drugs have specific features that make them more or less preferable for each patient. A possible flowchart based on the opinion of the authors is presented in Table 2.

Hormonal therapy is particularly indicated in women younger than 60 years old, within 10 years from their last menses, at risk for osteoporosis and without known risk factors for thromboembolism. In the presence of symptoms of menopause (hot flushes, vulvar and vaginal atrophy, etc.), HRT and TSEC are preferable. For protection from breast cancer risk, SERMs (RLX in particular) are more indicated.

Bisphosphonates (BPs). Oral BPs are widely available and should be considered the first-line treatment for most patients with mild to moderate osteoporosis. ZOL is the first choice in patients with intolerance to oral formulations or when they are contraindicated. ZOL, due to its yearly regimen and the long-tail effect can be also useful in patients with adherence issues. ZOL is contraindicated in patients with impaired kidney function.

Denosumab (DMAb) is preferable in patients who do not tolerate oral BPs or when they are contraindicated. As a side note, DMAb is not contraindicated in the presence impaired kidney function. DMAb can be also considered in patients incurring a new fragility fracture while already on treatment with BPs due to its stronger inhibition of bone turnover.

TABLE 2 Proposed Flowchart for Treatment Selection in Postmenopausal Osteoporosis

1. Primary prevention of fractures in osteoporotic postmenopausal women
   - Women, 50–60 years old, without risk factors for thromboembolism
     - First choice: hormonal therapy
     - Second choice: oral bisphosphonates
   - Women over 60 years old, or with risk factors for thromboembolism, or unwilling to begin hormonal treatment
     - First choice: oral bisphosphonates
     - Second choice: (i.e., in case of low compliance or tolerability of oral bisphosphonates) intravenous bisphosphonates or denosumab
2. Secondary prevention of fractures in postmenopausal women
   - Women with a single osteoporotic vertebral or nonhip fracture
     - First choice: oral bisphosphonates
     - Second choice: (i.e., in case of low compliance or tolerability of oral bisphosphonates) intravenous bisphosphonates or denosumab
   - Women with a more than one osteoporotic vertebral or previous hip fracture
     - First choice: teriparatide
     - Second choice: denosumab or bisphosphonates
3. Patients with severe osteoporosis who experienced a new vertebral fracture during treatment with bisphosphonates
   - First choice: add a treatment with teriparatide or start romosozumab
     - Second choice: denosumab or intravenous bisphosphonates (in patients previously treated with oral bisphosphonates)

J Popul Ther Clin Pharmacol Vol 26(4):e1–e17; 20 November 2019.

Teriparatide (TPD) is strongly recommended in severe osteoporosis, especially in the presence of history of vertebral fractures and for the management of GIOP. Its use is limited to 24 months of therapy and its benefits are maintained only if followed by an antiresorptive agent. Therefore, prompt treatment with these agents is recommended after TPD discontinuation.

Romosozumab (RMZ) represents the first true dual-action drug. Its unique metabolic effect is limited to the first 12 months of therapy and after that a sequential treatment with antiresorptive agents is needed. The BMD effects of RMZ are superior to any other osteoporosis treatment already in the first few months of therapy, with an impressive effect on fracture risk in the first year. For these reasons, it is recommended in patients with severe osteoporosis at high risk for imminent fragility fracture.

COMPLIANCE WITH ETHICAL STANDARDS
CONFLICT OF INTEREST

Davide Gatti reports personal fees from Abiogen, Celgene, Eli-Lilly, Janssen, Pfizer, UCB, and BMS, outside the submitted work.

Angelo Fassio reports personal fees from Abiogen and Novartis, outside the submitted work.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

INFORMED CONSENT

For this type of study, formal consent is not required.

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J Popul Ther Clin Pharmacol Vol 26(4):e1–e17; 20 November 2019.